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2026 BRAIN Initiative Conference

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August 11-13, 2026 | Rockville, MD

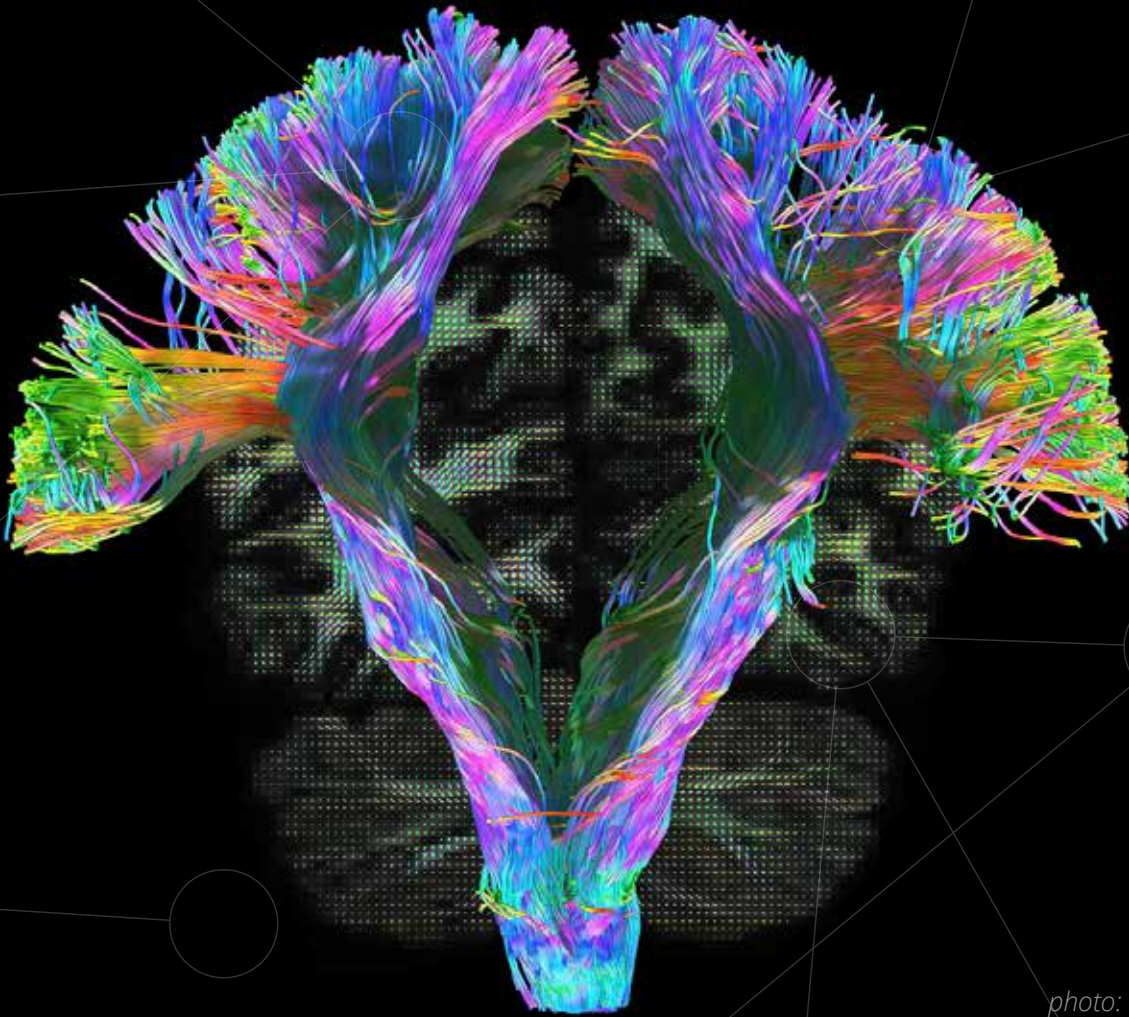


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National Institutes of Health
The BRAIN Initiative

Abstract Book

2026 BRAIN Initiative Conference

Abstract Book

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POSTER
NUMBER:

B001

TOPICS: *Brain Cell & Circuit Technologies*

Scalable nanoscopy of brain circuits by photochemical sectioning

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VIPS, volumetric imaging via photochemical sectioning, is a scalable optical nanoscopy platform for mapping brain circuitry across large intact specimens. A major barrier in high-resolution fluorescence imaging is the limited working distance of microscope objectives, which prevents continuous nanoscale imaging through large cleared or expanded brain tissues. Conventional mechanical sectioning can extend imaging depth, but it often introduces distortion, tearing, and sample loss, which are especially problematic for tracing fine neural processes. VIPS addresses this challenge by replacing mechanical sectioning with spatially precise photochemical removal of hydrogel-embedded tissue. In this workflow, repeated cycles of on-block lattice light-sheet microscopy and light-driven photochemical sectioning enable contiguous volumetric imaging far beyond the objective working distance.

Using VIPS, we imaged complete mouse olfactory bulbs from wild-type and neurodegenerative mice at nanoscale resolution. The resulting petabyte-scale datasets enabled reconstruction and quantitative analysis of axons and myelin sheaths across entire brain regions, rather than through sparse local sampling. This whole-region view revealed layer-specific axon degeneration and de- or dysmyelination in the neurodegenerative olfactory bulb, including spatial patterns that would be difficult to detect from smaller sampled volumes. These results demonstrate that VIPS can connect molecularly specific fluorescence imaging with large-scale circuit architecture, providing a path toward quantitative optical mapping of brain connectivity, pathology, and variability across intact neural tissues.

By removing physical sample size as a practical barrier to super-resolution volumetric imaging, VIPS establishes a foundation for scalable optical studies of brain circuits. Future integration with improved labeling, automated segmentation, and artificial intelligence-based analysis could further expand VIPS toward brain-wide nanoscale circuit mapping and disease-focused neuroanatomical discovery.

KEYWORDS: *Circuit Diagrams; Connectome; Physics or Microscopy/Optics; Software (analysis, etc.) and Engineering*

POSTER
NUMBER:

B002

TOPICS: *Human Neuroscience*

Recollection modulation via hippocampal indirectly targeted stimulation in humans with intracranial EEG

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Hippocampal Indirectly Targeted Stimulation (HITS) is a noninvasive approach that applies transcranial magnetic stimulation (TMS) to parietal cortical regions functionally connected to the hippocampus in order to influence hippocampal activity and memory performance. Previous studies have demonstrated that HITS delivered using a theta-burst stimulation (TBS) protocol enhances episodic recollection and increases hippocampal network activity measured with functional MRI compared with both high-frequency (20-Hz) stimulation and sham stimulation. These effects are hypothesized to be triggered because TBS more closely matches endogenous hippocampal theta oscillations. Nevertheless, the electrophysiological mechanisms underlying these memory improvements remain unclear. To investigate this question, we studied five patients with refractory epilepsy undergoing intracranial EEG (iEEG) monitoring with implanted hippocampal electrodes. Based on prior evidence favoring TBS over high-frequency stimulation and sham, we tested three stimulation conditions in separate blocks: TBS, 20-Hz stimulation, and sham TBS. After each stimulation session, they performed an episodic memory task involving recognition of naturalistic scenes with self-reported recollection and familiarity judgments. Memory performance differed across stimulation conditions (linear mixed-effects model, main effect of condition: $p = 0.009$). Recollection accuracy was highest following TBS (79.5%), exceeding performance after 20-Hz stimulation (68%, $q = 0.38$) and showing a significant improvement relative to sham TBS (71.3%, FDR-corrected comparison, $q = 0.041$). These results demonstrate that a single session of TBS-based HITS is sufficient to enhance episodic recollection in patients undergoing iEEG monitoring, extending previous findings reported in healthy participants. Ongoing analyses of the simultaneously recorded iEEG signals are examining the neural dynamics through which TBS influences hippocampal-dependent memory processing.

KEYWORDS: *Behavioral Sciences/Psychology; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Neural Networks (topology, etc.)*

POSTER
NUMBER:

B003

TOPICS: *Data Science & Informatics*

PIANO enables atlas-scale integration and spatially resolved generative modeling of multi-modal brain atlases across species and neurodegenerative disease.

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Single-cell sequencing has enabled the routine acquisition of brain datasets with millions of cells. Using this technology, the BRAIN Initiative Cell Atlas Network (BICAN) has developed comprehensive cell type atlases across multiple species. These data provide unprecedented opportunities to characterize the molecular architecture of mammalian brains—identifying conserved and species-specific biology that translates to improved understanding of human brain organization, function, and disease.

However, single-cell data are sparse and noisy, with overlapping sources of variation from donors, species, and sequencing platforms. Additionally, these data do not retain the physical locations of cells. In contrast, most spatial methods achieve spatial context in exchange for the sensitivity of single-cell sequencing. To leverage the strengths of both modalities, we developed PIANO (Probabilistic Inference Autoencoder Networks for multi-Omics), a deep learning framework for the integration and generative modeling of multi-modal data. PIANO learns robust latent representations that enable strong integration across species and modalities while preserving cell type structure. Through optimized GPU utilization, PIANO achieves 10x faster training than previous approaches and scales to atlases with over 100 million cells. Beyond integration, PIANO enables generative modeling to infer biological relationships that are not directly observable from any modality alone.

Applied to a primate basal ganglia atlas, PIANO enables robust cross-species integration by aligning homologous cell types across species while preserving species-specific differences. Integrating whole mouse brain atlases, PIANO aligns millions of cells across single-cell and spatial modalities while preserving cell type identities. Modeling Alzheimer's disease using data from over 80 human donors, PIANO recapitulates established disease signatures while revealing novel spatial disease-progression patterns for genes linked to amyloid- β pathology. Notably, these patterns were recovered for genes present in single-nucleus data but absent from spatial data, demonstrating how generative modeling can reconstruct transcriptome-wide spatial patterns beyond direct measurement.

These results establish PIANO as a robust framework for multi-modal integration and generative modeling, empowering discoveries that advance our understanding of brain cell types, spatial organization, and neurodegenerative disease.

KEYWORDS: *Cell Type/Interactions; Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

POSTER
NUMBER:

B004

TOPICS: *Neural Recording & Modulation*

Improving generalizable EEG-based speech decoding for neurocommunication: A cross-paradigm transfer learning study

PRESENTER: **B. Adeika**
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Loss of speech due to stroke, amyotrophic lateral sclerosis (ALS), traumatic brain injury, and other neurological conditions significantly impacts quality of life and communication ability. Brain-computer interfaces (BCIs) based on electroencephalography (EEG) offer a promising non-invasive approach for restoring communication in individuals with speech impairments. However, a critical barrier to clinical translation is subject-independent generalization—models trained on one group must perform reliably on new individuals without requiring individual calibration.

This study investigates cross-paradigm EEG-based speech decoding with a focus on improving generalization across individuals and datasets. We integrated two publicly available EEG speech corpora: the OpenNeuro Inner Speech Corpus (ds003626) and the KaraOne dataset, examining both imagined and overt speech modalities. Our preprocessing pipeline included 1-45 Hz band-pass filtering, notch filtering at 60 Hz, common average referencing (CAR), and independent component analysis (ICA).

We benchmarked classical Riemannian geometry approaches against modern convolutional neural networks (EEGNet) and investigated Transformer-based architectures to capture temporal dynamics in speech-motor activity. To enhance generalization, we incorporated spectral augmentation, instance normalization, and domain-adversarial training to reduce distributional shifts between datasets and individuals.

Performance was rigorously evaluated using leave-one-subject-out (LOSO) cross-validation and grouped cross-validation protocols. EEGNet demonstrated substantially improved generalization compared to baseline approaches, with significant improvements in subject-independent performance. Cross-paradigm training (mixing imagined and overt speech modalities) further improved robustness, particularly for participants unseen during training.

These findings demonstrate that deep neural networks can learn generalizable, subject-independent representations of speech from scalp EEG without participant-specific calibration. Mixed-paradigm training enhanced transfer learning performance, supporting domain adaptation strategies. This work advances the development of clinically viable, subject-independent neurorehabilitation BCIs for speech restoration in individuals with neurological impairments.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Monitor Neural Activity*

POSTER
NUMBER:

B005

TOPICS: *Neural Recording & Modulation*

Centimani: A precision robotic system for minimally invasive, large-scale, parallel implantation of flexible neural probes

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Flexible neural electrodes enable seamless integration with brain tissue and allow stable, long-term recordings from individual neurons without signal degradation. Distributed implantation of such electrodes facilitates the study of neural dynamics across a range of timescales—such as those underlying learning and memory—and provides valuable input for robust brain-machine interface systems.

Despite the handling challenges posed by probe flexibility, prior work has demonstrated months-long recordings from up to 1,024 channels using distributed implantation of ultraflexible electrode threads. However, these procedures remain labor-intensive and provide limited control over implantation trajectory, speed, and positioning. These formidable challenges have limited the broader adoption of large-scale, distributed neural recording technologies.

As a step toward automated precision implantation, Neuralink recently introduced a robotic system that uses a “sewing machine”-like mechanism for high-precision insertion of flexible probes. However, its strictly sequential strategy can lead to prolonged surgical times, increased tissue damage at higher speeds, and limited robustness to targeting errors.

Here, we present Centimani, a minimally invasive, high-precision robotic system capable of implanting up to 32 flexible probe threads with sub-100 μm targeting accuracy and inter-thread spacing down to 500 μm . Centimani offers fully programmable control over insertion speed (ranging from micrometers per second to 10 mm/s) and site selection, enabling precise targeting of arbitrary brain regions while actively avoiding vasculature. It supports both simultaneous and sequential insertion modes, with total implantation times as short as one minute.

We demonstrate that neural activity recovers following implantation, and that Centimani-implanted probes can simultaneously record from hundreds of channels. This enables tracking of monosynaptic neuronal connectivity and modulation of activity via microstimulation, providing a powerful platform for high-density, functional mapping of brain circuits.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Integrated Approaches; Monitor Neural Activity; Neural Recording & Modulation; Dissemination & Open Science/Education*

POSTER
NUMBER:

C001

TOPICS: *Human Neuroscience*

Implantable brain-controlled spinal stimulation promotes corticospinal neuroplasticity to improve motor function in chronic tetraplegia

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Spinal cord injury (SCI) disrupts descending motor pathways, leaving individuals with tetraplegia dependent on residual neural connections to generate voluntary movement, with limited recovery despite extensive rehabilitation. Epidural spinal cord stimulation (ESCS) can modulate spinal sensorimotor circuits to facilitate motor output following SCI. Integrating ESCS with a brain-computer interface (BCI) that decodes volitional motor intent may enhance recovery by synchronizing stimulation with attempted movements to drive activity-dependent plasticity. Here, we evaluated the single-session and one-month neuroplastic effects of a BCI-controlled ESCS system in three individuals with chronic cervical SCI (n=3; C3-C5 neurological levels; AIS A-D). The BCI decoded attempted movement-related cortical activity and triggered cervical ESCS during activity-based therapy. ESCS was delivered via two percutaneous eight-contact epidural leads targeting upper-limb sensorimotor circuits corresponding to C5-T1 segments using 80-Hz, 200- μ s biphasic pulses at intensities to facilitate volitional movement without causing involuntary contractions. Short-term effects were assessed by comparing corticospinal and spinal excitability before and after single sessions of BCI-ESCS and tonic stimulation (control). Longitudinal effects of BCI-ESCS intervention were also assessed by comparing corticospinal and spinal excitability alongside upper-limb function, measured using the Toronto Rehab-Hand Function Test and reaching kinematics. Assessments were conducted at Baseline, Endpoint, and one-month Follow-up. We demonstrated that BCI-ESCS facilitated corticospinal and spinal excitability after a single session, while tonic stimulation did not, suggesting the utility of BCI-driven neuromodulation for activity-dependent plasticity. One month of BCI-ESCS use yielded meaningful improvements in hand function, with TRI-HFT 10-object manipulation scores improving by an average of 17.3 points, exceeding clinically meaningful thresholds. These functional gains were accompanied by enhanced corticospinal excitability, suggesting that repeated intent-driven stimulation may progressively engage activity-dependent plasticity to improve voluntary function. Together, these findings support BCI-driven neuromodulation as a therapeutic modality that harnesses volitional intent to promote activity-dependent plasticity after chronic cervical tetraplegia.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Neural Recording & Modulation; Synaptic Plasticity; Implantable Devices (probes, etc.)*

POSTER
NUMBER:

C002

TOPICS: *Neural Recording & Modulation*

Multicolor HaloTag labeling enables in vivo reconstruction of synaptic activity histories

PRESENTER: **D. Kim**

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Synaptic transmission is essential for neuronal communication, yet tracking when and where synapses are activated across circuits remains challenging. Here, we introduce a multicolor HaloTag labeling method that enables time-resolved tagging of active presynaptic terminals in the live mammalian brain. We generated a Synaptophysin-HaloTag construct that is selectively labeled with membrane-impermeable ligands upon presynaptic vesicle exocytosis. In cultured neurons, optogenetic stimulation and chemical depolarization increased labeling with a membrane-impermeable HaloTag-ligand dye, reflecting enhanced presynaptic vesicle release. In live mice, both optogenetic stimulation in anesthetized animals and sensory deprivation in awake, freely moving animals produced clear and distinct labeling patterns in active presynaptic terminals.

We then performed multiplexed active synapse labeling in the basolateral amygdala and nucleus accumbens within the same brain to examine presynaptic terminals originating from the medial prefrontal cortex during aversive and rewarding stimulus encoding. Presynaptic terminals in the basolateral amygdala and nucleus accumbens showed distinct stimulus-associated labeling patterns, demonstrating that this platform can resolve projection-specific presynaptic recruitment across behavioral conditions. We further generated epitope-tagged Synaptophysin-HaloTag constructs for glutamatergic and GABAergic synapses, enabling cell-type-dependent multiplexed investigation of synaptic dynamics.

This presynaptic HaloTag activity labeling platform provides a genetically targetable and temporally controlled method to reconstruct synaptic activity histories at synaptic resolution. By combining in vivo activity labeling with ex vivo imaging, this approach enables scalable mapping of engaged presynaptic circuits across brain regions and cell types, offering a complementary strategy to existing methods for studying neural circuit dynamics.

KEYWORDS: *Cell Type/Interactions; Chemistry; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

POSTER
NUMBER:

C003

TOPICS: *Neuroethics*

Converging researcher, trial participant, and support partners post-trial support needs and solutions

PRESENTER: **E. Versalovic**

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As implantable neural device (IND) trials continue to expand, so too do the needs for adequate long-term support planning. Although participation in IND trials often lasts three years or less, many participants retain these implanted devices after the trials end. Those who receive symptom relief from the investigational devices often have treatment-resistant conditions or loss of function without other effective treatment alternatives. Battery replacements, stimulation adjustments, specialized clinical management, and adequate social and psychological support are among the ongoing needs that can go unaddressed.

This poster presents findings from a BRAIN-funded study that examines post-trial support for one large subset of IND trials—those for deep brain stimulation (DBS). We conducted qualitative interviews with over 100 stakeholders. Here, we present findings from three key groups involved in DBS clinical trials: researchers (n=26, including neurosurgeons, neurologists, engineers, psychiatrists), former DBS trial participants (n=25), and, when appropriate, support partners (n=5). Interviews explored key long-term support needs, current post-trial plans (or lack thereof), lingering uncertainties and challenges, and suggestions for potential solutions for improving long-term support. Findings show the impact that the lack of policies incentivizing and regulating long-term support have on all those involved: researchers carrying the burdens of ad hoc navigation of former trial participant needs as they arise, trial participants and their support partners holding the weight of uncertainty and frustration when maintenance needs go unmet.

These perspectives reveal both shared concerns and mutually beneficial intervention points for increasing the post-trial support scaffolding both for those conducting and participating in IND trials. These findings critically empirically inform both the design of future IND trials and ongoing efforts to improve policies to better support former IND trial participants. Strengthening the long-term support scaffolding, the field can ensure continued innovation is balanced with adequate stewardship and support for the patients, caregivers, and providers making progress in these novel therapies possible.

KEYWORDS: *Implantable Devices (probes, etc.); Neural Recording & Modulation; Neuroethics, Philosophy, Law; Human Neuroscience, Clinical Science, or Public Health*

POSTER
NUMBER:

C004

TOPICS: *Systems Neuroscience*

Whole body modeling of sensorimotor control during prey capture by freely moving marmosets

PRESENTER: **J. Walker**

Yale University

AUTHORS: J. Walker, J. MacLean, N. Hatsopoulos, S. Saxena

Prey capture by common marmosets exemplifies the sophisticated visuomotor coordination that defines primate behavior, requiring rapid integration of sensory information with precise motor control. While we can now record neural population activity during natural behaviors, understanding how neural dynamics generate complex movements remains challenging. Here, we demonstrate that a whole-body musculoskeletal model trained through deep reinforcement learning can replicate behavioral complexity while generating artificial neural activity that begins to mirror biological neural dynamics. We analyzed neural population dynamics during experimental prey capture, revealing behavior-specific patterns: familiar rotational structures during simple reaches but multimode oscillations and discontinuities during dynamic pursuit requiring sequential corrective movements. Our model, trained on recorded prey capture episodes using exponential reward scaling, shows improvements in recapitulating biological reaching trajectories compared to linear reward functions based only on inverse hand-to-target distance. We compared three training strategies (episode experts, category specialists, and generalists), finding that models trained on quick capture episodes fail to generalize to dynamic pursuit episodes. Conversely, models trained on dynamic pursuit transfer well to quick captures, suggesting behavioral complexity within training shapes neural solution space. Preliminary comparisons between recorded sensorimotor cortical activity and model-generated neural representations reveal coarse-grain structural similarities. Alternative approaches using guidance laws, while providing qualitative fits to hand trajectories, fail to capture pursuer dynamics and lack neural components entirely. Our results demonstrate that data-driven neuromuscular models can bridge the gap between neural recordings and behavior, though questions remain about computational principles needed to fully recapitulate biological neural dynamics during natural behavior. This work establishes a framework for understanding how the primate brain orchestrates complex feedback-driven, goal-directed movements by combining experimental neuroscience with embodied computational modeling, and promises to provide insights into the neural basis of adaptive motor control.

KEYWORDS: *Computational Biology/Modelling; Integrated Approaches; Monitor Neural Activity; Neural Networks (topology, etc.); Neural Recording & Modulation; Electrophysiology*

POSTER
NUMBER:

C005

TOPICS: *Systems Neuroscience*

Resource constraints drive memory externalization in brains and machines

PRESENTER: **R. Zhang**
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Brains do not operate in isolation from the body, yet how physical actions support internal computation remains unclear. Here, we investigate how intelligent systems maintain beliefs about hidden goals under limited computational resources. We show that primates and artificial agents spontaneously track invisible goals with their eyes, using gaze to preserve accurate spatial estimates. This strategy emerges in artificial agents only when internal memory capacity is constrained, mirroring the resource limitations of biological neural systems. Restricting gaze causes a dramatic collapse in performance in both systems, while behavioral variability and causal perturbations reveal that oculomotor state directly shapes internal spatial belief. Neural recordings from macaque parietal cortex further show that goal representations are organized around eye position and occupy a shared representational space with artificial networks. Together, these findings identify eye movements as a functional external memory mechanism and reveal a convergent principle of intelligence: When internal computation is constrained, both brains and machines recruit the body to support cognition.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Electrophysiology; Integrated Approaches; Neural Recording & Modulation; Theory & Data Analysis Tools*

Extracellular ATP sensitizes induction of calcium responses by magnetic fields in brain endothelial cells

PRESENTER: **A. Pal**

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AUTHORS: A. Pal, M. Hernández-Morales, V. Han, C. Liu, Z. Qin

Developing non-invasive approaches to modulate defined cell populations in the brain could expand the toolkit for studying brain function, including neurovascular signaling. Compared with light and ultrasound, magnetic stimulation provides a non-invasive approach to reach deep brain tissue. Recently, ferritin, an intracellular iron-storing protein, has been harnessed by multiple labs across various cell-types to induce calcium responses. However, these “magnetogenetic” methods require genetic linking of ferritin with a transmembrane calcium influx channel such as TRPV4 requiring precise design of genetic linkers and effective expression optimization.

In a novel approach, we implemented a TRP-channel sensitization strategy to induce calcium responses in wild-type brain endothelial cells (BECs) using adenosine triphosphate (ATP) as a “stimulant.” We used two in vitro models of the blood-brain barrier (BBB), 1) an immortalized mouse brain endothelial cell line (bEND.3) and 2) human iPSC derived brain endothelial cells (iBEC), for these experiments. Radiofrequency (RF)-based magnetic fields (100 μ T at 180 MHz) were generated using an in-house solenoid coil connected to a current amplifier and a signal generator.

We found that pre-incubation of cells with ATP enhances fast-acting, synchronous calcium responses in 100 μ T of magnetic fields. As positive control, we also showed that ATP-sensitization enhanced shear-stress associated responses, recapitulating previously published reports. To rule out experimental artifacts, we demonstrated that RF-based calcium induction was independent of temperature (up to 36°C) changes and pH (6-8). Rather, these responses were solely dependent on the concentrations of ATP used. In addition, we found that the BBB-like state of BECs promotes these responses not only via known intracellular contributors such as ROS generation and TRPV4 but also novel contributors such as the cellular iron status and intercellular communication gap-junction channels.

In conclusion, we report a novel approach for modulation of calcium signaling in BECs without genetic modification. Due to the transparency of tissue towards magnetic fields, we believe this method could have huge potential in modulating various endothelial-specific phenotypes such as angiogenesis, modulation of vascular tone, and the blood-brain barrier maintenance.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Molecular/Cellular Neuroscience; Cell Type/Interactions*

A cross-species enhancer-AAV toolkit for cell type-specific targeting across the basal ganglia

PRESENTER: **M. Wirthlin**
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The mammalian basal ganglia (BG) orchestrate motor control, reinforcement learning, and action selection, and their dysfunction is implicated in a host of neurological and psychiatric disorders. Despite advances in defining BG cell type diversity through transcriptomic, anatomical, and physiological characterization, precise genetic access has remained limited beyond canonical spiny projection neurons (SPNs) and beyond the mouse, with major nuclei including the pallidum, subthalamic nucleus (STN), and dopaminergic midbrain broadly lacking experimental tools for cell type-specific perturbation in non-human primates (NHPs). To ameliorate this, we developed the Cross-species Enhancer Ranking Pipeline (CERP), which integrates single-nucleus RNA-seq and ATAC-seq from mouse and macaque, mapped to the Human and Mammalian Brain Atlas (HMBA) consensus BG taxonomy, to prioritize enhancer candidates by chromatin accessibility, evolutionary conservation, and sequence modeling. Candidate enhancers were cloned into AAV vectors and screened in mouse via systemic retro-orbital delivery, with promising candidates advancing to cross-species validation by stereotaxic injection in macaque. Across 514 enhancers tested in mouse, we identified “best-in-class” enhancer-AAVs targeting 21 atlas-defined BG populations, spanning canonical and non-canonical striatal SPN subtypes (including D1-ICj granule cells, D1-NUDAPs, and D1/D2 eSPNs), GPe prototypic and arkypallidal projection neurons, STN glutamatergic neurons, anterior and posterior SNr subtypes, and dorsal- and ventral-tier midbrain dopaminergic neurons. Best-in-class enhancer-AAVs achieved >70% on-target specificity by single-cell RNA-seq, with many exceeding 90%, and cross-species comparisons demonstrated robust preservation of specificity between mouse and macaque. Sequence-based activity modeling (CREsted) of validated enhancers identified evolutionary conservation, chromatin accessibility, and motif grammar as features predictive of in vivo performance. This work represents the first comprehensive cross-species enhancer-AAV toolkit for the basal ganglia, unlocking previously inaccessible cell types for precise experimental interrogation in rodents and primates, and providing the groundwork for cell type-targeted gene therapies across mammalian model systems.

KEYWORDS: *Cell Engineering; Cell Type/Interactions; Computational Biology/Modelling; Genetics/Genomics; Molecular/Cellular Neuroscience; Interventional Tools*

Photorelease of oxytocin in vivo using photoswitchable nanovesicles

PRESENTER: **P.A. Slesinger**

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AUTHORS: J. Taura, H. Tajarenejad, Z. Qin, P.A. Slesinger

Achieving precise spatiotemporal control of neuropeptide delivery in vivo remains a major challenge because conventional approaches lack temporal precision and control over release kinetics. Here, we demonstrate that photoswitchable lipid nanovesicles ("azosomes") enable light-controlled neuropeptide release in the brains of awake, freely moving mice. Azosomes were infused into the hippocampus through optofluidic cannulas and activated by light. Release kinetics were systematically characterized in vivo using calcein-loaded azosomes by varying light power, pulse duration, and post-infusion time. Oxytocin (OT)-loaded azosomes were used to assess bioactivity and receptor specificity with dual-color fiber photometry using the genetically encoded OT sensor MTRIA-OT and pharmacological blockade with the oxytocin receptor antagonist OVTA.

Azosomes enabled robust, repeatable, light-dependent cargo release with tunable kinetics determined by stimulation parameters. Release efficiency increased with light power and pulse duration, while the system remained stable for several hours after infusion, exhibiting minimal baseline leakage and near-complete release within approximately 2 hours. Light-triggered OT delivery produced rapid, receptor-specific increases in MTRIA-OT signals and modulated CA2 hippocampal activity by reducing the frequency and amplitude of excitatory neuronal transients. It also altered social behavior by decreasing the latency to initiate social contact.

These findings establish photoswitchable nanovesicles as a versatile platform for spatiotemporally precise neuropeptide delivery in vivo, overcoming key limitations of existing delivery methods and providing a broadly applicable strategy for manipulating neuromodulatory signaling with high temporal precision.

KEYWORDS: *Behavioral Sciences/Psychology; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Mapping primate visual and dopaminergic circuits by Synapse-seq

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Broad Institute

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A central goal of connectomics is to link a neuron's molecular identity to its projection architecture, yet scalable methods to do so remain limited across species. Genetically defined tools for circuit neuroscience are particularly lacking in the primate brain, whose diverse neural populations and expanded circuitry may hold greater relevance to human behavior and disease. Synapse-seq addresses this by AAV-delivered, cell-identifying barcoded mRNAs directed to synaptic compartments via targeting proteins. These are read out with single-cell and spatial genomics, allowing a neuron's transcriptome and projections to be read out by shared barcodes. This has successfully been performed in mice, however a more diverse barcoded AAV library is required to label the larger primate brain while maintaining a negligible rate of barcode "collisions," where two cells receive the same barcode hindering unique assignment of projections to origin.

To meet this need, we scaled production of barcoded AAV libraries and used sequencing-based modeling to characterize their complexity and barcode distribution. This yielded a roughly 5-fold increase in usable barcode diversity, lowering the rate at which barcodes are expected to collide and thereby increasing the potential recoverable number of neurons.

With libraries diverse enough to address primate-scale circuits, we deployed them in the common marmoset to map two systems: the glutamatergic primary visual cortex and the dopaminergic midbrain. In each circuit, our presynaptic Synapse-seq system labeled both the injection site and expected long-range targets but not contralateral negative control regions, indicating specific trafficking of barcode transcripts by the presynaptic targeting protein. Reading these barcodes out with spatial transcriptomics, we recovered them in the expected projection targets: the dorsal lateral geniculate for visual cortex injections, and the striatum and motor cortex for the midbrain circuit. The resulting spatial distributions agreed closely with established anterograde tracing in marmoset and macaque, confirming that Synapse-seq functions in primate tissue and recaptures known connectivity.

By applying Synapse-seq into the primate brain, this work opens a path to integrated, cell-type-resolved maps of conserved and species-specific circuitry, and to the molecular logic of the connections that fail in neurodegenerative disease.

KEYWORDS: *Connectome; Neural Networks (topology, etc.); Molecular/Cellular Neuroscience*

Neuron-type-specific control of synaptic condensates tunes stress resilience and depression-like behavior

PRESENTER: **W. Xu**
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AUTHORS: Y. Li, K. Lesslie, R. Abdelaziz, W. Xu

Chronic stress disrupts synaptic strength and promotes dendritic spine loss in cortical circuits, contributing to the pathophysiology of depressive disorders. Excitatory synapses onto prefrontal cortical pyramidal neurons are particularly vulnerable to these stress-induced changes. Although both conventional and rapid-acting antidepressants can reverse these synaptic deficits, their effects are indirect and are often accompanied by a broad range of side effects, some of which can be severe. Here, we tested whether directly manipulating postsynaptic molecular assemblies is sufficient to promote stress resilience and produce antidepressant-like effects. The postsynaptic density (PSD) of excitatory synapses is organized as a liquid-liquid phase-separated protein condensate. We engineered molecular probes that bind core PSD scaffold proteins and modulate condensate dynamics. Cell type-specific expression of these probes in layer 5 extratelencephalic (ET) neurons of the prefrontal cortex produced graded changes in excitatory synapse density and synaptic transmission. These synaptic modifications were accompanied by corresponding increases in stress resilience and antidepressant-like behavioral effects. These findings demonstrate a causal role for excitatory synaptic function in a defined cortical neuronal population in regulating stress resilience, and establish manipulation of postsynaptic condensate dynamics as a new strategy for developing antidepressant therapies.

KEYWORDS: *Cell Type/Interactions; Circuit Diagrams; Electrophysiology; Interventional Tools; Molecular/Cellular Neuroscience; Synaptic Plasticity*

Patchy intra- and inter-layer hexagonal grid-like networks in mouse auditory cortex enable discrete tone integration

PRESENTER: **M. Wang**

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Sensory cortical neurons are organized in interconnected layers. While anatomical studies can reveal neuronal circuits, the crucial remaining gap is to link functional connectivity with functional properties. Here, we develop an all-optical in vivo approach that combines 2-photon imaging, holographic optogenetic stimulation, network inference, and statistical connectivity modeling for causal mapping of functional connections across layers. To better understand the connectivity in the ascending cortical sensory processing pathway, we simultaneously imaged layer 4 (L4) and layer 2/3 (L2/3) neurons of the mouse auditory cortex (ACtx) while delivering optogenetic activation of small subsets of neurons at the single-neuron level precision in either layer as a perturbation strategy to causally probe interlaminar functional connectivity. We mapped the connectivity of excitatory neurons (Ai203; Vglut1-Cre; Cdh23Ahl/ahl) and found that, in ACtx, functionally connected neurons in L4 and L2/3 exhibited both local and distal connectivity that varied with neuronal tuning relationships and cortical position in a hexagonal pattern with a spacing reflecting octave relationships. Interlaminar connections were mainly columnar and depended on the tonotopic axis. The existence of discrete patchy connections in ACtx defines a hexagonal circuit motif that could support the integration of discrete harmonic frequency components.

KEYWORDS: *Computational Biology/Modelling; Integrated Approaches; Neural Networks (topology, etc.); Neural Recording & Modulation*

Neuropathology and transcription in situ: A new spatial multi-omic framework applied to Alzheimer's disease

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The earliest pathological changes in neurodegeneration arise in selectively vulnerable neurons, often before symptom onset. By pairing spatial transcriptomics with in-section pathology staining and clinical staging, we can assess how tau and amyloid, the two pathologies of Alzheimer's disease (AD), reshape the neurons that bear them.

Using GeoMx, we simultaneously quantified mRNA and per-neuron tau status in hippocampal pyramidal neurons across primary age-related tauopathy (PART) and AD. While synaptic genes were broadly downregulated in disease, tau-positive neurons showed relative upregulation compared with tau-negative neurons in the same tissue. We then used our Bayesian nonnegative matrix factorization (NMF) algorithm, CoGAPS, to identify tau-associated expression programs. Agnostic to disease status, CoGAPS learned transcriptional signatures that were similarly utilized by neurons across PART and AD cases, suggesting that intraneuronal tau drives a shared transcriptional response across the aging-to-AD continuum.

To capture the amyloid arm in the earliest-affected neurons, we profiled the locus coeruleus, an early-vulnerable nucleus, in individuals without cognitive impairment spanning a range of cortical amyloid burden. LC neurons from individuals with cortical amyloid exhibited a CoGAPS signature enriched for immediate-early genes (FOS, CREM, JUNB), consistent with neuronal activation. Signature utilization increased with Thal phase and plaque severity.

Together, these studies show that AD pathologies impose distinct neuronal states, both within the local cellular niche and across brain regions. Resolving pathological interactions, common in the aging brain where mixed pathology is the norm, requires capturing both transcriptomic information and multiple pathological aggregates in the same section. To this end, we are developing a low-cost, FFPE-compatible platform for joint readout of mRNA and multiplexed neuropathology markers, preserving protein and RNA in the same cells. As a proof of concept, we present preliminary data on the concurrent detection of transcript targets, tau, and beta-amyloid in the same section, supporting a same-section, multi-omic framework for mapping how neuropathology shapes cellular states in human neurodegeneration.

KEYWORDS: *Genetics/Genomics; Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Molecular/Cellular Neuroscience; Software (analysis, etc.) and Engineering*

The contribution of neuronal glycolysis during motor learning

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Motor learning increases neuronal activity and induces changes in plasticity, imposing substantial energetic demands on neurons. While much of our understanding of neuronal metabolism comes from in vitro and ex vivo studies, how these demands are met in vivo in behaving animals during learning remains poorly understood. Oxidative phosphorylation is thought to be the main bioenergetic pathway engaged by neurons, but recent work has demonstrated the use of glycolysis during period of high neuronal activity. Thus, we hypothesize that glycolysis is particularly important during motor learning to meet rapid energy demands. To address this, we have established a modular lever press task to assay motor learning with the goal of performing two-photon imaging of genetically encoded metabolic and calcium sensors during motor learning. We focus on neurons of the primary motor cortex, an area that is necessary for motor learning. We have demonstrated that systemic delivery of 2-deoxyglucose, a glucose analog and inhibitor of glycolysis, elicited measurable changes in metabolic sensor signals in vivo. Current work is now focused on measuring the engagement of glycolysis across learning in the same neurons and comparing changes in this pathway to neuronal activity. We also continue to expand our metabolic sensor toolbox for in vivo use. Together, our results validate a new approach for measuring neuronal metabolic dynamics in behaving animals, opening the door to directly probing how the brain fuels learning.

KEYWORDS: *Molecular/Cellular Neuroscience; Neuroimaging (invasive, non-invasive imaging)/Radiology*

A molecularly conserved population of basolateral amygdala projection neurons regulates social novelty recognition

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Social dysfunction is common across all neuropsychiatric diseases and represents primary diagnostic criteria for some neurodevelopmental disorders, such as autism spectrum disorder. The lateral septum (LS) is a GABAergic region within the basal forebrain that exerts control over a variety of social behaviors, including aggression and kinship. Recent work from our group has demonstrated that ablation of inputs from the basolateral amygdala (BLA) into the LS are essential for social novelty recognition (SNR) or the ability for an experimental animal to distinguish between a novel or familiar conspecific. Additionally, BDNF-TrkB signaling within the BLA-LS circuit is necessary for SNR. While these studies begin to elucidate the neural circuits involved in social recognition, they do not provide evidence regarding the molecular identity of LS projecting, BLA neurons (BLA-LS) or whether they are conserved across mammalian species. Understanding the molecular identity and conservation of BLA-LS projection neurons is important for elucidating putative human cells important for social behavior and the development of novel therapeutics. To understand the molecular signature of BLA-LS projection neurons, we performed single-nucleus RNA sequencing of sorted BLA-LS neurons. Computational analyses revealed dozens of transcriptionally distinct neuronal subtypes. Several of these clusters, including one enriched for *Etv1*, were preferentially enriched for BLA-LS projection neurons. Differential expression testing identified that BLA-LS projection neurons were enriched for *Slc17a7*, *Bdnf*, *Rspo2*, and *Etv1*. Cross-species comparisons also identified that BLA-LS projection neurons are conserved with populations of BLA neurons in the non-human primate and human. Specifically, they are molecularly similar to BDNF-expressing populations derived from the basal and lateral subdivisions of the human BLA. Together, these results highlight a conserved population of BLA projection neurons that are essential for social behaviors and identify novel molecular targets for therapeutic development.

KEYWORDS: *Behavioral Sciences/Psychology; Genetics/Genomics; Molecular/Cellular Neuroscience; Cell Type/Interactions*

Examining parvalbumin cell-mediated inhibition in models of schizophrenia

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Understanding the circuitry of parvalbumin (PV) cell-mediated inhibition could provide insight into disorders such as epilepsy, autism, and schizophrenia. However, in vivo labeling specific IN subtypes in mice requires cumbersome genetic manipulation, which proves even more complicated when investigating in haploinsufficient models of schizophrenia. To overcome this problem, our lab has generated enhancer-AAV tools that allow for the targeting of specific IN types. We are using specific enhancers (BIPVe2, BIPVe3, BIPVe4) to characterize parvalbumin+ (PV) IN microcircuits in mice carrying mutations in schizophrenia risk genes. In these experiments we utilized BIPVe2, which broadening labels both basket and chandelier cells. By labeling this population using retro-orbital injection of BIPVe2, we are able to label PV INS and quantify synaptic density on enhancer-labeled interneurons in both wild type and specific haploinsufficient models of schizophrenia, including *Grin2a*, *Setd1a*, *Akap11*. This has allowed us to uncover whether disruption of these genes affects specific inhibitory neural pathways, furthering our understanding of the disease mechanism of schizophrenia.

KEYWORDS: *Cell Type/Interactions; Developmental/Systems Biology; Genetics/Genomics; Molecular/Cellular Neuroscience*

Scalable multi-modal single-nucleus and spatial transcriptomic mapping of NPD risk-gene perturbations across the developing mouse brain

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Neurodevelopmental and psychiatric disorders (NPDs) arise from diverse genetic lesions, yet many may converge on shared disruptions in brain cell-type maturation, spatial organization, and molecular circuit programs. A central challenge, and opportunity, is to move beyond one-gene, one-region studies toward a scalable, quantitative atlas that tests how diverse NPD-risk genes perturb cell-type composition, transcriptional state, and anatomical organization across sex and developmental time. As part of the SSPsyGene Consortium Project SING effort, we are building a standardized single-nucleus and spatial transcriptomic resource across mouse knockout models of approximately 100 high-confidence NPD-risk genes spanning chromatin regulation, synaptic signaling, cell adhesion, ion-channel function, translational control, mTOR signaling, and glial/lysosomal biology. Brains are collected from male and female mice at P14 and P56 to capture early postnatal circuit maturation and young-adult brain organization. To achieve cell-type and anatomical precision at consortium scale, we combine 10x GEM-X Flex v2 snRNA-seq with Vizgen MERSCOPE (MERFISH) imaging of coronal brain sections. Preliminary runs we recovered 13-17K nuclei per sample, detected median gene counts of 5-7K genes per cell, achieved 97% confidently mapped reads in cells, and detected approximately 17.5-18K genes per sample. In parallel, the spatial transcriptomics pipeline achieved a median transcript-count metrics of approximately 444-516 per cell, and initial brain-region registration to the CCF atlas underway. snRNA-seq resolves genotype-dependent shifts in excitatory neurons, inhibitory interneurons, glial, immune, and vascular-associated populations, while MERFISH preserves spatial context to map vulnerable cell states across anatomical and laminar domains. Integrated annotation, differential expression, gene-set enrichment, module detection, and cross-gene comparisons will identify whether distinct NPD-risk perturbations converge on shared cell-type-specific programs or produce functional-class-specific phenotypes. Together, this work provides a scalable and precise multimodal framework for connecting NPD-associated genetic risk to cell-type-specific transcriptional programs, spatial brain organization, and developing circuit architecture, creating a resource to identify shared and divergent mechanisms of vulnerability across neurodevelopmental and psychiatric disorders.

KEYWORDS: *Developmental/Systems Biology; Genetics/Genomics; Informatics, Statistics, or Applied Mathematics; Molecular/Cellular Neuroscience; Integrated Approaches*

Developmental mapping of excitatory, inhibitory, and vGlut1/VGAT co-positive neurons in the early postnatal cortex

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Glutamatergic and GABAergic neurons shape cortical circuit formation during early postnatal development. Moreover, recent studies have identified neurons that co-express vesicular glutamate transporters (VGLUT) and vesicular GABA transporters to fine-tune network activities and maturation. Despite their significance in brain development, it remains unclear how these neurons populate different cortical areas across key postnatal developmental periods. To address this gap, we established a triple-transgenic reporter mouse model (vGlut1-Flp;VGAT-Cre;Ai224) and a whole-brain quantification workflow to visualize and quantify vGlut1-positive, VGAT-positive, and vGlut1/VGAT co-positive neuronal populations during postnatal development. Using SHIELD-preserved whole-brain tissue clearing, light-sheet fluorescence microscopy, and deep-learning based cell detection, we quantified labeled neuronal populations across the cerebral cortex at every other postnatal day from P0 to P14. These data were mapped to age matched templates with anatomical labels based on the Allen Mouse Brain Common Coordinate Framework. In addition to defining developmental patterns of vGlut1+ and VGAT+ neurons, we identified a small, previously under-appreciated population of vGlut1/VGAT co-positive neurons, mostly observed in the hippocampus and deep cortical layers. Together, this project establishes a high-resolution cellular framework for studying excitatory and inhibitory neuronal organization across postnatal cortical development.

KEYWORDS: *Cell Type/Interactions; Developmental/Systems Biology; Molecular/Cellular Neuroscience; Genetics/Genomics*

Neuron-astrocyte associative memory

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Astrocytes, the most abundant type of glial cell, play a fundamental role in memory. Despite most hippocampal synapses being contacted by an astrocyte, there are no current theories that explain how neurons, synapses, and astrocytes might collectively contribute to memory function. We demonstrate that fundamental aspects of astrocyte morphology and physiology naturally lead to a dynamic, high-capacity associative memory system. The neuron-astrocyte networks generated by our framework are closely related to popular machine learning architectures known as Dense Associative Memories. Adjusting the connectivity pattern, the model developed here leads to a family of associative memory networks that includes a Dense Associative Memory and a Transformer as two limiting cases. In the known biological implementations of Dense Associative Memories, the ratio of stored memories to the number of neurons remains constant, despite the growth of the network size. Our work demonstrates that neuron-astrocyte networks follow a superior memory scaling law, outperforming known biological implementations of Dense Associative Memory. Our model suggests an exciting and previously unnoticed possibility that memories could be stored, at least in part, within the network of astrocyte processes rather than solely in the synaptic weights between neurons.

KEYWORDS: *Computational Biology/Modelling; Neural Networks (topology, etc.); Theory & Data Analysis Tools; Synaptic Plasticity*

Disruption of cystathionine gamma-lyase impairs hippocampal plasticity and cognitive function through altered neurotrophin signaling

PRESENTER: **S. Chakraborty**
Johns Hopkins University

AUTHORS: S. Chakraborty, S.J. Tripathi, S.H. Snyder, A.A. Pieper, B.D. Paul

The reverse transsulfuration pathway comprises enzymes that regulate the levels of glutathione, homocysteine, and the gasotransmitter hydrogen sulfide (H_2S), all of which are essential for brain homeostasis. In the central nervous system, these molecules contribute to the regulation of cerebral blood flow, maintenance of blood-brain barrier integrity, neuroplasticity, and redox balance. A key enzyme in this pathway is cystathionine γ -lyase (Cth), the primary neuronal source of the semi-essential amino acid cysteine and H_2S . H_2S modulates protein function through sulfhydration of reactive cysteine residues, a post-translational modification implicated in neurodegenerative disorders. However, the mechanisms linking Cth-derived H_2S signaling to neuronal health remain incompletely understood. To address this question, we performed a systematic characterization of Cth^{-/-} mice, examining cognition, neurogenesis, neurotrophic signaling, and neuropathological changes. Cth deficiency resulted in early-onset neurodegeneration and was accompanied by increased oxidative stress, reduced neurogenesis, and related pathological alterations in neurotrophic signaling and the blood-brain barrier. These molecular and cellular changes were associated with behavioral abnormalities and dysregulated stress responses. Collectively, our findings identify Cth as a critical regulator of brain function and cognitive performance through its role in maintaining neurogenesis and neuronal homeostasis. Disruption of Cth-dependent pathways promotes neurodegeneration and contributes to the development of behavioral and cognitive impairments.

KEYWORDS: *Behavioral Sciences/Psychology; Chemistry; Molecular/Cellular Neuroscience*

Advancing an aminopropyl carbazole compound toward therapy for Huntington's disease

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Huntington's disease (HD) is a progressive neurodegenerative disorder caused by CAG repeat expansion in the huntingtin gene, resulting in the accumulation of mutant huntingtin (mHtt) and selective vulnerability of striatal neurons. Clinically, HD is characterized by motor dysfunction, psychiatric symptoms, and cognitive decline. At the cellular level, mHtt aggregates elicit widespread deleterious changes, including general proteinopathy, oxidative damage, neuroinflammation, neuronal cell death, and impaired neurogenesis, collectively driving the aforementioned symptoms. Here, we examined the therapeutic effects of an aminopropyl carbazole compound (APC) with established neuroprotective properties in a cellular and R6/2 mouse model of HD. In cellular models, APC reduces mHtt aggregation and prevents neuronal cell death. In the R6/2 mouse model, treatment decreases neuroinflammation and oxidative stress, restores dopaminergic projections to the striatum, and increases expression of medium spiny neuron markers. These molecular and cellular improvements are associated with significant rescue of motor and cognitive deficits. Together, our findings suggest that APC mitigates key pathological and behavioral features of HD and represents a potential therapeutic candidate for Huntington's disease.

KEYWORDS: *Molecular/Cellular Neuroscience; Synaptic Plasticity*

Cross-species enhancer-AAV toolkit for cell- and circuit-specific dissection of cerebellar function

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The cerebellum participates in motor control, cognition, affect, and adaptive behavior via extensive bidirectional connections that position it as an integral node in distributed brain networks whose dynamics it actively modulates. Through the BRAIN Initiative, tools have been developed to examine and manipulate forebrain structures with cell-type resolution, but such tools are not available for the cerebellum, which remains one of the least genetically accessible major brain regions. This gap has grown more consequential as recent studies have identified previously unrecognized cellular and molecular diversity in the cerebellum, defining new cell types and redefining canonical ones into distinct subpopulations that evade genetic access. Without direct recording and manipulation of these diverse cerebellar cell types, we cannot assign their causal contributions within local circuits or their effects on brain-wide networks and complex behaviors. We have launched a project to develop a first-in-class, cross-species viral toolkit for targeting, recording, and manipulating all major cerebellar cell types and targeted subpopulations with circuit specificity using enhancer sequences. Enhancers regulate brain development and function and can be repurposed in adeno-associated virus (AAV)-based strategies for cell-type-specific genetic access. We generated single-nucleus multiome data from developing (P12) mouse cerebellum and performed chromatin accessibility-based prioritization to predict candidate cell-type-selective enhancers. We screened top candidates in vivo and identified enhancer-AAVs active in target cell populations including Purkinje cells (PCs), molecular layer interneurons, granule cells, and Bergmann glia. We further focused on PC enhancer-AAVs and developed tools with utility for fluorescence-activated nuclei sorting (FANS), circuit tracing, biosensor expression, and Cre recombinase expression in both juvenile and adult mice. Our results establish an enhancer-selection model that enables principled targeting of previously inaccessible cerebellar cell types, and an initial enhancer-AAV toolkit for labeling, recording, and manipulating PC populations. We aim to extend this work to all major cerebellar cell types in both rodents and non-human primates. Our work will fill a major gap in cerebellar methods, enabling cell-type- and circuit-specific deployment of sensors and actuators across species and discovery of how cerebellar cell types and circuits drive motor, cognitive, and affective behavior, propagate computations through brain-wide networks, and contribute to disease.

KEYWORDS: *Circuit Diagrams; Electrophysiology; Genetics/Genomics; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation*

Excitatory and inhibitory circuits orchestrate signal integration in the insular cortex

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Large-scale cell typing provides foundational insight into structure-function relationships for cortical processing. Most such studies to date have focused on primary sensory and motor cortices, and our understanding of the neuronal substrates underlying associative cortex function remains in its infancy. The insular cortex (IC), an associative cortical region, processes both external and internal stimuli to maintain homeostasis and drive diverse behaviors, such as taste perception, interoception, and decision-making. Anatomically, the IC is composed of agranular, dysgranular, and granular subregions, providing a unique opportunity to understand cortical structure-function relationships.

To identify neural substrates underlying diverse functions of the IC, we generated a comprehensive cell-type atlas of over 1,000 mouse IC pyramidal neurons across five different categories, including anatomical subregion, morphology, electrical properties, local input connectivity, and projection targets. Importantly, cross-species (mouse, macaque, and human) and cross-region (IC versus sensory and motor cortices) comparisons suggested that insular pyramidal neurons exhibit properties more similar to primate pyramidal neurons than to mouse primary cortical neurons. Leveraging this dataset to link structural features to function, we identified cell types that receive excitatory intra-insular inputs distinct from canonical cortical microcircuits, and demonstrated their role in linking sensory information to valence.

In concert with excitatory pyramidal neurons, IC inhibitory neurons also play pivotal roles in circuit integration. Combining electrophysiology with laser-scanning photostimulation and channelrhodopsin-assisted circuit mapping, we found that anatomically distinct IC subregions contain different proportions of inhibitory neuronal types and employ specialized mechanisms to achieve a comparable local E-I ratio. Furthermore, these E-I networks across IC subregions are differentially recruited by thalamocortical inputs, which may give rise to additional circuit processing capacity under distinct behavioral contexts.

Together, our work defines the cell types and E-I circuit motifs of the IC, providing mechanistic insights into how this evolutionarily distinct associative cortex orchestrates the integration of signals to support its diverse functions.

KEYWORDS: *Cell Type/Interactions; Electrophysiology; Circuit Diagrams*

A red fluorescence-lifetime PKA sensor for multiplexed imaging of neuromodulation

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A large number of neuromodulators act through hundreds of G-protein-coupled receptors and converge on a limited set of intracellular second messenger pathways. In particular, cyclic AMP (cAMP) and its major effector, protein kinase A (PKA), act as a central intracellular node that converts upstream neuromodulatory inputs into phosphorylation-dependent control of transcription factors, ion channels, and neurotransmitter receptors, thereby shaping neuronal excitability, synaptic transmission, and plasticity. Imaging PKA activity with genetically encoded sensors provides a critical readout of how neuromodulation is integrated and decoded within defined cell types and subcellular compartments.

Fluorescence lifetime imaging microscopy (FLIM) is well suited to quantify PKA activity, which changes on a relatively slow timescale (seconds to days), because fluorescence lifetime is insensitive to imaging depth, sensor expression level, light scattering, and motion, and can report both basal activity and longitudinal dynamics. At present, existing FLIM PKA reporters are beginning to permit in vivo detection, but their dynamic ranges (~0.45 ns) remain to be improved for more sensitive detection. In addition, most state-of-the-art FLIM PKA sensors are green, overlapping with the majority of sensors for calcium and neuromodulators and thus limiting applications that require multiplexed imaging.

Towards this end, we are developing a red PKA sensor based on circularly permuted mScarlet for sensitive FLIM and dual-color imaging. A current variant, R-PKA0.8, exhibits a lifetime decrease of up to 1.2 ns upon PKA activation. Through structure-guided directed evolution of the linker and chromophore-proximal residues, we are further optimizing this sensor for its dynamic range, brightness, and other properties to enable multiplexed, dual-color imaging of PKA together with cAMP or calcium to dissect neuromodulatory signaling in vivo.

KEYWORDS: *Molecular/Cellular Neuroscience; Monitor Neural Activity; Physics or Microscopy/Optics; Interventional Tools*

High-field multinuclear MRI of human cortical organoids as a vascular-free framework for NARS-fMRI mechanistic validation

PRESENTER: **G. Yu**

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Neuronal activity-related sodium functional MRI, or NARS-fMRI, aims to detect activity-linked ionic dynamics beyond conventional hemodynamic readouts. However, mechanistic validation in vivo remains challenging because activity-linked sodium signals are difficult to separate from vascular and systemic physiological effects. Human cortical organoids offer a vascular-free model for testing sodium MRI mechanisms under controlled conditions. Here, we established high-field multinuclear MRI of human cortical organoids using a dual-tuned proton/sodium-23 RF coil at 14 T. This platform enabled co-registered proton structural MRI, diffusion MRI, and sodium-23 MRI within the same fixed organoid preparation. Proton MRI resolved heterogeneous tissue organization, while multi-echo sodium-23 MRI enabled biexponential relaxation mapping of sodium microenvironments, revealing reproducible short and long $T2^*$ components consistent with heterogeneous ionic environments in organoid tissue. These results demonstrate that cortical organoids can support quantitative sodium relaxometry and provide a controlled platform for studying ionic microenvironment properties without vascular or hemodynamic confounds. Building on this initial platform, we are now developing a living organoid MRI preparation that can integrate media perfusion, thermal regulation, optical stimulation or recording, and multinuclear MRI. This ongoing work is designed to test whether activity-dependent sodium relaxation changes can be measured in living neural tissue and benchmarked against optical or electrophysiological readouts. Together, this work establishes organoid sodium MRI as a vascular-free experimental framework for studying sodium microenvironment properties in neural tissue. Ongoing development of living organoid imaging will provide a controlled testbed for evaluating proposed NARS-fMRI mechanisms beyond hemodynamic confounds.

KEYWORDS: *Cell Engineering; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Integrated Approaches*

NEMAR and hierarchical event descriptors: Advancing FAIR, searchable, and reproducible human EEG research

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The NeuroElectroMagnetic Archive and Repository (NEMAR) provides an open platform for sharing, exploring, and analyzing large-scale human neuroelectromagnetic data while promoting the FAIR principles of findability, accessibility, interoperability, and reusability. NEMAR builds on the BIDS standard for EEG, MEG, and intracranial electrophysiology and integrates cloud accessible tools for visualization, search, and high performance analysis. A central feature of the platform is support for Hierarchical Event Descriptors (HED), a machine actionable event annotation framework that captures both experimental events and their behavioral context in a standardized and reusable form.

By combining standardized data organization with rich event annotation, NEMAR enables researchers to search across studies based on experimental paradigms, behavioral events, cognitive processes, and recording characteristics rather than relying solely on dataset level metadata. HED annotations facilitate automated analyses, large scale meta analyses, and reproducible workflows across laboratories. Together, BIDS and HED provide a foundation for integrating heterogeneous electrophysiological datasets into unified computational pipelines.

We will present recent developments in the NEMAR platform, including expanded support for HED based search and visualization, improved interoperability with open neuroscience software, and scalable analysis using high performance computing resources. We will also introduce EEGDash, an open deep learning library tightly integrated with NEMAR that provides streamlined access to curated EEG datasets for training, benchmarking, and evaluating machine learning models. EEGDash leverages standardized BIDS organization and HED annotations to simplify dataset selection, harmonize event labels across studies, and enable reproducible deep learning workflows. Together, NEMAR, HED, and EEGDash provide an integrated infrastructure for data sharing, semantic annotation, cloud computing, and reproducible AI, increasing the long-term value and reuse of BRAIN Initiative neurophysiology datasets.

KEYWORDS: *Dissemination & Open Science/Education; Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches*

3D gaze tracking in freely moving marmosets

PRESENTER: **L. Claudino**

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Accurate gaze measurement is essential for visual field mapping in marmosets, but standard approaches typically require head fixation or body restraint, which can disrupt natural visual behavior. Wearable eye-tracking backpacks permit head-free recordings, but they are bulky, require months of habituation, and prior work suggests that gaze cones can be substantially larger than in restrained settings. We are developing a naturalistic, markerless eye-tracking system that combines a purpose-built operant conditioning chamber optimized for gaze tracking with real-time 3D facial landmark estimation adapted from human face-mesh models. Motivated by recent evidence that human-trained 2D object-detection models can track marmoset facial patches, we test whether human-based 3D face tracking can recover time series of head pose, eye position, and iris location from videos of freely moving animals. During calibration, marmosets are trained to attend to visual targets on a screen and report detection by moving a lever. We then combine estimated 3D facial features with the 2D coordinates of visual targets to fit a model that predicts the attended screen location. Here, we present preliminary tracking performance and key technical challenges for achieving robust, real-time gaze estimation in unconstrained marmosets. This approach could enable visual neuroscience experiments under conditions that better preserve natural eye-head coordination.

KEYWORDS: *Software (analysis, etc.) and Engineering*

Operational cognitive workload assessment for improving human-AI team performance

PRESENTER: **A. Abrar**

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Cognitive workload, defined as the mental effort required to perform a task, is a critical determinant of human performance in safety-critical applications such as aviation and healthcare. Both cognitive overload and underload can severely degrade attention, reduce efficiency, and increase error rates, which can severely deteriorate task performance. Traditional subjective assessments, like the NASA Task Load Index (NASA-TLX), provide valuable retrospective estimates but fail to capture dynamic, moment-to-moment fluctuations in a user's cognitive state. To address this limitation, this study investigates the continuous measurement of cognitive workload utilizing multi-modal physiological signals—specifically electroencephalography (EEG) and heart rate—complemented by self-reported NASA-TLX data. We recorded multimodal data from 25 participants who completed four tasks, namely the Letter N-back, Flanker N-back, Multiple Object Tracking, and simulated aerial drone navigation through a sequence of obstacles in both day and night conditions. These tasks are explicitly designed to collectively modulate varying levels of working memory, attention, inhibitory control, and perceptual demand.

A fundamental challenge in physiological workload assessment is the lack of consistency in biosignatures across tasks, and predictive models trained on a single task frequently learn task-specific neural signatures rather than generalized markers of mental effort. Consequently, the primary objective of this research is to evaluate whether EEG-based models can identify task-agnostic neural patterns capable of robustly classifying workload into low, medium, and high states. We systematically evaluate classification performance across single-task, multi-task, and cross-task paradigms. Furthermore, to mitigate the challenge of high inter-subject variability, group-level models are adapted to individual users utilizing one- and few-shot learning techniques that require minimal participant-specific calibration data.

Our computational pipeline evaluates several advanced architectures, including Convolutional Neural Networks (CNNs), EEGMamba-inspired architectures for long-sequence physiological modeling, and Convolutional Spiking Neural Networks (CSNNs). To translate these models into practical operational environments, the CSNNs are optimized for neuromorphic deployment on the BrainChip Akida platform, enabling ultra-low-energy, real-time workload assessment at the edge.

KEYWORDS: *Electrophysiology; Informatics, Statistics, or Applied Mathematics; Monitor Neural Activity*

A compact and interpretable feature set for classification of abnormal EEG

PRESENTER: **R. Sondawle**
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Clinical electroencephalography (EEG) is one of the most accessible tools for measuring brain activity, yet interpretation still depends heavily on expert visual review. This limits scalability, reproducibility, and translation of complex recordings into objective markers of neural dysfunction. Although machine learning models can achieve strong EEG classification performance, many rely on opaque features that are difficult to interpret physiologically. We ask whether abnormal EEG can instead be detected using a compact feature set that preserves predictive value and biological meaning. We analyzed 138 resting-state clinical EEG recordings labeled normal or abnormal by clinician inspection (96 normal, 42 abnormal), collected at Johns Hopkins Hospital. Signals were preprocessed using bandpass filtering, ICA-based artifact correction, and average referencing. Candidate features were extracted across spectral parametrization, connectivity, and linear dynamic network modeling, then screened for statistical separation, redundancy, coefficient stability, and biological interpretability. The final model identified a three-feature abnormality signature. Abnormal EEG showed elevated broadband background offset compared with normal EEG (median 1.45 vs. 0.95; $p = 3.81 \times 10^{-7}$), suggesting elevated aperiodic background activity. Abnormal EEG also showed increased delta-band synchrony across channels (median 0.454 vs. 0.432; $p = 0.0104$), reflecting greater shared slow-frequency activity. Alpha peak frequency trended lower in abnormal recordings (median 9.56 Hz vs. 9.86 Hz; $p = 0.0920$), consistent with mild rhythm slowing. These features were evaluated using logistic regression with a stratified train-test split. Across 10-fold stability analysis, the final features recurred in all folds, with mean training AUC of ~ 0.81 . In the final model, these features achieved ROC-AUC of 0.80 in training and 0.84 in the held-out test set. At a derived Youden threshold, held-out performance reached 81.0% accuracy, 69.2% sensitivity, and 86.2% specificity. These findings suggest that abnormal EEG can be effectively captured by a compact, biologically meaningful pattern: elevated background activity, increased delta synchrony, and alpha slowing. Rather than compromising physiological interpretation, this framework identifies transparent markers that can be verified and refined. With further validation, it could support objective EEG decision tools while preserving clinical trust.

KEYWORDS: *Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Electrophysiology*

AI-enabled neurosurveillance reveals seizure-induced reorganization of neurobehavioral representations

PRESENTER: **S. Das**

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A central goal of systems neuroscience is to understand how neuronal dynamics give rise to complex behavior and how this relationship is reshaped by neuroelectric disorders such as seizures and epilepsy. Continuous long-term neuroimaging in freely behaving animals provides a new opportunity to study this problem by capturing disease-related changes in the neuronal activity that encode behavior. Here, using our cloud-connected miniscope, we acquired fluorescence imaging of GCaMP-reported neuronal activity in four awake, freely behaving mice (M1-M4), before, during and after seizure induction, while simultaneously recording natural behavior. This enabled us to relate behavior to neuronal activity across healthy and seizure-burdened brain states and examine how seizure-associated dynamics disrupt this neurophysiology-to-behavior relationship. We asked whether state-of-the-art computer vision models trained to decode behavior from healthy neuronal activity remain valid when the underlying physiological premise is reorganized by seizures. We annotated three behavioral syllables from synchronized behavioral movies: running, eating and sleeping. Each one-minute neuronal activity clip was assigned its corresponding behavioral label. We trained a Video Vision Transformer (ViViT) on continuous 24-hour neuronal activity data from three healthy mice and evaluated performance on a fourth animal under both healthy and seizure-state conditions. Performance on the unseen animal was quantified using macro-F1 score. To test whether seizures created distinct neurobehavioral representations, we retrained ViViT with six state-specific classes: healthy and post-seizure running, eating and sleeping. Maximum mean discrepancy (MMD) was used to measure separation between healthy and seizure neuronal activity distributions in the learned feature space. Healthy-trained ViViT performance declined when evaluated on seizure neuronal activity, with macro-F1 decreasing by 26.2%, from 0.667 ± 0.019 to 0.493 ± 0.032 . MMD showed an animal-dependent healthy-to-seizure distribution shift of 0.0126 ± 0.0180 . Behavior-specific MMD was highest for Run (0.0426 ± 0.0194), followed by MiniMOB (0.0224 ± 0.0314) and EoNB (0.0109 ± 0.0103). These findings show that seizures reorganize neurobehavioral feature space, exposing a domain shift that weakens healthy-trained decoders and highlights the need for disease-specific or domain-adaptive AI models for altered physiological brain states in disease.

KEYWORDS: *Behavioral Sciences/Psychology; Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Theory & Data Analysis Tools; Monitor Neural Activity*

A latent state space null model for spontaneous cortical spiking

PRESENTER: **K. Van Antwerp**

Manta Array

AUTHORS: K. Van Antwerp

Linear latent state-space dynamics with nonnegative observation models offer a compact way to describe and replicate neural activity patterns across scales, from muscle synergies and neural manifolds for coordinated behavior to scale-free signatures associated with neural criticality.

I present LMOU-NNO as a family of probabilistic latent state space null models for spontaneous cortical spiking with multiple latent timescales. The model uses a latent multivariate Ornstein-Uhlenbeck process to drive nonnegative noisy neural variables, which generate spikes through threshold crossing and independent refractory reset. This builds minimal neural constraints into the spike-generation step, rather than relying only on coarse grained time binning that can introduce artificial shared correlations across units. Applied to Neuropixels spontaneous activity from Allen Brain Observatory, LMOU-NNO replicates brain-area-specific autocorrelation function distributions, firing rate statistics and eigenspectra of the sample covariance matrix with three to five latent variables when the full LMOU parameters are allowed to vary, mixing timescales and latent state interactions. I report the interpretable timescale characterization across the mouse cortex. Decoding the fitted latent state also reveals structure correlated with the running state of the spontaneously behaving mouse.

This project also addresses a practical problem I encountered in the NIH BRAIN Initiative Secondary Analysis project: preprocessing choices, model configurations, validation results, and scientific claims often become fragmented across files, scripts, and notebooks. I use Palantir Foundry to organize the workflow around an ontology that links recordings, preprocessing decisions, model runs, fitted parameters, validation outputs, and interpretations with explicit provenance. This makes large public neuroscience datasets easier to reuse, compare, and interpret, supporting more efficient secondary analysis of data produced through efforts such as the NIH BRAIN Initiative.

KEYWORDS: *Cell Type/Interactions; Computational Biology/Modelling; Electrophysiology; Informatics, Statistics, or Applied Mathematics; Theory & Data Analysis Tools; Neural Networks (topology, etc.)*

Modernizing the NWB data modeling framework

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Neurodata Without Borders (NWB) is the leading data standard for neurophysiology, with over 500 public datasets from more than 150 labs worldwide hosted on the DANDI Archive. NWB is built on the Hierarchical Data Modeling Framework (HDMF), a general-purpose, open-source framework for designing and implementing scientific data standards with modular support for schema languages, storage backends, and programmatic data access APIs.

As NWB adoption grows, so does the cost of maintaining custom systems for schema handling, validation, and documentation that were developed nearly a decade ago. To ensure long-term sustainability and interoperability, we are modernizing HDMF by integrating LinkML, a widely adopted data modeling language used across biomedical research. LinkML enables human-readable, machine-processable schema definitions with built-in support for ontologies, controlled vocabularies, and complex validation rules. It also facilitates translation between data representations, including JSON, RDF, OWL, and SQL, broadening compatibility across data ecosystems.

We have begun to refactor HDMF to support LinkML as its primary schema language and are providing tools to convert existing NWB schema and community extensions to LinkML. These changes will enhance interoperability between NWB and other data standards (e.g., BIDS) and organizational schemas, including those used by DANDI, BICAN, and EBRAINS, enabling data crosswalks and harmonization across resources. In parallel, we are modernizing the HDMF Python API by replacing a custom type validation system with Pydantic, improving IDE integration, code clarity, and data validation, and reducing the technical barriers to community contribution.

Together, these modernization efforts will strengthen the long-term sustainability of NWB and HDMF, improve interoperability with the broader neuroscience data ecosystem, and strengthen HDMF as a foundation for scientific data standardization for the neurophysiology community and beyond.

KEYWORDS: *Dissemination & Open Science/Education; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Informatics, Statistics, or Applied Mathematics*

Parameterization of intracranial auditory evoked responses reveals cortical novelty and attention effects

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Event-related potentials (ERPs) provide a powerful framework for studying the timing and organization of neural activity across sensory and cognitive systems. Among ERP paradigms, auditory evoked potentials (AEPs) are among the most well-characterized and clinically used, yet common analyses focus on averaged waveforms and visually determined predefined peaks. These approaches overlook the broader temporal structure and trial-to-trial variability of cortical responses. Here, we modify Canonical Response Parameterization (CRP)—a data-driven method originally developed for single-pulse electrical stimulation—and apply it to intracranial stereo-electroencephalography (sEEG) recordings collected during a modified auditory oddball task. CRP resolves a set of intuitive parameters for each response, capturing its characteristic shape, magnitude, onset, duration, and enables direct comparison of AEPs across single trials, regions, and task conditions. By focusing on algorithmically discovered significant portions of the response rather than hand-picked latency windows, this approach provides a common unbiased and quantitative representation of neural activity across participants and modalities. We found robust responses across the temporal lobe, with stronger responses to novel tones and modulation by attentional state during a concurrent visual task. These findings demonstrate that CRP offers a generalizable, data-driven framework for quantifying naturally evoked brain dynamics, enabling common statistical interpretation of different response shapes, and unifying response characterization across sensory and cognitive domains.

KEYWORDS: *Computational Biology/Modelling; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Theory & Data Analysis Tools*

Nonlinear information-theoretic analysis of collective neural population dynamics at scale

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Understanding how collective neural activity is organized across cortical areas, behavioral states, and cell types is a central goal in systems neuroscience. Yet the dominant tools for quantifying statistical dependencies in large-scale recordings remain linear: PCA and pairwise correlations miss the nonlinear structure that likely underlies collective dynamics. Methods that operate at population scale without linearity constraints are needed.

Mutual information (MI) provides a principled path forward: model-free, in bits, directly comparable across areas, conditions, and cell types. Classical estimators fail beyond ~10 neurons, but recent work by us and others showed neural network-based MI estimators can be made reliable and scalable for large-dimensional systems, including neural populations. Beyond estimation, the same $MI(X;Y)$ calculation can be repurposed for a broad class of analyses, including intrinsic and shared dimensionality estimation, inter-area information flow, spike-timing precision analysis, and transfer entropy. NeuralMI, our open-source Python library, implements these advances and opens a space of analyses previously inaccessible at population scale.

We demonstrate such four analyses: 1) Using MI-based dimensionality estimation, we show that in large-scale V1 recordings ($N \sim 10k$ neurons) information saturates below 10 dimensions despite a power-law PCA eigenspectrum implying thousands, suggesting apparent high-dimensionality is a linear artifact. 2) Applying the same estimator to pairwise dependencies, preliminary analysis of prefrontal cortex recordings from resting mice suggests fast-spiking neurons exhibit significantly higher mutual information than regular-spiking neurons, a distinction pairwise correlations fail to capture. 3) Preliminary inter-area MI between visual cortex and hippocampus suggests condition-dependent coupling across static and dynamic stimulation. 4) Conditional MI analysis of hippocampal spontaneous activity further suggests navigational direction contributes approximately 1 additional bit beyond spatial position alone.

Standard linear methods are often inapplicable or systematically underestimate the nonlinear structure of collective neural activity. Nonlinear MI estimation at scale opens a principled route towards the questions this work is built around: how information is organized in neural populations, how it flows across cortical areas, and how it reflects the functional roles of specific cell types.

KEYWORDS: *Cell Type/Interactions; Dissemination & Open Science/Education; Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Neural Networks (topology, etc.)*

Optimus STARsolo in WARP: High-performance cloud pipelines for integrated single-cell and multimodal neuroscience

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Bioinformatic pipelines for analysis need to scale and utilize cloud computing resources efficiently. Warp Analysis Research Pipelines (WARP) provides scalable pipelines, which can combine data modalities to form multi-omic pipelines. WARP Optimus STARsolo is a single-cell RNASeq alignment pipeline. It combines the best in class performance of the STAR aligner, the simultaneous computation of the solo metrics, with additional optimizations added in the Optimus STARsolo pipeline to provide high scalability and low cost.

We have validated Optimus STARSolo, compared to the 10X Cell Ranger pipeline, and show best-in-class performance which can be scaled on the cloud. Optimus STARsolo provides the standardized solution needed by the BICAN consortium and NeMo project. The consortium required unified processing of single-cell RNA-seq as the central modality for unifying ~20 individual efforts. Optimus STARsolo is that unified pipeline that can scale to input sizes of greater than 100 GB. Optimus STARsolo has been used for standardized processing of over 60 million single-cells by the BRAIN Initiative® Cell Atlas Network (BICAN), including several multi-omic assays like ATAC-seq. This includes references constructed for multiple species and optimizations gained from standardization.

Multi-omic studies leverage multiple data modalities, such as single-cell gene expression and single-cell Assay for Transposase-Accessible Chromatin (ATAC) to provide a comprehensive picture of cell state. Optimus STARsolo has been combined with other modalities to produce best in class multi-omic workflows. Its modular design allows for the creation of entirely novel multimodal analyses as required. Multiomics empowers new analytic methods, including label (Cell type) alignment and transfer between modalities.

Optimus STARsolo is published in WARP, along with validated scientific tests, methods, and documentation. The WARP repository provides an authoritative source of the Optimus STARsolo pipeline, the pipelines for additional modalities, and the multi-omic pipelines. This includes plumbing and scientific tests of all published pipelines and extension documentation and methods.

KEYWORDS: *Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Machine learning for female-focused autoimmunity

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Autoimmune disorders show a pronounced biological sex skew with females comprising nearly 80% of the total cases. Systemic lupus erythematosus alone shows female-to-male ratios of up to 13:1. Such diseases arise from immune disruption and neuroinflammation at the molecular and cellular levels, prompted by microglial dysregulation, blood-brain barrier disruption under hormonal change, and HPA-axis sensitization through chronic stress and trauma with every additional early-life stressor raising the disease risk by 9-11%. Neuroimmune mechanisms are also responsible for the disruption of serotonin and dopamine pathways, creating a self-reinforcing cycle wherein disease burden and mental health comorbidities are biologically entangled rather than mere co-occurrence. This paper synthesizes literature from PubMed and Google Scholar across autoimmune diseases, neuroimmune mechanisms, machine learning models, sex-stratified immunology; revealing that current computational methods leave female-specific biology unaddressed. Most contemporary models are sex-agnostic that fail to integrate the systemic and brain-infiltrating immune cell data, and do not capture neuroimmune mechanisms that hold relevance to mental health outcomes. A Pearson correlation (where $r = 0.04$) between study quality and sex-bias across multiple rheumatoid arthritis ML studies confirms this is a structural failure, not an oversight. Bridging this gap requires moving from sex-agnostic to sex-aware models focusing on the incorporation of longitudinal transcriptomics, pathway-level molecular models and explainable AI—with ensemble approaches like Random Forest already demonstrating strong baseline performance (AUC 0.84 in SLE genetic risk prediction). Neuroimmune and female-focused methods stand to substantially advance prediction, mechanistic understanding and personalised treatment of autoimmune disorders and their mental health comorbidities.

KEYWORDS: *Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Molecular/Cellular Neuroscience; Behavioral Sciences/Psychology*

A comprehensive study of classical machine learning and deep learning approaches for EEG artifact elimination

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Translating brain-computer interfaces (BCIs) from the lab to clinical settings faces major challenges due to EEG signal contamination. Both physiological and environmental factors often distort the data, making real-time noise removal essential. However, researchers do not fully agree on the best method to address this issue. This study provides a detailed comparison of optimized classical machine learning and deep learning techniques for detecting EEG artifacts. A common problem in artifact research is the lack of annotated data, which often leads to studies depending on unrealistically high-amplitude noise. To create a more realistic benchmark, a low-signal-to-noise ratio (SNR) synthetic data pipeline was developed. Using the BCI Competition IV Dataset 2b, four subtle artifact patterns were introduced: eye blinks, EMG noise, electrode drift, and power-line interference. A strict temporal data split was also applied to prevent any data leakage. For the classical ML models, a 30-dimensional feature space was created that included time-domain statistics, multi-band spectral densities, Hjorth descriptors, and wavelet transform energies. These features were then used with Bayesian-optimized SVM, Random Forest, KNN, and AdaBoost classifiers. At the same time, 1D-CNN, LSTM, and BiLSTM deep learning models were trained directly on the raw EEG sequences. The analysis revealed that ensemble methods like Random Forest and AdaBoost achieved high accuracy of around 98%, significantly surpassing typical models like KNN and SVM. Notably, these ensemble classical models matched the classification accuracy of the deep learning networks, which also reached about 98%, but required much less computational power and training time. These results show that well-designed classical ML algorithms can provide a clear and efficient alternative to complex deep learning methods, making them suitable for practical, real-time BCI applications where resources may be limited.

KEYWORDS: *Cell Engineering; Human Neuroscience, Clinical Science, or Public Health; Theory & Data Analysis Tools; Informatics, Statistics, or Applied Mathematics*

Motor commands embedded in neural activity of cerebella and motor cortex populations during reach assessed through physiological muscle simulations

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Dexterous motor control requires well-timed, coordinated, and accurate movements. To achieve successful movements, a multitude of motor centers within the brain and spine coordinate activity to plan and execute descending commands. While there is a longstanding effort to understand movement through the lens of neural recordings during behavior, it is often difficult or impossible to capture the full suite of ongoing muscle activity. Therefore, discrimination between planning, predicting, or commanding motor activity in high-level motor control regions of the brain is impeded by our lack of knowledge concerning muscle patterning. We developed a musculoskeletal model of the murine forearm to aid based on optical dissection of muscular anatomy and validated the activity of muscle patterning using reach kinematics with paired electromyographic (EMG) recordings. Here, we leverage the simulation of limb musculature to examine population neural recordings from motor cortex (MCX) and cerebellar cortex (CBX) during reaching movements to determine what degree of motor command-like activity arises in the neural populations of these structures during movement. We replicated recorded kinematics in our forelimb model and then used the resulting predictions of muscle patterns to align neural activity, both in a trial-by-trial manner and in the mean activity of cell activity. We are currently analyzing the neural activity with representational and neural network models. We created open-source tools to produce physics-based simulations and neural network models.

KEYWORDS: *Theory & Data Analysis Tools*

DANDI Archive: Open infrastructure for sharing and reusing neuroscience data at scale

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The Distributed Archives for Neurophysiology Data Integration (DANDI) is an NIH BRAIN Initiative data archive that enables scientists to share, visualize, and reuse neuroscience data. DANDI provides a cloud-based, openly accessible platform where datasets can be deposited, versioned, and assigned persistent identifiers, lowering barriers to collaboration, reproducibility, and reuse across the neuroscience community.

To date, contributors from across the globe have uploaded more than 1.7 PB of data spanning a broad range of modalities, including electrophysiology, optophysiology, microscopy, and magnetic resonance imaging. This includes contributions from major BRAIN Initiative programs such as the BRAIN CONNECTS center for Large-scale Imaging of Neural Circuits (LINC), the BRAIN Initiative Cell Atlas Network (BICAN), and the Allen Institute's OpenScope program. Data are standardized through established community specifications such as Neurodata Without Borders (NWB), Brain Imaging Data Structure (BIDS), and Open Microscopy Environment (OME), enabling interoperability and machine readability. The archive has become a global resource, with users downloading more than 12 PB of data across 182 countries.

Beyond the primary archive, the open-source DANDI codebase has been adapted to deploy independent instances serving specific use cases, including LINC BRAIN (<https://lincbrain.org>; MPIs: Yendiki, Haber, Hillman; NIH BRAIN CONNECTS UM1 NS132358) and EMBER-DANDI (<https://dandi.emberarchive.org>; PI: Wester; NIH BBQS R24 DA064430). These deployments demonstrate the extensibility of DANDI's infrastructure as a reusable foundation for emerging data-sharing needs across the BRAIN Initiative and the broader neuroscience ecosystem.

KEYWORDS: *Software (analysis, etc.) and Engineering; Dissemination & Open Science/Education*

Explainable graph attention network for depression screening

PRESENTER: **S. Ghosh**

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Depression is a major cause of global mental illness and significantly influences suicide rates. Effective intervention requires a timely and correct diagnosis. Electroencephalography (EEG) provides a non-invasive and accessible method for examining cerebral activity and identifying disease-associated patterns. We propose a novel graph-based deep learning framework, named Edge-gated, axis-mixed Pooling Attention Network (ExPANet), for differentiating major depressive disorder (MDD) patients from healthy controls (HC). EEG recordings are preprocessed to remove artifacts and segmented into short activity periods. We extract 14 features from each segment, which include time, frequency, fractal, and complexity domains. Electrodes are represented as nodes, whereas edges are determined by the phase-locking value (PLV) to represent functional connectivity. The brain graphs are examined using an adapted graph attention network. This architecture balances classification accuracy and model interpretability by modeling feature-level dynamics with large-scale functional connections. The proposed framework outperforms current EEG-based techniques on two distinct datasets under subject-independent evaluation protocols, and cross-dataset experiments show the model's ability to generalize across cohorts. Explainability is a major advantage of our method. We analyzed features, edges, channels, and intrinsic attention weights to gain multilevel insights. We also quantify explainability using fidelity, sparsity, and stability criteria. These studies highlight features, cerebral areas, and connectivity associations that are especially relevant to MDD, many of which correspond with previous literature. Our findings demonstrate a reliable and transparent framework for EEG-based screening of MDD that also improves interpretability.

KEYWORDS: *Connectome; Informatics, Statistics, or Applied Mathematics; Neuroimaging (invasive, non-invasive imaging)/Radiology; Theory & Data Analysis Tools*

After the Cures cliff: A non-federal and allied architecture to fund brain-data collection and hold its access governance

PRESENTER: **T. Deaton**
Brainmaker

AUTHORS: T. Deaton, M. Potter

The NIH BRAIN Initiative reaches about \$429M in FY2026, but that figure misleads: Roughly \$195M is the final tranche of the 21st Century Cures "Innovation Account," which expires after FY2026, dropping the program to a base of about \$234M. The most exposed asset is not curation. The archives, standardized pipelines, and ML-ready datasets, owned and open by charter (Allen, DANDI and NWB, EBRAINS), keep standardizing whatever data exists. The two gaps no one owns are collection, the expensive and slow primate recording no single grant covers, which dominates a brain foundation model's cost and timeline far more than curation, and governance, keeping a dual-use capability in allied-democratic hands when whoever holds the canonical training data decides who competes. We ask whether collection and governance can be carried without reauthorization, and conclude they can.

From public sources (June 2026) we map non-federal and allied funding mechanisms and model restoration as a five-stream portfolio: US cross-agency funding outside the Cures account (ARPA-H, NSF, DARPA, IARPA, DOE), science philanthropy, Focused Research Organization build capital, allied co-funding (Canada, the UK, the EU, Japan, Australia), and pre-competitive industry consortia. We characterize each stream's leverage: Brain Canada's dollar-for-dollar federal match, NIH-Brain Canada and NIH-NHMRC letters of agreement under which each country funds its own researchers, the Structural Genomics Consortium's open pre-competitive model, and Horizon Europe third-country participation.

The finding reframes the problem. Verified adjacent allied science-funding pools total roughly \$4.3B per year, so the expiring \$195M is about 5% of flows already in motion. A conservative five-stream portfolio replaces it nearly twofold, restoring capacity to roughly \$604M, within reach of the prior \$680M peak. Restoration is only the floor: because these pools sit an order of magnitude above the gap, the architecture can fund primate collection past the peak with allied-access terms, keeping a dual-use capability in democratic hands. Our partnership architecture spans the US, North America, and allied nations, coordinated through existing bodies; we argue that funding collection and holding its governance after the cliff is a problem of allocation and coordination, not scarcity, that private allied capital fills.

KEYWORDS: *Dissemination & Open Science/Education; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Neural Recording & Modulation; Neuroethics, Philosophy, Law*

The economic case for post-trial coverage for implantable neural devices: A meta-analysis

PRESENTER: **A. I. Beck**

Massachusetts General Hospital

AUTHORS: A.I. Beck, A.R. Merner, E. Versalovic, G. Lázaro-Muñoz

Treatment-resistant patient-participants enrolled in clinical trials of implantable neural devices for non-FDA-approved indications (e.g., depression) often face uncertainty regarding coverage of device-related expenses after the trial concludes. To inform decisions about financial responsibility for post-trial care, we conducted a meta-analysis evaluating long-term cost-effectiveness compared to best alternative medical treatment (BMT).

We extracted values for medical costs (e.g., device hardware, surgery, complications) and societal costs (e.g., lost productivity, travel, social systems) from prior cost-effectiveness studies (n=8, six clinical indications) and estimated 15-year annual costs with 3% annual discounting from Year 2 onward, applying hardware/surgery costs only to Year 1. Because the bulk of costs associated with implantable devices occur in Year 1, we modeled costs for either years 1-15 (all-cost) or years 2-15 (post-trial). All devices were assumed to be rechargeable with an implantable pulse generator (IPG) replacement in Year 10. For studies with health utility values (n=7), using only medical costs, we calculated quality-adjusted life years and incremental cost-effectiveness ratios (ICERs) using a 3% discount rate. All values were adjusted to 2026 USD.

For medical costs, in the all-cost case, implantable devices became cheaper than BMT around Year 6; in the post-trial case, implantable devices were consistently cheaper than BMT. This difference is similarly reflected in ICER values; in the all-cost case, most indications steadily trended toward the break-even threshold (primarily converging around Year 13), with some crossing into negative territory, indicating cost-saving/dominance. Conversely, in the post-trial case, omission of Year 1 implantation costs resulted in most indications maintaining primarily negative ICERs across all 15 years. Finally, when comparing societal costs to medical costs alone, the cost-savings gap widened progressively, reaching ~\$200,000 by Year 15.

These findings suggest that, compared to BMT, insurance coverage of post-trial device-related medical expenses would be economically advantageous while simultaneously improving the health of the patient-participants and reducing societal costs. Findings of this study will thus inform pathways for providing post-trial care to patients who participate in future experimental implantable device clinical trials.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neuroethics, Philosophy, Law*

BundleMind: Natural language exploration of white matter pathways

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Tractography via diffusion MRI reconstructs white-matter (WM) pathways in vivo, non-invasively. However, isolating specific pathways remains a bottleneck for neuroscience. Current workflows require atlas-based fixed definitions, manual region-of-interest selection, deep-learning methods trained on predefined bundles, or expert knowledge. We present BundleMind, a large language model based system that lets investigators select tracts by describing them in natural language. It turns free-form queries into streamline selections from whole-brain tractograms. Queries such as “the left arcuate,” “fibers connecting Broca’s area to the temporal lobe,” or “short U-fibers that do not cross the midline” return matching streamlines, ready to visualize and quantify.

BundleMind uses two complementary query paths, selected by a router. For specific requests, a compact on-device language model converts the query into a precise tractogram filter, which a deterministic geometric engine applies to the tractogram. For loose descriptions or informal bundle names, a second path matches text directly to streamlines. Both paths are grounded in a layered atlas of known bundles and brain regions that integrates bundle shape, functional associations, clinical disconnection data, and anatomical naming systems. This lets one interface answer questions about location, function, clinical associations, exclusions, pathway length, and regional connectivity.

We evaluated BundleMind on more than 200 queries spanning seven categories: simple naming, functional, spatial, compositional, negation, categorical, and clinical. For reference-selection queries, precision and recall were computed at the streamline level as overlap between the system’s selected streamlines and executor-generated reference selections for predefined question-streamline pairs, yielding precision 0.82, recall 0.90, and F1 0.85. The full pipeline runs locally in seconds on consumer hardware, keeping sensitive imaging data on device.

By collapsing tract selection from a scripting task into a conversation, BundleMind lowers the barrier to hypothesis-driven exploration of WM pathways, enabling rapid, reproducible interrogation of streamlines across individuals and cohorts. We will release the framework to the community to accelerate WM pathway research.

KEYWORDS: *Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Connectome*

A novel liver de-targeted blood-brain barrier penetrant AAV capsid robustly transduces the CNS while minimizing transduction of peripheral tissues

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Recent advances have improved the ability of adeno-associated viral vectors (AAVs) to cross the blood brain barrier (BBB) at lower doses than naturally occurring serotypes such as AAV9, allowing intravenous delivery of AAV gene therapies. By targeting known BBB shuttles, such as transferrin receptor 1 (TfR1), we identified peptide insertions in the VR-VIII loop of AAV9 that enable TfR1 binding and allow for greater BBB penetrance. However, transduction of peripheral tissues such as the liver remains quite high, potentially yielding off-target challenges. Here, we present a novel capsid that efficiently crosses the BBB while also de-targeting peripheral organs to achieve maximum expression in the CNS with negligible off-target transduction.

Using REGENXBIO's proprietary directed evolution platform, NAVIGATE, we identified a novel VR-VIII peptide insertion that binds human transferrin receptor (hTfR1) that can be combined with additional capsid mutations to de-target the liver and other peripheral tissues. Three weeks after IV injection of AAV.BBB.P2 at 5×10^{13} GC/kg into humanized-TfR1 knock-in mice, we found robust transduction in the CNS. Vector DNA biodistribution assessed by ddPCR was 50x higher in the brain (~ 30 GC/cell) and 175x higher in the spinal cord (~ 90 GC/cell) compared to wild-type AAV9 levels at the same dose (< 1.0 GC/cell). Remarkably, vector DNA in the liver was $> 2,000$ x lower than AAV9, yielding an average of < 0.1 GC/cell for AAV.BBB.P2. Similarly, biodistribution in heart was < 1.0 GC/cell and skeletal muscle was < 0.1 GC/cell. Analysis of mRNA transcripts for tdTomato followed these trends.

Histological processing revealed that AAV.BBB.P2 broadly transduces the CNS, with robust expression observed throughout the entire cortex (particularly layer 5 pyramidal neurons), hippocampus, thalamus, and striatum. We further characterized AAV.BBB.P2 at a wider range of doses including 5×10^{12} , 1×10^{13} , and 1×10^{14} GC/kg, as well as performing single-nucleus RNAseq (snRNAseq) on whole brain hemispheres to assess the cell-type specific transduction profile.

These results demonstrate that AAV.BBB.P2 achieves significantly reduced off-target expression while maintaining efficient CNS transduction, yielding 300x greater vector biodistribution in brain compared to liver and skeletal muscle. This novel AAV capsid achieves unprecedented tissue specificity in the brain, ideal for non-invasive gene transfer to the CNS to treat a range of neurologic diseases.

KEYWORDS: *Cell Type/Interactions; Genetics/Genomics; Human Neuroscience, Clinical Science, or Public Health; Interventional Tools; Molecular/Cellular Neuroscience; Integrated Approaches*

The National Museum of Health and Medicine: A hidden gem for neuroscience

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The National Museum of Health and Medicine (NMHM) in Silver Spring, MD, is home to one of the most comprehensive neuroanatomical collections in the world and has been amassed over 170 years from 20 different brain repositories. The Neuroanatomical Collections Division contains tens of thousands of specimens from 175 different species and 30 orders. Of note, the human collections range in age from fetal brains to 100 years, and represent both typical as well as a variety of neuropathological cases, such as lobotomy patients, traumatic brain injury, carcinoma, and anencephaly. Materials include alternating Nissl and myelin slide series, photographs and, in some cases, medical records. The high number of cases in many age brackets, and the high frequency sampling (sub-centimeter) therein, provides an opportunity to better understand variance both within and between human brains. These rare materials allow researchers and educators insight into brain development and neural architecture.

Currently, access to the NMHM collection is limited to in-person only, and requires direct handling of delicate specimens. Our goal is to create a digitized, high resolution online repository of materials that would provide global access to this rare and extensive collection, allowing researchers faster and easier access. Furthermore, this would expand the educational use of the collection through online modules. Teaching programs spanning professional to scholastic endeavors, digital pathology to Brain Awareness Week, become possible year-round while collaborative efforts and may be customized to remain public or private. Additionally, creating this digital collection and therefore limiting physical handling would aid in preserving this resource for years to come, allowing us to indefinitely increase our understanding of the human brain, as well as its evolution in relation to other species, on a scale currently unavailable.

KEYWORDS: *Behavioral Sciences/Psychology; Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics*

Decoding movie identity using hippocampal spiking activity, ripples, and peripheral biomarkers in humans

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The hippocampus is critical for episodic memory. Through its ability to generate spike sequences bound to a spatiotemporal context, the hippocampus can effectively create neuronal representations of continuous experiences. Hippocampal ripples are brief, high-frequency population activity patterns that support the consolidation and retrieval of behaviorally relevant spike sequences. Whereas hippocampal ripples occur predominantly during offline periods, gamma oscillations occur during high-arousal states and are important for encoding episodic content. Rather than relying exclusively on intracranial physiology to assess arousal, peripheral signals, such as pupil diameter and heart rate variability, are becoming increasingly used as non-invasive biomarkers. However, the relationship between hippocampal activity and peripheral biosignals has not been previously assessed in a naturalistic learning paradigm in humans.

For this study, we enrolled surgical epilepsy patients with hippocampal depth electrodes to participate in a task consisting of five movie-watching periods, eyes-closed rest, free recall, and cued recall. Pupil size was simultaneously measured using the Tobii eye-tracking system. Electrophysiological data used for ripple detection and single-unit recordings were collected from microwire contacts in the hippocampal CA1 subregion. Ripple events were detected after filtering the broadband LFP in the ripple frequency band (80-120 Hz) and applying thresholding criteria, excluding events near interictal spikes and those simultaneously detected on a local white matter channel. Across patients, the highest ripple rates were observed during cued recall, followed by free recall; movie-watching and eyes-closed rest exhibited significantly lower ripple rates compared to either recall period. Ripples tended to occur mostly during constricted pupillary states, associated with elevated parasympathetic tone. Putative hippocampal single-unit firing rates demonstrated movie-specific tuning, suggesting that hippocampal activity may encode movie identity even after a single viewing. To test this hypothesis, hippocampal spiking activity during each movie was used to train a linear classifier. The classifier was then used to decode movie identity during recall, with an accuracy substantially above chance. Our preliminary results suggest a precise interplay between hippocampal activity, peripheral measures of arousal, and episodic memory retrieval.

KEYWORDS: *Computational Biology/Modelling; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation*

Patient-specific mapping of deep brain stimulation pathway engagement using a high-definition subthalamic tract atlas

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Deep brain stimulation (DBS) is an established therapy for Parkinson's disease (PD), yet outcomes vary despite comparable anatomical targeting. One explanation is that stimulation fields engage different white matter pathways depending on lead location and stimulation parameters. We used a high-definition basal-ganglia tractography atlas developed by the Center for Large-scale Imaging of Neural Circuits (LINC) to characterize pathway engagement across 44 motor, limbic, and association pathways. Unlike normative datasets, this atlas includes small pathways underrepresented in standard analyses. Two patients with PD treated with DBS were included. Both were implanted with Boston Scientific Vercise directional leads targeting the subthalamic region. Patient 1 was classified as a responder based on Parkinson's Disease Questionnaire-39 (PDQ-39) improvement from 62 preoperatively to 37 postoperatively. Patient 1 was 72.5 years old, had a preoperative levodopa equivalent daily dose of 785 mg/day, and was stimulated bilaterally at 3.0 milliamperes with a pulse width of 60 microseconds. Patient 2 was classified as a non-responder based on PDQ-39 worsening from 46 to 53. Patient 2 was 65.8 years old, had a preoperative LEDD of 1868 mg/day, and received 3.5 milliamperes left-sided and 3.0 milliamperes right-sided stimulation with a 60-microsecond pulse width. Patient-specific volumes of tissue activated were generated using LeadDBS v3.0 from postoperative lead reconstructions and clinical programming settings. Preoperative and postoperative images were co-registered, normalized to MNI space, and used to reconstruct directional lead trajectories and contact locations. Stimulation fields were modeled with a finite-element approach, thresholded into binary stimulation volumes, and overlapped with the LINC tract atlas in MNI space to generate connectivity fingerprints of tract engagement. The responder showed wider engagement of motor and basal-ganglia pathways, including the nigrostriatal pathway, subthalamic pathways, and motor thalamic projections. The non-responder showed a more restricted fingerprint, with prominent overlap in fewer pathways, particularly dentatorubrothalamic and inferior frontal-associated tracts, and less apparent engagement of subthalamic motor-related pathways. We'll extend this analysis to larger cohort to evaluate whether motor tract engagement demonstrates group-level association with clinical response and supports tract atlas-guided targeting and programming in PD patients.

KEYWORDS: *Circuit Diagrams; Connectome; Human Neuroscience, Clinical Science, or Public Health; Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Relevance-modulated frontoparietal and fusiform dynamics enabling flexible object-based attention

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Attentional mechanisms in our brains seamlessly and rapidly prioritize relevant visual information, enabling flexibility and relevant decision making. The neural mechanisms that enable this rapid shifting of visual attention are not well-understood. To address this gap, we performed SEEG recordings in 31 patients (3734 electrodes) with extensive concurrent coverage of frontoparietal and ventral occipitotemporal cortex (vOTC). We designed a task to flexibly manipulate object category and behavioral relevance, enabling a dissociation of relevance-related neural dynamics from category-selective responses. A population based linear mixed-effects analyses of broadband gamma activity (BGA; 70-150 Hz) revealed that a frontoparietal network (FPN) composed of inferior frontal cortex (IFC), frontal operculum, and intraparietal sulcus tracks relevance across trials. We uncovered a spatial gradient within IFC, with anterior IFC exhibiting specific, category-sensitive dynamics, and posterior IFC exhibiting generalizable, relevance-sensitive neural coding. Clear category-selective gradients were isolated across the ventral occipitotemporal surface, and the mid-fusiform cortex was the earliest region to encode stimulus relevance across a range of object categories. We used BGA-driven partial directed coherence (PDC) to quantify relevance-sensitive changes in directed functional connectivity. We found significantly increased top-down signaling to fusiform cortex from FPN with increased object relevance, and this signaling significantly varied across fusiform cortex depending on object category tuning. Directed FPN influences preferentially targeted fusiform populations not tuned to the relevant category, while category-tuned fusiform populations showed increased directed signaling back to frontoparietal cortex. This population-specific interaction pattern is consistent with competitive models of attentional selection and provides a detailed network-level account of how goal-directed object recognition is supported by highly stereotypic yet rapidly flexible operations between the FPN and vOTC. This demonstration empirically validates a key prediction of the biased competition framework by showing that top-down feedback signals selectively influence neural populations based on tuning, alongside the enhancement of neural responses to relevant visual stimuli within fusiform cortex.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.)*

A human subcortical connectome at 400 μm resolution

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The fiber pathways of the human subcortex are of particular importance in clinical neuroscience, as they are targeted by neuromodulation therapies, such as deep brain stimulation (DBS) and lesion approaches, in various motor and psychiatric disorders. However, the complexity, size, and position of these pathways make them challenging to image non-invasively with diffusion MRI (dMRI). As a result, recent efforts in atlas of these pathways to guide neuromodulation have resorted to using synthetic data. Here we present the first comprehensive reconstruction of basal-ganglia thalami-cortical fiber pathways with ultra-high-resolution dMRI. We leverage a unique, ex vivo dMRI dataset acquired by the BRAIN CONNECTS Center for Large-scale Imaging of Neural Circuits (LINC) on the first-of-its-kind Connectome 2.0 scanner. Our contribution is twofold. First, by showing the feasibility of reconstructing these pathways with non-invasive neuroimaging at the single subject level, we set the stage for future research into reconstructing them in vivo in individual patients. Second, we provide a high-definition atlas of basal-ganglia-thalamocortical circuits that is readily extensible via our publicly released data and annotations. As a first demonstration of its clinical validity, we align our atlas to “hotspots” from previous DBS studies and identify pathways associated with therapeutic or side effects. Beyond DBS applications, this atlas can serve as a foundation for studies of various disease mechanisms and network-level dysfunction, advancing the field by providing more complete and precise models of human brain circuitry. Importantly, the dMRI-based reconstructions presented here are only the first iteration of our atlas, which will be updated as the LINC project collects data with additional modalities, including optical and X-ray microscopy, in the same specimens and in additional specimens. These enhancements will further improve anatomical precision and allow the investigation of inter-individual variability.

KEYWORDS: *Connectome; Human Neuroscience, Clinical Science, or Public Health; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology*

Characterizing sleep neurophysiology after breaching: The missing link in comprehensive neurological blast assessments

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Breaching is a common source of repetitive low-level blast exposure (rLLBE) in military training, with cumulative impulses of 11.9 psi/ms. Neurological consequences of rLLBE include insomnia, headache, cognitive dysfunction, and stress symptoms, yet the mechanisms driving these outcomes remain understudied. Emerging evidence links neuroinflammatory biomarkers to sleep physiology following blast-related trauma, suggesting that sleep disruption after blast may serve as an early biomarker and possible target for intervention. Despite this, objective sleep data in active breacher cohorts remain limited. We are using wearables to characterize sleep physiology in active-duty warfighters undergoing breacher training.

This prospective observational cohort enrolls active-duty warfighters (current N=15) attending a breaching schoolhouse (students/instructor cadre). Assessments occur at baseline and across 3 weeks of training. Blast dose is quantified via overpressure gauges. Sleep physiology is captured nightly using a wearable electroencephalogram (EEG) headband and a smart ring (accelerometry, heart rate, and temperature). Cognitive performance, oculomotor and auditory measures, and validated symptom scales covering sleep quality, mood, pain, and post-concussive symptoms complete the battery. Statistical models will evaluate the within-subject change in EEG spectral and microarchitecture features as a function of cumulative blast dose.

Data collection is ongoing. Preliminary results will include sleep physiology, autonomic metrics, and cognitive performance outcomes. Planned analyses will evaluate relationships among cumulative blast exposure, sleep disruption, neurobehavioral symptoms, and neuroinflammatory biomarkers.

This study adds objective sleep physiology measures to daytime neurological assessments in warfighters exposed to rLLBE. Aims will establish the first EEG sleep dataset in an active breacher population, identify neuroinflammatory signatures of blast-related sleep disruption, and support development of predictive tools to help identify warfighters at risk for operationally significant symptoms following exposure.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Monitor Neural Activity; Neural Recording & Modulation; Theory & Data Analysis Tools*

REM sleep without atonia in combat service members with post-traumatic stress disorder

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REM sleep without atonia (RSWA), a condition where the body fails to experience normal muscle paralysis during rapid eye movement (REM) sleep, is an emerging factor of sleep dysregulation in post-traumatic stress disorder (PTSD). Recent evidence shows increased incidence of RSWA in Veterans with PTSD, which may be related to later diagnoses of alpha-synucleopathic neurodegeneration. However, the measurement of RSWA is sensitive to REM fragmentation. Using RBDtector, an open-source algorithm for scoring RSWA, this study first evaluated whether RSWA was elevated in SMs with a PTSD diagnosis (PTSD+) compared to those without (PTSD-). Secondly, this study investigated how REM fragmentation interacted with RSWA quantification. We aimed to clarify whether fragmentation acted as a technical confound or physiological driver of RSWA in SMs with PTSD.

We retrospectively analyzed polysomnography (PSG) data from 12 SMs (7 PTSD+, 5 PTSD-) at the Walter Reed Sleep Disorder Center, excluding sleep apnea and the use of serotonin-norepinephrine reuptake inhibitors. Sleep scoring was performed by certified technicians according to American Academy of Sleep Medicine (AASM) standards. We used RBDtector to quantify RSWA with chin EMG activity, categorized as "tonic," "phasic," or "any," similar to the established SINBAR visual scoring criteria. We used a one-way ANOVA to determine if RSWA was higher in PTSD+ SMs compared to PTSD-. REM density was calculated by dividing the total number of REM bouts by minutes of REM sleep, computed for the entire night and the first period of REM sleep lasting at least 3 minutes. A regression was used to see if fragmentation predicts RSWA.

PTSD+ SMs had significantly higher phasic (0.1-5.0 s) bouts of chin EMG activity ($p = 0.024$, $d = 1.41$). Further, there was increased EMG activity ($p = 0.003$, $d = 0.64$) in PTSD+ SMs. The quantification and interaction of sleep fragmentation is ongoing.

Preliminary results indicate PTSD+ SMs exhibit greater symptoms of RSWA than PTSD- SMs. Investigating the overlapping neurological pathways in PTSD and RSWA may reveal a targetable pathophysiology, ultimately enhancing our understanding of PTSD treatments and improving REM sleep.

KEYWORDS:

Human hippocampus tracks event boundaries with a shifting anterior-posterior gradient during naturalistic film watching

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Continuous experience is parsed by the brain into discrete events, a process known as event segmentation. While fMRI studies of naturalistic film viewing have implicated the hippocampus in this process, the millisecond-scale neural dynamics in humans remains poorly understood. Moreover, it is unclear whether the hippocampus uniquely indexes meaningful event transitions or simply reflects responses to low-level visual changes.

We recorded sEEG from 25 surgical epilepsy patients during naturalistic film viewing (short films, 2-5 min each). High-gamma activity (HGA; 80-150 Hz) was examined in medial temporal lobe structures including the hippocampus (HPC), parahippocampal gyrus (PHG), amygdala (AMY), and entorhinal cortex (ENT), in a -2 to +3 s window surrounding event boundaries. Meaningful event boundaries, defined by consensus ratings from 100 independent online raters, were contrasted against matched scene cuts (visual transitions not coinciding with narrative change) as a perceptual control.

We found that HPC selectively dissociated event boundaries from scene cuts whereas PHG responded to both type of events. AMY and ENT exhibited no reliable boundary-locked response, indicating a hippocampus-specific role in narrative event segmentation. Within HPC, a spatiotemporally organized gradient emerged along the anterior-posterior axis, with greater HGA in posterior HPC immediately preceding an event boundary, while anterior HPC showed preferential engagement following the boundary ($p_{\text{cluster}} < 0.01$). The effect was independent of hemisphere and no comparable pre-boundary gradient was observed at scene cuts.

These findings reveal a distinct hippocampal signature of event segmentation. The observed pre-to-post-boundary gradient shift suggests that posterior hippocampus tracks the unfolding event up to the boundary, while anterior hippocampus engages only after the boundary has occurred. This anterior-posterior dissociation may reflect the hippocampus's dual role in translating ongoing experience into discrete episodic memories at event boundaries.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Electrophysiology*

Multimodal biometrics to optimize and scale decision support for depression DBS

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The subcallosal cingulate (SCC) white matter deep brain stimulation (DBS) is a novel and potentially effective treatment for treatment-resistant depression (TRD). While advances in targeting using DTI have helped improve treatment outcomes, clinical management of patients remain challenging due to extraneous factors that are not related to DBS effects. This project aims to address these challenges by identifying multi-modal biomarkers that can aid patient selection, monitor antidepressant response, and identify scenarios where stimulation changes are necessary to support clinical decision-making.

The first phase of the project focuses on retrospective analysis of local field potential (LFP), resting-state electroencephalography (EEG), multi-modal neuroimaging including structural, functional, and diffusion MRI, naturalistic behavior, and clinical assessments collected longitudinally from 27 participants across 3 cohorts. This includes SCC LFP collected using implanted neuromodulation devices with sensing capabilities (Medtronic PC+S, RC+S, Percept), video diaries collected longitudinally over the course of treatment in 17 participants across 2 cohorts, baseline presurgical neuroimaging in 27 participants and longitudinal neuroimaging data from 7 participants in 1 cohort.

Previously reported LFP biomarker that tracked antidepressant response in the PC+S cohort was replicated in an independent cohort to similarly track stable recovery achieved over 6 months of SCC DBS treatment. Markers predictive of treatment response were identified from video diaries and functional connectivity in neuroimaging. Estimates of emotional, trait, and related psychosocial constructs extracted from video diaries using natural language processing model provide insight into potential psychosocial determinants of treatment response. Functional connectivity between key nodes of the targeted network, including SCC, insula, and ventral striatum were predictive of treatment response. These findings will be leveraged to develop a multimodal latent state model in a unified framework to serve as a decision support system for managing SCC DBS.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Interventional Tools*

Structural connectivity between human ventral temporal and parietal cortex favors hub-based integration over topographic mapping

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Topographic organization is a common feature of cortical systems, but it remains unclear whether long-range white-matter projections preserve this organization between spatially separated cortical networks. In humans, the ventral temporal cortex (VTC) and parietal cortex are each organized along a medial-to-lateral axis. They process different aspects of visual perception and must coordinate during behavior but lack direct cortical contact. We tested two competing hypotheses: (H1) topographically ordered white-matter projections preserve the medial-to-lateral gradient across VTC and parietal cortex, with parahippocampal gyrus connecting to medial parietal, fusiform gyrus to superior parietal, and inferior temporal gyrus to lateral parietal regions; or (H2) projections converge onto some integrative hub regions.

We analyzed diffusion MRI data from 92 Human Connectome Project subjects using anatomically-constrained probabilistic tractography. The HCP-MMP1.0 atlas was projected to each subject's native T1 volume using ribbon-constrained surface-to-volume mapping, and inter-region connectivity was quantified using volume normalization. Six bilateral region groups were defined along the medial-to-lateral gradient of each cortex: VTC into parahippocampal, fusiform, and inferior temporal gyri; parietal cortex into medial, superior, and lateral regions. Then we summarized inter-region connectivity as a 3x3 temporal-by-parietal matrix.

Superior and lateral parietal regions both showed significantly stronger connectivity with inferior temporal cortex than with fusiform or parahippocampal cortex (Wilcoxon signed-rank, $p < 10^{-16}$ FDR-corrected, holding in $\geq 91/92$ subjects). Medial parietal connections to inferior temporal and parahippocampal cortex were each stronger than to fusiform, but statistically indistinguishable from each other ($p = 0.39$, 45/92 subjects). Reciprocally, fusiform and inferior temporal cortex both showed their strongest connection with lateral parietal (all $p < 10^{-16}$, 92/92 subjects), while parahippocampal preferentially connected with medial parietal (both $p < 10^{-16}$, holding in 90/92 and 92/92 subjects).

These findings suggest that, rather than preserving a strict point-to-point topographic mapping, white-matter connections from both networks converge onto their lateral termini—inferior temporal gyrus and lateral parietal lobule—which may function as anatomical convergence zones supporting cross-network communication.

KEYWORDS: *Connectome; Human Neuroscience, Clinical Science, or Public Health; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

How color shapes memory: Insights from intracranial recording

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Color is a fundamental visual feature that powerfully shapes attention, arousal, and memory formation. While behavioral studies indicate that color can modulate working memory performance, the neural mechanisms by which color information influences memory encoding and maintenance remain poorly understood. Defining how color properties interact with memory circuits is therefore a critical mechanistic question in cognitive neuroscience. Establishing a normative neural framework for color-modulated working memory will provide an essential foundation for interpreting atypical sensory-cognitive interactions observed in neurodevelopmental conditions. Notably, individuals with autism spectrum disorder (ASD) frequently exhibit altered color sensitivity and reduced working memory capacity, highlighting the potential clinical relevance of understanding how color shapes memory at the neural level.

To address this gap, we leverage a unique clinical opportunity to record intracranial EEG in epilepsy patients undergoing presurgical monitoring, thereby capturing direct neural signals from deep brain regions involved in color perception and working memory with superb spatial and temporal resolution. For each trial, participants viewed four objects presented in the same color (high-arousing or calming hue), and were later asked to identify the novel object among those previously shown. Color perception was additionally assessed using a continuous color wheel. Their eye movement data (e.g., pupil diameter and fixation) and neural signals are recorded simultaneously, enabling precise temporal alignment of behavioral events, pupil dynamics, and neural signal.

To date, behavioral data have been collected from approximately 4 healthy participants, with intracranial recordings obtained from 1 adult epilepsy patient. Initial results confirm the technical feasibility of simultaneously acquiring iEEG, behavioral responses, and eye-tracking data within a clinical inpatient setting. We hypothesize that high-arousing hues, by driving heightened arousal responses, will elicit increased high-frequency activity (HFA) and single-unit firing in the amygdala during encoding, coupled with disrupted PFC-mediated maintenance signals during the delay period—collectively impairing working memory performance relative to calming hues.

KEYWORDS: *Neural Networks (topology, etc.); Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Behavioral Sciences/Psychology*

Impact of occipital stroke and recovery on visual metacognition

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Stroke-induced damage to the occipital cortex induces a severe visual impairment in static orientation and motion discrimination (among other functions), known as cortically induced blindness (CB). Although some visual abilities can be restored through training within the blind field, whether brain areas involved in motion processing, decision-making, and metacognition can accurately interpret information at recovered locations is unknown. Here, we contrasted blind field perceptual and metacognitive abilities for static orientation discrimination before and after motion discrimination training. We analyzed data from 9 naive (5M/4F; 57.8 ± 18.5 yrs old; 18.1 ± 17.7 mths post-stroke) and 15 post-training CB patients (11M/4F; 56.2 ± 15.8 yrs old; 15.0 ± 5.8 mths post-stroke). Orientation discrimination performance was assessed via a gamified task that collected confidence reports simultaneous with orientation assessments. Data were fit with the CASANDRE (Confidence as a Noisy Decision Reliability Estimate) computational model to calculate meta-uncertainty, with higher meta-uncertainty equated with noisier confidence computations. Pre-training, blind-field orientation and motion discrimination was poor compared to performance in their own intact field ($p < 0.001$). However, confidence for orientation discrimination at these locations was appropriately low, leading to similarly small meta-uncertainty at both blind and intact-field locations (0.71 ± 1.3 and 1.21 ± 1.46 , respectively; $p = 0.33$). After direction discrimination training, direction discrimination improved to a threshold of 8.4 ± 10.6 deg, which generalized to static orientation discrimination in 6/15 patients, averaging 3.8 ± 2.4 deg. The remaining 9/15 patients failed to transfer, with orientation thresholds remaining at ceiling. CASANDRE fitting of confidence reports in 8 patients (4 improved, 4 unimproved) revealed that, despite differences in final threshold performance, meta-uncertainty for orientation discrimination was similarly small in the two cohorts, averaging 1.8 ± 2.2 in the improved and 1.4 ± 2.2 in unimproved patients ($p = 0.81$). Our results suggest that metacognition appears intact following damage to early visual cortical areas, both before and after training. We thus conclude that the metacognitive system adapts to correctly process activity from visual circuitry damaged by occipital strokes, and it successfully tracks processing changes that underlie training-induced visual recovery.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Interventional Tools*

Visual activation during imagination increases following visual restoration

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Ultra-low vision can be restored to the late blind with prostheses that electrically stimulate retinal cells. The Argus II relays visual information from a head-mounted camera to the retina and is implanted in individuals with light perception or less. Decades of profound vision loss can result in multisensory reorganization and structural atrophy of visual cortex; however, it is yet unclear the extent that visual restoration can functionally reengage visual circuits. To address this, we collected fMRI data on two Argus II patients before and after implantation (and 10 patients post-implantation) while they performed a visual imagery task. Since the Argus II device cannot be activated in the scanner, participants were asked to imagine a visual object, or place during the task-active blocks, interleaved with rest phases without any visual imagining. Participants also performed a visual flash task, during which they viewed a bright flashing screen (task vs. rest). In the imagination task, the longer-using participant (44.5 months) showed increased BOLD response in multiple early visual areas following implantation (task > rest), while a second, shorter-using participant (6.5 months) did not. Group analysis (Argus: N=10, Sighted: N=3, Blind: N=4) indicated that the Argus II patients had higher activation relative to the blind controls in visual regions. The activation during the visual flash task (natural vision) and the imagination task correlated in the Argus II patient group in the left pericalcarine and lingual gyri. Overall, these case study and group results complement our recent cortical thickness research showing that visual regions can be reinvigorated following visual restoration in longer-using patients.

KEYWORDS: *Behavioral Sciences/Psychology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Synaptic Plasticity*

A naturalistic multimodal platform for capturing brain-body interactions in people during physical effort-based decision making

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Motivational deficits are transdiagnostic symptoms across neurological and psychiatric disorders manifesting as apathy, anhedonia or amotivation. These deficits severely impair goal-directed behavior and are primary drivers of poor quality of life. However, developing targeted therapies remains difficult due to incomplete understanding of the underlying neural circuits. While traditional effort-based decision-making (EBDM) paradigms have helped us understand key regions underlying motivational deficits, they often rely on low-stakes laboratory tasks (e.g., repetitive button-pressing). These paradigms fail to capture the complex physiological demands and metabolic costs of real-world activities.

To address this gap, we aim to develop HOListic Realtime Measurement of Effort-based deciSion-making (HORMES), an experimental framework that integrates multimodal brain-body measurements with behavioral assays requiring naturalistic effort expenditure. By synchronizing high-resolution neural recordings with physiological indices of exertion, HORMES captures brain-body interaction during naturalistic effort, instrumented as walking on a treadmill.

Our preliminary results from healthy volunteers identify neural signatures within the dorso-medial prefrontal cortex (dmPFC) that track effort expenditure. Using linear state-space models to capture lagged interactions between EEG and physiological measures, we found that dmPFC activity, predominantly in the theta band, was preferentially driven by metabolic (i.e., indirect calorimetry) changes. Specifically, indirect calorimetry features robustly predicted theta activity (FDR-corrected $p < 0.05$, $F > 40$) after ~100 seconds of incline walking, consistent with the observed time delay to reach metabolic steady state. In contrast, PSID models with gait-derived features mapped onto higher-frequency (high-beta) activity, supporting that dmPFC theta modulation reflects metabolic demand rather than moment-to-moment movement.

Given the established role of the dmPFC in EBDM, our findings highlight a crucial brain-body interaction underlying the neural processes that govern motivation. Characterizing these integrated pathways will therefore help establish an ecologically valid foundation for identifying novel biomarkers and developing next-generation treatments for motivational dysfunction.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Von Economo neuron loss in scans of people who had traumatic brain injury

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Although the myriad of ways the brain is damaged from TBI is unknown, the scientific community understands that the resulting damage is widespread and can progress throughout the injured person's life. TBI may cause or lead to internal hemorrhage, bruises, lacerations, hypoxia, axonal injury, glial injury, demyelination, and reduced white matter volume. Compared to the general population, people who have had TBI have higher rates of depression, substance abuse, incarceration, suicide, and death from neurodegenerative causes such as dementia and Alzheimer's disease. With the goal of developing better treatments for improved outcomes, it is important to understand the extent of the neurological damage which leads to mental vulnerability.

Our group is at the beginning stages of investigating our hypothesis that TBI leads to a statistically significant decrease in the number of Von Economo neurons (VENs) in the frontal insula and anterior cingulate cortex, as measured in stereological analysis of postmortem brain slices. VENs are long and thin neurons, with a single large basal dendrite which seems to enable fast transmission over large distances. VENs are found in the frontal insula and the anterior cingulate cortex of some mammals. VENs are more likely to be found in larger brain animals that exhibit empathy, social awareness, and self-control. Recent studies link problems with social skills and emotional function with decreased number of VENs. These symptoms overlap with people who have suffered from TBI.

We plan to analyze brain samples from the Defense Health Agency National Museum of Health and Medicine Yakovlev-Haleem Neuroanatomical Collection with the Olympus VS200 Universal Whole Slide Imaging Scanner2 and Stereo Investigator stereological software by MBF Biosciences.

Research is primarily being conducted at the National Museum of Health and Medicine and the Catholic University of America.

We expect our data will help to establish plausible connections between TBI with VENs and add to our understanding of how TBI and VENs influence brain health.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Cell Type/Interactions*

Mapping and modulating reading behaviors using intracranial recording and stimulation

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As you read the words in this abstract, your eyes sequentially saccade to and fixate on each word, for a duration associated with how frequently you see it in natural language, and you will occasionally regress back to words you have previously fixated. You will also skip fixating up to a third of the words, instead only processing them parafoveally. These behaviors are well characterized in large population studies, and are disrupted in those with dyslexia, Alzheimer's, and Parkinson's; however, the neural basis for them remains unclear.

We recorded eye movements of 12 epilepsy patients as they read isolated sentences and long-form prose, and we aligned these with activity recorded from implanted intracranial electrodes. We found that mid-fusiform cortex acts as a bottleneck to reading speed, with its activity sensitive to word frequency and determining how long a word is fixated. The reading network shows functional hallmarks of processing unfamiliar words when first fixating on words that are later revisited. We find that parafoveal previewing of upcoming words increases the speed and efficiency of neural processing of those words once they are fixated. To confirm causal relationships between neural activity and behavior, we used brief, 200 ms bursts of chronometric stimulation, time-locked to reading onset, to transiently disrupt their ability to read. This revealed critical time periods of mid-fusiform activity underlying successful reading, inducing reading errors included mispronunciations, letter intrusions and substitutions, and reading arrests.

Together, these findings provide a robust neural map of crucial reading behaviors, act as a precursor to novel interventions for those with disrupted literacy abilities, and provide opportunities for more informative behavioral neurodiagnostic tests for people with early-stage dementia.

KEYWORDS: *Behavioral Sciences/Psychology; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Electrophysiology*

Epileptiform activity decreases while performing risky multi-attribute decision making task in stereotactic electroencephalogram recordings

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Epilepsy is characterized by recurrent, unprovoked seizures as well as interictal epileptiform discharges (IEDs) recorded in EEG between seizures such as brief, sharp, abnormal electrical signals (spikes) and high-frequency oscillations (HFOs). This study investigates the modulation of epileptiform activity during cognitive engagement using stereoelectroencephalography (sEEG) in epilepsy patients performing a risky multi-attribute decision-making task. The analysis focuses on the prevalence and temporal dynamics of spikes and HFOs during periods of engagement in this cognitive task versus rest periods. Results indicate a general pattern of reduced epileptiform activity during task engagement, suggesting a suppressive effect of the decision making task on epileptic brain activity. Across 29 task sessions from 10 patients, 22 showed significantly reduced spikes during the task period, and 23 showed significantly reduced HFOs. For some patients, the opposite pattern was observed, particularly in those patients whose epileptogenic zones overlapped with regions implicated in decision-making and cognitive control. These findings highlight the intricate relationship between cognitive engagement and epileptiform activity and they may lead to a better understanding of the mechanisms underlying cognitive modulation of epilepsy. They also point towards implications for therapeutic strategies aimed at seizure control through targeted cognitive interventions.

KEYWORDS: *Behavioral Sciences/Psychology; Human Neuroscience, Clinical Science, or Public Health; Monitor Neural Activity; Neural Recording & Modulation*

Decoding movement dynamics during epidural stimulation-enabled motor rehabilitation after spinal cord injury

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AUTHORS: K. Joshi, S.J. Harkema, M. Boakye, C.A. Angeli

Motor complete spinal cord injury (SCI) severely impairs the ability to stand and step independently. Spinal cord epidural stimulation (scES) combined with activity-based training has led to various degrees of stand and step function recovery. However, optimizing these interventions has largely relied on subjective metrics (e.g., observed performance, participant/trainer feedback), underscoring the need for objective, quantitative measures to guide neurorehabilitation strategies. We aimed to establish movement dynamic outcomes that track both longitudinal improvements and real-time adaptations during scES-enabled motor rehabilitation. Three individuals with motor complete SCI performed 160 scES-assisted alternating stand and step sessions. Kinematics and kinetics were evaluated before training (pre-), at midpoint (mid-), and after training (post-). In standing, reduced representation of postural dynamics captured progressive improvements in independence. All participants achieved full unassisted trunk extension using upper extremity for balance. One participant showed progressive unassisted hip extension (1.12% increase per session, reaching 33% of overall time), while two achieved unassisted knee extension for at least 84% of standing duration. From mid- to post-training, center of pressure excursion from force platforms during a representative 1-minute maximal independent stand decreased by 68%. This stresses the potential of postural sway from instrumented insoles for real-time scES and training adjustments. In stepping, reduced sensor-derived dynamics captured gains in gait independence and adaptability. Two participants achieved prolonged independent swing phase bouts (>25 cycles). Cycle-to-cycle correlations of foot acceleration and shank velocity peaked mid-bout and declined near termination, suggesting dynamic locomotor network output modulation. Within-session adaptability in one participant was demonstrated by higher intralimb correlation in the final versus initial bouts during treadmill-to-overground transition. From mid- to post-training, two participants showed increased cycle-to-cycle and phase correlation indices in a standardized multi-speed, multi-intent bout. Overall, wearable sensor-derived dynamics objectively track immediate adaptations and long-term improvements, aiding data-driven refinement of scES and training to maximize functional neurorecovery.

KEYWORDS: *Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Human Neuroscience, Clinical Science, or Public Health*

Spectral characterization of single-neuron spiking in the human subthalamic nucleus

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Pathological synchronization in the beta frequency band within the motor network is a hallmark of Parkinson's disease (PD) and is considered a biomarker for assessing disease state and for closed-loop deep brain stimulation (DBS). While beta-band activity is well characterized in local field potentials (LFPs) and using spectral analysis, the spectral structure of spiking activity from individual subthalamic nucleus (STN) neurons is less understood, in part because spectral estimation of spike trains poses challenges distinct from those of continuous signals. This limits the clinical and translational applications of single-cell recordings from the STN. To address this gap, we apply a dedicated point-process spectral analysis method using an FFT-based procedure to quantify the frequency content of single-neuron spiking in the human STN. We recorded single neuron spiking activities from the STN of patients with PD undergoing awake DBS lead placement surgery. Target verification and identification of single neuron recordings were verified by the neurologist intraoperatively. Spike timing of single neurons was identified via offline spike sorting, and the spectrum of each spike train was estimated using a point-process spectral estimator. Each recording was divided into discrete segments and tapered with a sliding window, and the resulting periodograms were averaged to obtain the unit power spectrum. Statistical significance was determined using surrogate spike trains generated by randomly shuffling the original interspike intervals. Across the recorded population of neurons from STN, we identified individual neurons with elevated power in the beta band relative to neighboring frequencies, indicating that beta-rhythmic structure is expressed at the level of individual STN neurons and is not limited to LFPs. These findings demonstrate that pathological features associated with Parkinsonian state, such as exaggerated neuronal oscillations recoverable from single-cell spiking activity, and the spectral analysis provides a principled framework for extracting them. In conclusion, this single-unit approach may complement LFP-based measures for monitoring disease state and offers a PD biomarker in a single-cell resolution for closed-loop DBS systems.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Electrophysiology*

Quantum transformers for cognitive processing elucidation

PRESENTER: **D. Hamilton**
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AUTHORS: D. Hamilton

The quantum transformer may be more significant than we first thought. Because quantum computers with their qubits facilitate a closer analogy to human brain information processing at the molecular level than do classical computers, the potential exists that this may facilitate an increase in our ability to understand human brain information processing through quantum transformers. And because quantum transformer architecture-based large language models are more human-like in their capabilities while being orders of magnitude faster than humans, it becomes paramount that we increase our understanding of cognitive processing at the molecular level.

KEYWORDS: *Circuit Diagrams; Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Molecular/Cellular Neuroscience; Neural Recording & Modulation*

The integrated neuron: Biophysical mechanics, glial dynamics, and pathological implications

PRESENTER: **B. Adebisi**

Institute of Cell Biology, Anatomy, Brain and Neurodegeneration

AUTHORS: B. Adebisi

This literature review aims to synthesize current scientific understanding of the neuron as the fundamental unit of the nervous system, mapping its electrical and reactive properties alongside glial interactions to elucidate the cellular underpinnings of brain pathology.

Objectives: To delineate the biophysical and chemical mechanisms driving neuronal excitability.

I. To evaluate the homeostatic and metabolic relationships between neurons and neuroglia.

II. To correlate disruptions in these integrated cellular networks with the onset of neurodegenerative and neuroinflammatory diseases.

A comprehensive literature search was conducted across PubMed, ScienceDirect, and Google Scholar databases, spanning foundational neurobiology and recent advancements in neurophysics and neurochemistry.

Keywords included “neuronal excitability,” “glial-neuronal signaling,” “action potential,” “biophysics,” and “neurodegeneration.”

The review synthesized peer-reviewed articles focusing on cellular mechanics, ion channel dynamics, and synaptic pathophysiology, excluding non-peer-reviewed or narrow clinical trial data to maintain a broad mechanistic focus.

The literature underscores that neuronal reactivity relies on precise electrochemical gradients governed by the Hodgkin-Huxley model of voltage-gated sodium ion and potassium ion channels.

Chemically, synaptic transmission bridges these electrical events through neurotransmitter fluxes.

Crucially, data highlights that neurons do not operate in isolation; astrocytes and microglia are active participants in tripartite synapses, regulating neurotransmitter clearance (e.g., glutamate) and maintaining ion homeostasis.

Disruptions in this delicate energetic and chemical balance are central to brain pathology. Biophysical failures, such as channelopathies or ATP depletion, lead to excitotoxicity—a hallmark of conditions like Alzheimer’s disease and ischemic stroke.

Furthermore, when reactive glia fail to support neuronal metabolic demands or trigger chronic neuroinflammation, synaptic pruning becomes aberrant, accelerating cognitive decline.

Understanding the neuron therefore requires a holistic view of its microenvironment.

Neurons and glia form an inseparable functional continuum.

KEYWORDS: *Cell Engineering; Chemistry; Molecular/Cellular Neuroscience; Synaptic Plasticity*

PRIME (PReserving Memory in Epilepsy): Within-patient evaluation of low-frequency stimulation across four limbic targets in the first enrolled subject

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Objective: To test whether low-frequency stimulation (LFS; intended to induce long-term depression) of limbic targets reduces seizure burden while preserving memory and whether the optimal target can be identified within a single patient. PRIME (NCT05608408) is a planned 8-subject trial in drug-resistant epilepsy; we report PR001, the first to complete all four arms.

PR001 (34-year-old woman, mesial-temporal lobe epilepsy) received two sensing-enabled Percept PC devices, four leads across four limbic sites, and was followed approximately 2.5 years. LFS was delivered continuously at 0.4 Hz. These were piriform cortex (PIC), entorhinal cortex (ERC), anterior nucleus of the thalamus (ANT), and fornix, evaluated sequentially, each an approximately 4-month LFS block separated by approximately 3-month standard-of-care (SOC; high-frequency ANT) washouts, with a follow-up visit after each period. Per arm we tracked the seizure diary and a chronic-BrainSense outlier rate (per-day high-amplitude events), plus serial memory and quality-of-life testing.

Pre-trial seizures were approximately 2 to 4 per month. Overall, LFS reduced seizure rate relative to SOC washouts (pooled all-LFS vs all-SOC = -25%), with the largest diary reductions at ERC (0.71 seizures/month, -51% vs the SOC washout mean) and fornix (-36%). The chronic-BrainSense outlier rate, a continuous seizure proxy, reproduced this ranking, falling most under ERC (-82 to -88% vs baseline) and fornix (-90%). Under LFS, power consumption was approximately 10 times lower than high-frequency ANT, projecting approximately 10 times longer battery life. Memory was preserved: RAVLT delayed recall trended upward across phases (Spearman rho = 0.89, p = 0.04) and was unchanged from baseline at ERC; at ERC, mood and quality of life remained stable.

In this first patient completing all four arms, ERC low-frequency stimulation produced the greatest seizure suppression while preserving memory and quality of life, at approximately 10 times lower power consumption than high-frequency ANT. Chronic BrainSense supplied an objective seizure-burden proxy concordant with the diary, supporting device-guided best-site selection.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation; Interventional Tools; Electrophysiology; Monitor Neural Activity*

Auris: A soft in-ear bioelectronic platform for continuous EEG monitoring and neurological assessment following traumatic brain injury

PRESENTER: **D. Luong**
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AUTHORS: D. Luong

Traumatic brain injury (TBI) is a leading cause of mortality and long-term neurological disability, with patient outcomes often dependent on timely recognition of secondary neurological deterioration. Continuous electroencephalographic (EEG) monitoring can provide critical insight into evolving brain dysfunction; however, conventional scalp EEG systems require extensive setup and specialized personnel and are poorly suited for prolonged or ambulatory monitoring. We developed Auris, a soft in-ear bioelectronic platform that enables continuous EEG acquisition through a conformable conductive composite electrode integrated within the external auditory meatus.

Auris employs a compliant PEDOT bulk composite engineered to achieve stable electrode-tissue coupling while conforming to the anatomical geometry of the ear canal. The platform was designed for long-term neurological monitoring with minimal user burden and was evaluated through electrical, mechanical, and physiological characterization. EEG recordings were assessed for signal quality, recording stability, waveform fidelity, and the ability to capture clinically relevant neurophysiological features associated with traumatic brain injury. Performance was benchmarked against conventional EEG recordings using established electrophysiological analyses.

Auris demonstrated stable long-duration EEG acquisition with preserved waveform morphology and reliable recording quality throughout experimental testing. The soft composite architecture maintained consistent electrode contact within the mechanically dynamic ear canal while minimizing motion-related artifacts. Neurophysiological signatures relevant to TBI were successfully identified from Auris recordings and demonstrated strong agreement with conventional EEG measurements. Quantitative analysis further demonstrated robust recording performance, reliable detection of neurological biomarkers, and accurate characterization of brain activity associated with traumatic injury. Detailed quantitative validation and statistical analyses will be presented.

Auris establishes a wearable, non-invasive in-ear EEG platform capable of continuous neurological monitoring in traumatic brain injury. By integrating materials-engineered soft bioelectronics with anatomically conformable sensing, Auris provides a scalable approach for continuous brain monitoring beyond traditional critical care environments.

KEYWORDS: *Electrophysiology; Integrated Approaches; Monitor Neural Activity; Neural Recording & Modulation; Human Neuroscience, Clinical Science, or Public Health*

Wearable closed-loop LIFU targets deep REM-regulatory circuits: Target-specific effects on sleep microstructure and vigilant attention

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Service members (SMs) face elevated PTSD risk, often linked to trauma or delayed effects of mild traumatic brain injury (mTBI). Chronic REM disruption is a hallmark of both, impairing emotional regulation and sustaining hyperarousal, suggesting REM enhancement as a therapeutic target. Preclinical work shows transcranial ultrasound during NREM modulates NREM and REM in rodents, with optogenetic targeting of basolateral amygdala (BLA) and centromedian thalamus (CMT)-established REM-regulatory targets, enhancing REM, has not yet been stimulated in humans for sleep.

This pilot evaluated a low-intensity focused ultrasound (LIFU) device in 14 participants completing overnight polysomnography in a randomized crossover design across three conditions: unfocused LIFU (active control), CMT-targeted, and BLA-targeted LIFU, delivered closed-loop during NREM stage 2 (11 completed all three nights). Outcomes included REM architecture (percentage, intrusions), neurophysiology (stage-specific spectral powers and ratios, spindle slow-wave coupling), and next-day vigilant attention via the Psychomotor Vigilance Task (mean RT, lapses, LSNR). Linear Mixed Effect models with participant as random intercept were used for inference.

Macro sleep architecture was preserved across conditions. BLA stimulation produced more consolidated REM ($p < 0.001$, $d = 1.13$ vs. CMT), the strongest spindle-slow-wave coupling ($p < 0.005$, $d = 0.92$ vs. CMT), and delta-dominant NREM ($p < 0.05$, $d = 0.58$ vs active control). CMT stimulation produced elevated theta/beta spectral power in REM ($p < 0.001$, $d = 1.04$ vs active control) and the strongest association between coupling directionality (PSI) and next-day LSNR ($r = 0.73$, $p < 0.05$). BLA significantly outperformed other conditions on PVT lapses and LSNR (17% LSNR improvement vs. active control, $p < 0.01$). Mixed-effects models identified PSI and REM intrusions as drivers of LSNR and lapses, while BLA-related NREM delta/beta drove lapse reduction, revealing two complementary sleep-to-cognition pathways.

Wearable LIFU targeted to deep REM-regulatory circuits produces target-specific REM modulation translating into next-day cognitive benefits, with BLA enhancing slow-wave depth and PVT performance, and CMT reshaping spindle-slow-wave coupling with performance. This offers promise for deployable non-pharmacologic options for PTSD and mTBI-related REM sleep pathology, with potential to support Warfighter sleep and readiness.

KEYWORDS: *Behavioral Sciences/Psychology; Human Neuroscience, Clinical Science, or Public Health; Interventional Tools; Monitor Neural Activity; Neural Recording & Modulation; Computational Biology/Modelling*

A mobile ecosystem for synchronized multimodal human intracranial recording and stimulation during naturalistic behavior

PRESENTER: **U. Topalovic**
Duke University

AUTHORS: U. Topalovic, M. Vallejo Martelo, N. Hasulak, S. Hiller, D. Markovic, N. Suthana

Recent advances in neural engineering are extending intracranial recording and stimulation beyond constrained laboratory settings, transforming the study and treatment of human brain disorders. We present a mobile ecosystem for synchronized human intracranial EEG (iEEG), single-neuron recording, behavioral sensing, and stimulation during naturalistic behavior. The same multimodal sensing and synchronization stack (eye tracking, scalp EEG, VR/AR tasks, wearables, and wireless control) supports two deployment modes. The first integrates chronically implanted commercial neurostimulators, including the NeuroPace RNS and Medtronic Percept systems, to enable mobile experiments in and beyond the laboratory. The second pairs the identical modalities with in-hospital micro/macro depth electrodes, using our custom Neuro-stack and commercial Ripple systems, which support ambulatory single-neuron recordings. A unified synchronization architecture combines TTL pulses, electromagnetic artifacts, wireless local-network communication, and low-latency radiofrequency (RF) protocols to achieve sub-millisecond alignment across neural, behavioral, and device streams.

The Mobile Deep Brain Recording and Stimulation platform, built for the RNS System, consolidates multiple programmer, wand, and compute components into a compact control box while preserving wireless, synchronized iEEG acquisition. A lightweight flexible inductive coil reduces wearable weight while supporting both telemetry and synchronization. For the Medtronic Percept system, we introduce electromagnetic artifact-based synchronization, enabling full-channel recordings without delivering electrical stimulation or sacrificing channels solely for timing alignment. Synchronization protocols operate over Wi-Fi, Bluetooth, and custom RF, with RF achieving sub-millisecond accuracy. We report synchronization validation and representative multimodal data acquired with the platform.

These advances show how miniaturization, wireless synchronization, and multimodal integration can move human neuroscience from static clinical environments into mobile, real-world contexts. Such platforms can accelerate mechanistic studies of memory, navigation, movement, and neuropsychiatric symptoms, and enable next-generation adaptive neuromodulation tailored to individual neural dynamics. The platform bridges fundamental discovery and translational neuroengineering by prioritizing patient mobility, ecological validity, and scalability.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Integrated Approaches; Neural Recording & Modulation; Software (analysis, etc.) and Engineering*

Effects of contact diameter on neural activation and charge density limits in intracortical microstimulation

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Intracortical microstimulation (ICMS) is widely used to map neural circuits, restore sensory function, and probe brain functions, yet how electrode contact geometry shapes neural activation and charge density limits remains incompletely understood. Ultra-micro contacts elicit percepts at low stimulation amplitudes, but the biophysical basis of this sensitivity and its relationship to stimulation dynamic range are not fully quantified. Electrode-tissue interface (ETI) nonlinearities also impose charge-density-dependent constraints that may limit usable current ranges in a contact-size-dependent manner. We focus on platinum microelectrodes, where ETI behavior is well-characterized, to examine how contact diameter influences activation sensitivity and non-damaging operating regimes, and whether distributing charge across small contacts improves performance versus a single larger contact.

We developed finite element models (FEM) of a NeuroNexus ultramicroelectrode array (5-50 micrometer site diameters) in a cortical column, coupling FEM-derived extracellular potentials to a biophysically detailed cortical column model with realistic neuron morphologies to calculate neural responses across stimulation intensities and contact diameters. The ETI was modeled as a thin layer with a parallel constant phase element and charge transfer resistance to capture nonlinear impedance changes with intensity; frequency-domain simulations quantified overpotentials and current density.

Smaller contacts produced higher activation than larger contacts at low intensities; activation converged at higher intensities, reflecting greater near-field recruitment from steeper potential gradients. The ETI model showed nonlinear onset at lower amplitudes and higher edge current density in smaller contacts, constraining usable range. Distributing current across small contacts produced higher activation than an equivalent-area large contact while per-contact charge remained non-damaging; wider spacing increased recruitment and selectivity by reducing population overlap.

Contact geometry strongly influences ICMS efficacy and charge limits. Ultra-micro contacts enhance activation at low intensities via steeper near-surface fields, but decline rapidly in impedance and show higher edge current density, reducing usable range, a tradeoff that is contact-size dependent. Distributing stimulation across small contacts partially mitigates this, enabling scalable, efficient high-density ICMS designs.

KEYWORDS: *Computational Biology/Modelling; Implantable Devices (probes, etc.); Neural Recording & Modulation*

Translational platform for brain-computer interface and adaptive neuromodulation research: Brain Interchange—BCI2000 Ecosystem

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Brain-computer interfaces (BCIs) and adaptive neuromodulation systems hold considerable promise for treating neurological disorders. However, their broader translation into research and clinical practice remains limited by technological complexity, regulatory constraints, and limited access to accessible research platforms. To address these challenges, we are developing an open-source neuromodulation ecosystem by integrating CorTec's Brain Interchange (BIC), a commercially available implantable neural sensing and stimulation (INSS) device, with the BCI2000 software platform. This versatile platform is designed to support diverse preclinical and clinical research applications while providing openly accessible protocols to accelerate translational neuromodulation research.

CorTec's 32-channel implantable BIC system was integrated with BCI2000, enabling real-time neural sensing, stimulation, visualization, and closed-loop processing. The platform was systematically evaluated through comprehensive benchtop, in vitro, and in vivo testing. Five canine subjects implanted with cortical and/or deep brain stimulation electrodes underwent long-term monitoring, functional task experiments, and translational use-case studies to assess system performance, stability, and suitability for chronic neuromodulation and BCI applications. Additionally, the platform was validated for BCI control in a patient undergoing clinical epilepsy monitoring using the benchtop version with externalized stereoencephalographic (SEEG) leads.

Comprehensive validation demonstrated reliable system performance, including low packet loss (<5%), stable power consumption, and the ability to capture neural biomarkers in both the temporal and spectral domains. Across five chronically implanted canines, the platform enabled long-term neural recordings and the successful execution of multiple functional and translational experiments, demonstrating its feasibility for chronic neuromodulation and BCI research. The benchtop platform further enabled successful BCI control in a patient undergoing epilepsy monitoring, demonstrating its translational potential. To facilitate broader adoption, we developed standardized experimental protocols disseminated through peer-reviewed publications and the BCI2000 Wiki. These results establish a validated open-source ecosystem that accelerates the translation of next-generation BCI technologies.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Comparative performance of AURIS and scalp EEG for neural signal acquisition in real-world use

PRESENTER: **E. Cox**

John Hopkins School of Medicine

AUTHORS: E. Cox, P. Perkins, Z. Rimzan, S.M. Cho, N.V. Thakor

Electroencephalography (EEG) is central to neuroscience and neurotechnology research, but conventional scalp EEG can be limited by setup burden, user discomfort, and sensitivity to motion and long-term wear. Auricular EEG, recorded from our AURIS sensors, placed in the external auditory meatus, offers a promising alternative for more discreet and wearable neural monitoring. This study compares auricular EEG with standard scalp EEG across recording quality, spectral features, signal stability, and task-related neural responses in a matched cohort. We completed a set of resting-state and cognitive tasks while signals were collected simultaneously from auricular and scalp electrodes. We evaluated signal-to-noise ratio, artifact burden, spectral power distributions, and the ability to detect canonical EEG signatures, including alpha modulation and event-related changes. We further assessed agreement between modalities using correlation-based and classification-based metrics. Results clarify which neural features are reliably captured by AURIS and where performance diverges from scalp EEG. This work is designed to inform the development of wearable EEG systems that balance usability with physiological fidelity. Demonstrating robust correspondence between auricular and scalp measures would support auricular EEG as a scalable option for ambulatory monitoring, cognitive state tracking, and hybrid brain-computer interface applications.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Neural Recording & Modulation; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Monitoring and manipulating dendritic calcium stores in vivo

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Synaptic plasticity is thought to support behavioral adaptation by updating how information propagates through neuronal circuits, but this process remains enigmatic due to its many levels of complexity. For instance, multiple circuits transmitting distinct streams of information often target anatomically- and functionally-specialized regions of a neuron's dendritic arbor. This combinatorial complexity is likely key to a neuron's ability to form complex receptive fields that faithfully represent the dynamic environments in which we live. Intracellular Ca^{2+} release (ICR) from endoplasmic reticulum (ER) was recently shown to operate at this circuit-subcellular intersection, acting preferentially in apical dendrites of hippocampal CA1 pyramidal neurons (CA1PNs) to shape the experience-dependent formation of spatial receptive fields commonly referred to as "place fields." However, it remains an open question as to when ICR is engaged: ER-resident Ca^{2+} has never been directly monitored in mammalian neurons in vivo. To address this foundational gap in knowledge, we simultaneously imaged ER Ca^{2+} dynamics and ongoing neuronal activity in radial oblique dendrites of individual CA1PNs as mice learned to navigate a series of novel virtual environments. We are now assessing ER Ca^{2+} dynamics to determine when ICR occurs relative to ongoing somatic and dendritic activity, place field formation, and animal behavior. In tandem, we have generated an ER-localized, red-shifted optogenetic construct to causally probe the role of ICR in synaptic plasticity induction and maintenance at high temporal resolution in vivo.

KEYWORDS: *Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation; Synaptic Plasticity*

AURIS: An auricular sensor for ECG and HRV assessment

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Accurate cardiac monitoring is essential for assessing autonomic state, stress, recovery, and cardiovascular health, but conventional ECG setups may be inconvenient for continuous or ambulatory use. Auricular cardiac recording, using our AURIS sensors positioned within the external auditory meatus, may enable unobtrusive measurement of cardiac rhythms and heart rate variability. This study evaluates auricular ECG-derived heart rate and HRV metrics against lead I ECG, used as the reference standard. Simultaneous recordings were obtained during rest and mild physiological challenge paradigms to assess agreement across stable and dynamic conditions. We compared beat detection accuracy, inter-beat interval correspondence, HRV time-domain metrics, and frequency-domain indices between auricular and lead I signals. Agreement was quantified using error analysis, correlation, and Bland-Altman methods, with attention to performance under movement and low-amplitude conditions. Findings from this work will help determine whether AURIS can support reliable wearable cardiac monitoring in settings where conventional lead placement is impractical. AURIS provides a compact and user-friendly alternative for longitudinal autonomic monitoring and mobile health applications.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Neural Recording & Modulation; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

A polymer neural interface for long-term, large-scale monitoring of neural activity in different brain regions across various species

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Linking neural activity to behavior is a major research goal in neuroscience and requires stable, chronic recordings of neural activity from different brain regions. However, high-channel-count penetrating microelectrode arrays (MEAs) based on rigid silicon are available only in limited formats and are difficult to customize for different experimental needs. These limitations become more significant when targeting deep brain structures or adapting devices across species with vastly different brain sizes. Soft polymer MEAs offer advantages for long-term implantation, including reduced mechanical strain in the surrounding neural tissue compared to rigid MEAs, but their flexibility poses challenges for reliable packaging, scalable electrical interconnection, and accurate insertion into deep targets.

To advance polymer MEAs, we aim to develop an open-source polymer MEA design library for different targets across multiple animal models, including mouse, rat, sheep, and nonhuman primate. We designed and fabricated different MEA designs in both Parylene C and polyimide for these animal models. A low-profile packaging strategy based on a printed circuit board was developed that simultaneously accommodates high pitch interconnections and surgical insertion aids.

Using polymer ultrasonic bump (PUB) bonding, a modified flip-chip bonding method using conventional wire bonder tools, polymer MEAs were directly bonded to PCBs populated with Omnetics connectors for interfacing to commercial headstages. We further demonstrated that PUB can be used to directly bond integrated circuits for multi-channel electrophysiology to MEAs, leveraging the integrated multiplexers to reduce the number of externalized electronic connections required.

We evaluated long-term stability of uncoated electrode sites ($\varnothing$ 15, 30, 45 μ m) in reactive accelerated aging to assess 1 kHz impedance stability over 112 accelerated days. Concurrently, we evaluated and compared four insertion methods for accurately deploying soft polymer MEAs to their neural targets. These strategies enabled implantation to depths of 4-5 mm in multiple rodent hippocampal subregions, including CA1, CA3, and DG, as supported by electrophysiological recordings and preliminary histological evaluations. Chronic in vivo studies and large-animal studies are ongoing.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Dissemination & Open Science/Education*

ePACStim: A phase-dependent neuromodulation system for precision treatment of neurological disorders

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Neurological disorders such as Parkinson's disease often involve abnormal neural oscillations that disrupt the normal function of the brain. Current neuromodulation therapies use high-frequency, continuous stimulation. This is a practical approach, but it usually lacks the necessary precision, causes side effects, and limits the ability to target sensitive areas such as the cortex. Alternatively, phase-dependent stimulation (PDS) could be an option. This approach times the stimulation to particular phases of ongoing neural oscillations. PDS may provide a more precise, patient-specific therapy that is responsive to the dynamic state of the brain in real time and is more effective and better tolerated by the majority of patients.

Despite its potential in treating neurological disease, PDS has not yet been applied in clinical settings due to several technological challenges. These include the need for real-time detection and prediction of oscillatory phase; the computational challenges of synchronizing stimulation with rapidly changing brain activity; individual differences in neural dynamics that require adaptive calibration; and, more importantly, stimulation artifacts that disrupt the neural signals necessary for phase detection. Addressing these challenges will require innovative algorithms and devices capable of operating with sub-millisecond latencies.

To address these challenges, we plan to develop a fully functional PDS system using Adaptive System-on-Chip and Field-Programmable Gate Array technology. This platform offers hardware acceleration for processing neural signals, allowing for real-time phase prediction, artifact removal, and closed-loop stimulation with sub-millisecond latencies. Our team has already developed a robust phase-targeting algorithm and a new method for removing stimulus artifacts. By implementing both of these techniques, we will build a fully functional PDS prototype system.

The system integrates phase-dependent neuromodulation techniques with customizable hardware acceleration to address technological challenges in PDS. The goal is to develop a fully operational prototype to demonstrate the feasibility of a working PDS system. This project will enable the next generation of phase-dependent neuromodulation therapies by developing an implantable neuromodulation device for long-term treatment of neurological diseases associated with abnormal neuronal oscillations.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation*

Electric field orientation within the cortical plane determines Purkinje cell entrainment during cerebellar AC stimulation

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Electric fields (E-fields) oriented along the somatodendritic axis were shown to induce much larger perturbations in the somatic transmembrane potential than other directions in cortical cells. Consequently, tangential fields parallel to the cortical surface are currently considered to have a negligible effect on modulation of somatic spikes. Here, we leveraged the planar dendritic architecture of cerebellar Purkinje cells to systematically rotate the electric field relative to their dendritic plane and determine how field orientation influences spike entrainment.

Extracellular recordings were obtained from PCs in the anesthetized rats while sinusoidal alternating-current stimulation was delivered through a custom 16-contact electrode that can rotate the electric field in 22.5° increments in the plane parallel to the cerebellar surface. Spike entrainment was quantified using phase-locking value (PLV) and preferred phase of the response (PPh).

Purkinje cells exhibited robust phase locking that depended strongly on the orientation of the tangential E-field. Entrainment was maximal when the field was aligned with the plane of the Purkinje dendritic arbor and reached a sharp minimum when the field was perpendicular to this plane. These minima were consistently accompanied by abrupt ~180° reversals in PPh. Across 17 PCs recorded in eight animals, PLV minima clustered near opposing field orientations separated by 180°, and the angles producing minimal entrainment closely matched those producing phase inversion. Although E-field orientation scaled the magnitude of entrainment, it did not alter its frequency dependence; all orientations exhibited a similar frequency tuning profile.

These findings demonstrate that tangential E-fields can strongly entrain cortical neurons and that their orientation within the cortical plane is a major determinant of neuromodulatory effect. The results challenge the prevailing emphasis on radial electric fields alone and suggest that the three-dimensional orientation of the E-field relative to neuronal morphology should be considered when designing electrode montages and current-steering strategies for cerebellar transcranial electrical stimulation.

KEYWORDS: *Monitor Neural Activity; Neural Recording & Modulation*

Transsynaptic modulation of deep brain structures by cerebellar transcranial AC stimulation

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Deep brain stimulation (DBS) electrodes require surgical implantation into brain parenchyma to achieve targeted neuromodulation. In contrast, noninvasive electrical stimulation mainly affects superficial brain regions because electric fields attenuate rapidly with depth. Here, we demonstrate that surface stimulation of the cerebellar cortex can modulate deep brain structures by exploiting anatomical connections through the cerebellothalamic pathway. Furthermore, we show that conventional alternating current (AC) stimulation efficiently drives multisynaptic modulation at mid-to-high frequencies, whereas amplitude-modulated (AM) stimulation extends this approach to produce low-frequency modulation.

Extracellular recordings were obtained from Purkinje cells (PCs), cerebellar nuclear (CN) neurons, and motor thalamic neurons in anesthetized rats during cerebellar stimulation. Conventional AC stimulation produced phase locking in PCs, which separated into two populations approximately 180° out of phase because of orientation-dependent polarization of Purkinje dendrites. This temporal organization propagated transsynaptically through the cerebellar nuclei to the motor thalamus, demonstrating that surface stimulation can modulate neuronal activity across downstream post-synaptic sites. Entrainment was strongest at intermediate frequencies (~100 Hz) and progressively weakened at higher frequencies in downstream structures. Preferred phase of the response increased linearly with stimulation frequency, consistent with cumulative propagation delays through the cerebellothalamic pathway.

Although conventional AC efficiently generated multisynaptic modulation at mid-to-high frequencies, it produced relatively weak low-frequency modulation. To overcome this limitation, we applied amplitude modulated (AM) stimulation using 100- and 200-Hz carriers with 2- to 20-Hz envelopes. AM produced substantially stronger low-frequency entrainment in both CN and thalamic neurons, with the greater enhancement observed using the 200-Hz carrier. Purkinje cells remained primarily entrained to the carrier frequency, indicating that envelope-frequency modulation emerges through inhibitory PC-CN pathway rather than direct envelope tracking. At the population level, AM also overcame the phase cancellation arising from the bimodal response of cerebellar circuits, which limits conventional AC stimulation, by organizing neuronal responses into a common envelope-frequency temporal structure.

KEYWORDS: *Neural Recording & Modulation; Monitor Neural Activity*

Short-latency responses to transcranial magnetic stimulation in awake nonhuman primate brain

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Transcranial magnetic stimulation (TMS) is a non-invasive form of neuromodulation used for both clinical and research purposes. While the macroscopic effects of TMS have been observed in humans, its effects on individual neurons and local networks are not well-understood. In this study, we report TMS-evoked single neuron activity and local field potentials (LFPs) in primary motor cortex (M1), somatosensory cortex (S1), and parietal cortex across two nonhuman primate (NHP) subjects, with a focus on responses within the first 10 ms of the TMS pulse. We are currently recording in prefrontal cortex in a third animal to study the occurrence on TMS-evoked LFPs and spiking there.

Leveraging our novel electrophysiology system that allows for simultaneous neural recordings and TMS stimulation at the same site, we can recover low-latency neural signals within 0.5 ms of the start of the TMS pulse. These include high-frequency oscillations at ~600-1000 Hz approximately 1-7 ms after the TMS pulse, whose amplitude and frequency are dose-dependent. These oscillations were observed in areas M1 and S1, but not in parietal cortex, suggesting that TMS recruits large populations of neurons to synchronously fire in these brain regions. Additionally, these oscillations were not observed in the sham configuration. Single neurons also exhibited TMS-evoked responses in the form of low latency excitation followed by a rebound. Some neurons in areas M1 and S1 fired synchronously with high-frequency oscillations in the active TMS configuration, but not in sham. These results demonstrate the differences in local, electrophysiological responses to TMS across distinct regions of primate cerebral cortex.

KEYWORDS: *Electrophysiology; Neural Recording & Modulation; Monitor Neural Activity*

Neural signatures and clinical effects of cerebellar deep brain stimulation in dyskinetic cerebral palsy

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Managing symptoms of dyskinetic cerebral palsy (DCP) is difficult as medications often provide only modest improvement and deep brain stimulation (DBS) of the basal ganglia or thalamus has shown limited efficacy in CP-related dystonia. The cerebellum may serve as an alternate stimulation target. In this clinical trial (NCT06122675), we evaluate clinical efficacy of cerebellar DBS in DCP. Further, we aim to identify electrophysiological and kinematic markers reflecting disease severity and response to neuromodulation.

Three pediatric and young adult patients with DCP were implanted with the Medtronic Percept and SenSight electrodes targeting the dentate nucleus. Beginning one month after surgery, stimulation was activated and increased over the following months. At monthly visits, local field potentials (LFPs) were recorded during rest and movement. Kinematics were simultaneously captured using a markerless motion-tracking system. Moreover, symptoms were evaluated using standardized patient- and caregiver-reported questionnaires.

Prior to stimulation onset, cerebellar LFPs showed prominent peaks in the 8-30 Hz range during rest, which were reduced during movement. Chronic tracking of cerebellar activity in the alpha (8-12 Hz) and beta (13-35 Hz) frequency range revealed circadian rhythmicity with alpha increasing and beta decreasing at nighttime. Increasing stimulation amplitude progressively suppressed power within the dominant oscillatory peak, whether in the alpha or beta range. All three patients and their families reported modest subjective symptomatic improvements, which were supported by kinematic analysis.

Our study is among the first to characterize neural activity recorded from the human cerebellum. Our findings show that cerebellar oscillatory activity exhibits neural dynamics similar to those observed in other motor regions, such as the basal ganglia, with comparable frequency-specific activity, modulation by movement, DBS and circadian variation. Understanding if cerebellar activity relates to disease severity and how DBS-induced changes in neural activity relate to clinical improvements will be important for identifying a reliable physiologic marker in DCP.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation*

A high-density bidirectional neural interface enabled by integration of ultraflexible probes with a 512-channel ASIC

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Penetrating neural probes enable extracellular recordings from neuronal populations with single-unit resolution and millisecond temporal precision. Scaling these interfaces is important for mapping distributed brain dynamics and for brain-computer interfaces, where larger and more stable neural populations support richer decoding and feedback. High-density silicon probes such as Neuropixels have transformed systems neuroscience by providing dense, scalable recordings across local circuits and multiple brain regions. However, most high-channel-count penetrating probes are optimized primarily for recording. Because electrode geometry, implant mechanics, and front-end electronics are tightly coupled, it remains challenging to combine large-scale single-unit recording with flexible probe designs, chronic tissue compliance, and freely configurable multi-site stimulation.

Here, we present a modular 512-channel bidirectional neural interface integrating an ultraflexible e-beam-lithographed probe with a custom application-specific integrated circuit (ASIC). The ASIC supports simultaneous recording from 512 channels and stimulation from up to 128 channels. The probe uses dense e-beam-defined interconnects to route each electrode to an independent trace, increasing channel count within a small implantation footprint while preserving the mechanical compliance of an ultraflexible substrate. This one-electrode-one-trace architecture enables recording and stimulation across arbitrary combinations of contacts, including on the same contact with submillisecond switching.

The design supports freely configurable patterned stimulation with ± 10 V compliance, tens-of-microsecond control of waveform timing, and programmable stimulation channels in monopolar or bipolar configuration. During stimulation, recording channels are blanked for less than 2 milliseconds to suppress the artifact before spiking activity is resolved again. We validated the assemblies through in vitro electrical characterization and in vivo neural interfacing, recording spiking activity at single-unit resolution across hundreds of channels and maintaining functional performance over months after implantation. Together, these results establish a scalable bidirectional neural interface combining high-density ultraflexible probes, custom integrated electronics, and programmable multi-contact stimulation for chronic, large-scale interrogation of neural circuits.

KEYWORDS: *Monitor Neural Activity; Neural Recording & Modulation; Software (analysis, etc.) and Engineering; Electrophysiology*

NeuroHub: A software-defined neural interface for dynamic electrode routing, biosignal acquisition, and four-wire impedance monitoring

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High-density neural interfaces are increasingly used in electrophysiology, functional mapping, and neuromodulation studies, but existing recording and stimulation systems provide limited flexibility for dynamically accessing large electrode populations. This creates a routing bottleneck, where many electrode contacts are available but only a limited number of recording, stimulation, or impedance-measurement channels can be connected at a given time. NeuroHub addresses this challenge with a software-defined interface that dynamically allocates selected electrode contacts to shared analog pathways.

The current NeuroHub prototype implements a compact 32-input to 4-output architecture integrating solid-state analog electrode routing, high-resolution biosignal acquisition, and two-wire/four-wire impedance spectroscopy. Electrode signals remain in the analog domain, while digital control configures the routing network. This allows selected contacts to be assigned to acquisition, stimulation, or impedance measurements without manual rewiring. The prototype was implemented on an 8 cm x 6 cm printed circuit board as a scalable proof of concept for future high-channel-count systems.

Bench validation demonstrated that relay-routed ECG signals preserved waveform morphology with an RMS error of 0.43 μV relative to a direct connection, comparable to passive jumper routing. Sequential routing tests confirmed software-controlled access to all 32 channels at 10 ms intervals while preserving timing and waveform integrity. Onboard biosignal acquisition using the ADS1299 reproduced Lead-I ECG morphology comparable to a clinical amplifier.

The AD5940-based impedance subsystem reproduced the expected frequency-dependent magnitude and phase response of RC test circuits. Two-wire measurements captured gross impedance, including lead and electrode contributions, while four-wire Kelvin measurements reduced lead-resistance effects by separating current injection from voltage sensing. These results support the use of NeuroHub for conventional electrode checks and localized impedance tracking.

Together, these results demonstrate the feasibility of integrating dynamic electrode routing, biosignal acquisition, and impedance spectroscopy within a unified modular neural interface. NeuroHub provides a scalable platform for future 256- to 1024-channel systems supporting neuromodulation research, impedance-guided neural monitoring, and implantable neurotechnology.

KEYWORDS: *Circuit Diagrams; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Monitor Neural Activity; Neural Recording & Modulation; Implantable Devices (probes, etc.)*

Evaluating a benchtop configuration of a wireless implantable neural interface for high-frequency oscillation sensing in drug-resistant epilepsy

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High-frequency oscillations (HFOs, 80 to 500 Hz) recorded in intracranial EEG (iEEG) have emerged as candidate neurophysiological biomarkers for delineating epileptogenic tissue and identifying the seizure onset zone (SOZ). HFOs occur as brief, transient bursts that tend to be spatially restricted and specific to pathological brain regions. Beyond localization, HFOs hold potential as actionable biomarkers for closed-loop, targeted neuromodulation.

We sought to determine whether pathological HFOs can be reliably captured with the Brain Interchange (BIC, CorTec GmbH, Germany), a wireless, bidirectional implantable platform, and to assess whether HFO-based SOZ localization derived from BIC recordings is concordant with that obtained from standard clinical amplifiers (CA), despite differences in sampling rate and noise.

Simultaneous iEEG was acquired for up to 24 hours during routine epilepsy monitoring evaluations using a CA (2 kHz) alongside two benchtop BIC units (64 channels total, 1 kHz) in 10 patients. HFO detection was carried out on synchronized data using an in-house CNEL detector that flags oscillatory events exceeding baseline activity. Hardware differences were characterized, including noise floor within the HFO band (RMS noise: CA 1.2 microvolts versus BIC 2.5 microvolts). A machine learning-based refinement step then removed pseudo-HFOs (pHFOs).

Despite its lower sampling rate and elevated noise floor, the BIC system reliably detected HFOs. Spatial distributions of HFO rates were highly concordant between BIC and CA recordings, with spatial similarity reaching 0.98 across patients. Contact-level SOZ localization based on BIC-derived HFO distribution yielded 84 percent sensitivity and 90 percent specificity, comparable to CA-based results.

The BIC benchtop system reliably captures HFOs despite constrained hardware and higher intrinsic noise. When paired with post-detection refinement, BIC-based HFO localization of the SOZ was comparable to that of standard clinical systems. These results support the feasibility of wireless implantable devices for long-term HFO monitoring and future closed-loop neuromodulation.

KEYWORDS: *Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Electrophysiology*

Fos ensembles during motor learning

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Motor learning requires the stable encoding of movement sequences within motor circuits, but which subsets of neurons participate in this process to provide the necessary plasticity remains poorly understood. The immediate early gene Fos is induced by calcium-dependent signaling downstream of neuronal activity and has been widely used to demarcate neuronal engagement. However, recent work in spatial memory circuits has demonstrated its specificity to behaviorally relevant neurons suggesting more complex regulation of Fos expression rather than a simple, binary readout of neuronal activity. Thus, we aim to examine whether Fos expression marks a functionally distinct subpopulation of neurons during motor learning, and how Fos induction relates to specific activity features during behavior.

To examine changes in Fos expression brain-wide during motor learning, we have performed whole mount tissue clearing and light sheet imaging of Fos expression at three time points during motor learning. Comparisons across regions revealed a greater number of regions engaged at early learning relative to late learning. Furthermore, while some regions maintain elevated Fos expression throughout learning, others show engagement restricted to a specific learning stage. To further explore region specific dynamics across learning, we have focused on the primary motor cortex and have begun to perform longitudinal and simultaneous two-photon calcium imaging and Fos induction monitoring. We have begun by exploring the relationship between neuronal activity and Fos expression during two types of walking: voluntary, self-initiated walk and forced continuous walk. We plan to extend this approach to a head-fixed forelimb motor task and examine whether changes in neuronal activity across training sessions and their correlation with movement influence Fos expression.

KEYWORDS: *Cell Type/Interactions; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation*

Uncovering how the serotonergic pathway in the dorsal raphe nucleus modulates thermal preference in larval zebrafish

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The serotonergic system is an important regulator of temperature homeostasis. Disruption within the serotonergic pathway leads to impaired body temperature regulation, which can be partially recovered by selective serotonin reuptake inhibitors. Preferred body temperature is flexible and can be adjusted in response to environmental cues, with serotonergic signaling proposed to play a role in this adjustment, yet how this signaling regulates the underlying set-point remains poorly understood. To investigate the underlying thermoregulatory role of the serotonergic system, we will leverage the larval zebrafish model. Larval zebrafish 1) possess a highly conserved serotonergic system; 2) have a transparent brain during the larval stage, providing access to large-scale visualization of neuronal activity; and 3) display a stereotyped behavioral repertoire that can be readily quantified. The dorsal raphe nucleus (DRN) is a prominently serotonergic region and has been suggested to play a role in regulating body temperature. Our preliminary behavioral data indicate that functional cell ablation of the DRN increases warm avoidance behaviors, thus shifting thermal preference to cooler temperatures. This suggests that the DRN may be involved in modulating body temperature by regulating the gain of warm avoidance behaviors. Recently, we identified a crucial relay of the behavioral thermoregulatory circuit in the zebrafish medulla, which encodes temperature. Furthermore, serotonergic neurons within the DRN project to the medulla and may possibly modulate temperature encoding neurons. This link between the DRN and the medulla may be critical for tuning thermoregulatory behaviors by refining motor output. This gives us context to further explore the DRN neural mechanisms that influence preferred temperature and modulation of motor commands in the medulla. To uncover these neural computations, we will test how the DRN affects temperature encoding in the medulla, by combining functional calcium imaging, 2-photon cell ablation, and computational modeling. Furthermore, we will characterize the thermoregulatory behavioral strategies by allowing fish to freely swim in a thermal gradient in experimental and sham conditions. This work will advance our understanding of how neural circuits anticipate environmental changes and drive adaptive behaviors, providing a model for sensorimotor integration.

KEYWORDS: *Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation*

A rapid prototyping environment for closed-loop neuromodulation using the brain interchange system

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Implantable closed-loop neuromodulation systems require reliable real-time neural sensing, biomarker detection, and adaptive stimulation to enable personalized therapy. However, existing implantable devices are often limited by low sampling rates and a small number of recording channels, restricting their ability to capture distributed neural activity and high-frequency biomarkers important for disorders such as epilepsy.

Here, we present a modular rapid prototyping environment for the CorTec Brain Interchange (BIC) system, a wireless, externally powered implantable platform capable of simultaneous sensing and stimulation across up to 32 channels at a 1 kHz sampling rate. The proposed framework integrates real-time data streaming, a Simulink-based signal processing pipeline, biomarker detection, configurable stimulation control, and a graphical user interface supporting both open- and closed-loop stimulations. System performance was evaluated through electrode impedance measurements, latency characterization across three stimulation modes, and real-time closed-loop stimulation using electrocardiogram (ECG) signals as a surrogate physiological data. The mean latency across 100 trials was measured for each stimulation mode: 96.67 ± 22.72 ms for Volatile Mode (VM), 35.58 ± 2.77 ms for Persistent Command Mode (PCM), and 35.14 ± 2.83 ms for Persistent Function Mode (PFM).

The modular architecture enables rapid development, testing, and validation of neuromodulation algorithms while remaining adaptable to diverse sensing modalities and stimulation paradigms. This environment provides a practical research platform for advancing closed-loop neuromodulation and facilitates the future integration of sophisticated biomarker detection algorithms and multi-channel neural interfaces for preclinical and clinical applications.

KEYWORDS: *Implantable Devices (probes, etc.); Neural Recording & Modulation*

Interim analysis of BITES trial: From human accumbens biomarker discovery to responsive deep brain stimulation outcomes for loss-of-control eating

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An early safety and feasibility trial (EFS, NCT03868670) was conducted using responsive deep brain stimulation (rDBS) of the nucleus accumbens (NAc) to ameliorate loss of control (LOC) eating in a small cohort of human subjects (N = 4) with treatment-resistant obesity. Here, we report an interim analysis of electrophysiological biomarker data from the ambulatory setting across the cohort and primary outcomes of this first-in-human NAc rDBS study. Ambulatory NAc intracranial recordings were acquired at participant-triggered or preset times during food preoccupation or rest in a six-month biomarker discovery phase and a one-year of stimulation phase. Primary outcomes included the number of LOC eating episodes and intervention-related adverse events. A largely conserved electrophysiological biomarker was identified across four participants in the ambulatory setting; low-frequency power (1-7 Hz) in the NAc increased in all participants during moments of food preoccupation vs. at rest (permutation test, $p < 0.05$). rDBS has been activated in three of four participants and the low-frequency power was attenuated at a higher stimulation dose. A generalized mix-effect model fit demonstrated an inverse association ($\beta = -0.25$ [SE=0.018], -0.31 [0.056], and -0.11 [0.002], respectively with $p < 0.001$) between the number of the low-frequency signal detection from the device and the stimulation does change. Moreover, Participants 1 and 2 experienced 75% and 73% decrease in the number of LOC eating episodes at the end of stimulation phase. Participant 3 experienced 95% decrease in LOC episodes after 6 months of stimulation and remains under evaluation. No serious adverse occurred and ~73% of reported adverse events were mild. This EFS provided a novel platform for ambulatory biomarker discovery and insights into brain-based mechanisms of LOC eating. Moreover, NAc rDBS appears safe and feasible with preliminary efficacy in reducing LOC eating episodes.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Interventional Tools; Monitor Neural Activity; Neural Recording & Modulation*

Microscopic magnetic stimulation arrays for direction-selective interrogation of cortical layer 1

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Layer 1 (L1) of the neocortex is the outermost cortical layer and serves as an integrative hub that combines sensory inputs, top-down cortical signals, and neuromodulatory influences to regulate cortical processing. Despite its central role in cortical computation, selectively stimulating L1 remains a major challenge because of its thin anatomy and the close proximity of deeper cortical layers. Microscopic magnetic stimulation (μ MS) generates electric fields through electromagnetic induction that decay approximately with the cube of distance and exhibit strong orientation dependence with respect to local axonal geometry, providing the potential for highly focal, direction-selective activation of superficial cortical circuits.

We developed flexible double figure-8 μ MS arrays for chronic stimulation of the rat trunk primary somatosensory cortex (S1Tr). Neuronal activation was quantified using whole-brain cFos immunohistochemistry, a well-established molecular marker of neuronal activity, enabling both laminar analysis at the stimulation site and mapping of distributed brain-wide network activation.

μ MS produced highly localized neuronal activation that was confined primarily to L1, with minimal recruitment of neurons in layers 2/3 and deeper cortical layers. The observed activation pattern is consistent with the steep spatial confinement expected from inductively generated electric fields and the preferential activation of horizontal axons and U-fibers within L1. Beyond the stimulation site, whole-brain cFos mapping revealed activation of distributed cortical regions known to be functionally connected with S1Tr, including the anterior cingulate/motor cortex and piriform cortex, together with additional cortical and subcortical areas. In contrast, the contralateral non-stimulated hemisphere showed little or no corresponding cFos activation, supporting the specificity of μ MS-evoked network recruitment.

These findings provide the first in vivo evidence that μ MS can selectively activate neocortical L1 while preserving engagement of anatomically distributed cortical networks. The combination of laminar specificity and brain-wide circuit recruitment establishes μ MS as a promising neurotechnology for investigating the functional organization of superficial cortical circuits and the L1 connectome.

KEYWORDS: *Connectome; Implantable Devices (probes, etc.); Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics*

Individual response to connectome-based deep brain stimulation in depression depends on functional network organization

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Treatment-resistant depression (TRD) affects a substantial proportion of individuals with major depressive disorder, posing a significant clinical and societal burden. Tractography-guided subcallosal cingulate deep brain stimulation (SCC-DBS) has emerged as a promising intervention for TRD, yet considerable variability in clinical response remains across individuals. Here, we investigated whether preoperative functional network organization contributes to this variability by analyzing diffusion and resting-state functional MRI data from SCC-DBS patients, incorporating individualized stimulation modeling and weekly clinical assessments over the first 24 weeks of treatment. Patient-specific stimulation of the cingulum bundle, forceps minor, and ventral amygdalofugal pathway was quantified using stimulation-tract proportion (STP), and functional network organization was characterized using within- and between-network functional connectivity of the default mode (DMN), action mode (AMN), and salience (SN) networks. STP of the cingulum bundle was positively associated with clinical improvement. Although FC alone was not directly associated with clinical outcome, patterns of within- and between-network functional connectivity moderated the relationship between STP and clinical improvement. Specifically, greater DMN segregation and SN integration with the AMN strengthened the relationship. These findings suggest that integrating tract-specific stimulation with baseline functional network connectivity may advance personalized DBS for TRD and support the development of multimodal circuit-based neuromodulation strategies.

KEYWORDS: *Connectome; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Effects of shuttle geometry and ultrasonic actuation on flexible neural probe insertion

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Penetrating polymer-based neural probes offer an alternative solution for long-term neural recording with potential advantages in interface stability afforded by the hundred-fold reduction in mechanical stiffness compared to rigid counterparts. However, their low stiffness in turn poses difficulty for accurate implantation beyond 3 mm depths. One solution is to apply a rigid insertion shuttle as temporary mechanical support, allowing insertion without mechanical buckling to reach deeper targets. At the surface of the brain, high penetration forces and tissue dimpling may adversely impact tissue, minimizing their magnitude is desired to improve experimental and physiological outcomes. In this work, we investigated how shuttle tip geometry and ultrasonic vibration affect insertion mechanics of polymer neural probes with laser micromachined tungsten shuttles.

Insertion mechanics were evaluated using two tungsten shuttle designs, each 20 μm thick, fabricated from a CAD file by femtosecond laser micromachining (515 nm) under galvo mode that vary in length, width, and spacing. The four-shank design was 3.5 mm-long with 125 μm wide shanks separated by 100 μm spacing. The eight-shank design was 3 mm-long with 73 μm -wide shanks separated by 100 μm . Tips were either fabricated or sharpened by grinding against abrasive paper at a 30° angle. Single-shank versions of each were also evaluated. All configurations were inserted into 0.6% agarose blocks, mimicking brain mechanical properties. Insertion force, dimpling, and ending force were identified from load cell data and compared between fabricated and sharpened tips. The effect of ultrasonic vibration was subsequently evaluated using the NeuralGlider® Inserter (NeuralGlider, Actuated Medical, Inc.) by comparing insertion mechanics under non-actuated and actuated conditions.

Sharpening the eight shank tungsten shuttle tips reduced insertion force from 0.1384 ± 0.0007 mN to 0.1368 ± 0.006 mN, corresponding to a reduction of 1.16%. Application of NeuralGlider® actuation further reduced insertion force from 0.1368 to 0.1317 mN, representing an additional reduction of 3.73%. These findings suggest that shuttle sharpening and ultrasonic actuation improve insertion mechanics for multi-shank probes and may reduce tissue deformation during implantation. Further in vivo and histological studies will determine whether these mechanical improvements translate into reduced tissue injury and improved long-term recording stability.

KEYWORDS: *Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Interventional Tools*

Cell-type-specific neuromodulation by transcranial focused ultrasound and its application in bidirectional sensory pathway modulation

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Transcranial focused ultrasound (tFUS) is a promising neuromodulation technique with high spatial precision, deep brain penetration, and cell-type selectivity. To characterize the cell-type-specific effects of tFUS, we used ultraflexible nanoelectronic thread (NET) electrodes to record neural activities during stimulation of the somatosensory cortex (S1) in anesthetized wild-type rats ($n = 10$) using the 128-element random array ultrasound transducer H276 (f_0 : 1.5MHz) with a broad range of acoustic pressure (100-1300kPa), pulse repetition frequencies (PRFs, 30-4500Hz), and duty cycles (DCs, 0.6%-60%). Unlike conventional silicon probes, NET electrodes minimized vibration-induced artifacts during high-pressure stimulation. For the first time, we demonstrated the tFUS cell-type selective effects under high acoustic pressure with varied ultrasound parameters. We observed a positive nonlinear relationship between acoustic pressure and both time-locked and delayed spiking responses across multiple cell types. Higher pressure levels also produced distinct response profiles across independently varied PRFs and DCs, highlighting the importance of pressure-dependent parameter optimization.

To investigate the functional relevance of tFUS-induced cell-type selectivity in sensory processing, we examined how S1 tFUS modulates neural activities within cortico-thalamo-cortical (CTC) sensory pathway during hind-paw vibration-tactile stimulation. Vibration-tactile evoked potentials and multi-unit activity were recorded in S1 and posterior medial thalamic nucleus (POm) of anesthetized male rats ($n = 34$). Optogenetic tagging identified S1 CaMKII-positive, PV-positive, and SST-positive neurons, while waveform features classified putative excitatory neurons (regular-spiking units, RSUs) and inhibitory neurons (fast-spiking units, FSUs) in POm. Tactile responses were primarily driven by S1 CaMKII-positive neurons and POm RSUs. High PRF, high DC, and high-pressure stimulation produced excitatory modulation of the sensory pathway, whereas low PRF, low DC, and low-pressure stimulation induced inhibitory effects. The excitatory modulation was associated with activation of S1 CaMKII-positive neurons, while inhibitory effects were linked to their deactivation. These findings provide further mechanistic insight into cell-type-specific, bidirectional neuromodulation by tFUS in a sensory pathway and may inform optimizations of stimulation parameters to achieve targeted therapies.

KEYWORDS: *Neural Recording & Modulation*

Informed decision-making about DBS for Parkinson's disease: Patient and clinician perspectives

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Deep brain stimulation (DBS) is a second-line treatment for Parkinson's disease (PD). Decision-making about DBS has become increasingly complex for PD patients and their clinicians: The technology is more sophisticated, it's offered to patients earlier, and there are more alternative therapies to consider. Further, research indicates that some PD patients are under- or mis-informed about Parkinson's and its treatments. In light of these factors, it is important to improve our understanding of the decision-making processes of patients and their clinicians in order to facilitate shared decision-making.

We recruited 16 U.S.-based neurology clinicians and 16 PD patients with DBS, using purposeful and convenience sampling, respectively, for semi-structured interviews. Interviews were recorded, transcribed verbatim, and analyzed using qualitative content analysis. Here we present results from these interviews, focusing on the factors patients weigh, the information sources they utilize, and the information deemed necessary for informed decision-making about DBS for PD.

Patients and clinicians shared substantial agreement across three key areas: the biomedical and procedural information necessary for informed decision-making about DBS for PD, the information sources patients consult, and the factors influencing treatment decisions. However, the two groups diverged in the extent to which experiential information (i.e., information about the first-person experience of getting and living with DBS) is recognized as a core component of DBS decision-making. Patients indicated a desire for experiential information, a reliance on the experiences of other patients in their own decision-making, and a belief that experiential information is necessary for other patients to make informed decisions about DBS for PD.

Experiential information emerged as a central factor in patients' decision-making that clinicians underrecognized. This finding is noteworthy and highlights an opportunity to improve counseling, as patients' preferences and values are essential components of shared decision-making. Future research is needed to better understand how and when experiential information is most helpful to patients and how it affects their decision-making.

KEYWORDS: *Implantable Devices (probes, etc.); Neuroethics, Philosophy, Law*

Human fidelity to promote trust, access, and uptake of implantable neural devices

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As investment in implantable neural devices (IND) research grows (e.g., new indications for deep brain stimulation (DBS), adaptive DBS, brain-computer interfaces (BCI), and other INDs), many patients stand to benefit. In addition, there are significant economic benefits, as these developments are expected to create a market of hundreds-of-billions-of-dollars per year in the U.S. However, to materialize the health and economic promise of INDs, it is important to address development and implementation challenges for currently available INDs and those in the pipeline. FDA-approved INDs are underutilized; for example, only 1% of patients with Parkinson's disease and 2% of those with seizure disorders receive FDA-approved INDs annually despite the potential patient pools being much larger (i.e., 15% in PD and 30% of seizure patients). Studies on DBS underutilization suggest challenges include structural difficulties in matching eligible patients who could benefit from INDs and stakeholder perceptions (e.g., patient concerns, clinician perceptions about effectiveness and candidacy factors). To promote the development of devices and infrastructures best aligned with stakeholder needs and expectations and facilitate greater trust and willingness to adopt the technology among patients, we present the concept of human fidelity and illustrate its use by applying it to post-trial IND maintenance.

Human fidelity is informed by 10 years of BRAIN-funded research, over 300 interviews and survey data with stakeholders from IND trials and IND clinical care contexts, and U.S. public perception research on INDs. Drawing from convergent traditions in human-centered design, human-computer interaction, human factors engineering, and patient-centered outcomes research, we define human fidelity as "the measurable degree to which a device, its access workflows, and associated messaging are aligned with the empirically determined needs and expectations of key stakeholders...treated as a performance variable analogous to reliability or scalability in systems engineering, human fidelity is not a static property of a device but a dynamic outcome of an iterative, evidence-driven process." We present post-trial device maintenance as a fixable human fidelity challenge. We discuss how human fidelity can promote the development of devices more likely to be trusted, adopted, and ultimately materialize the health and economic promise of INDs.

KEYWORDS: *Implantable Devices (probes, etc.); Neural Recording & Modulation; Neuroethics, Philosophy, Law; Interventional Tools*

Population descriptors in human neuroscience research: Guidance for researchers on measurement, analysis, and reporting

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Decades of neuroimaging research have been characterized by participation that does not reflect the demographic diversity of populations affected by neurological and psychiatric diseases. Contemporary neuroimaging research continues to rely heavily on convenience samples.

Findings from non-representative samples have limited external validity and generalizability, while the absence of diverse participation perpetuates historical patterns of exclusion and injustice. There is consensus there is a need for more diverse representation. The question that remains, though, is how researchers go about achieving that goal.

In this article, we identify and provide ethical guidance on seven key questions that human neuroscience researchers face with respect to whether and how to measure, collect, analyze, and report population descriptors. Our recommendations are the result of a multi-year consensus process supported by an NIH BRAIN Neuroethics grant, Improving Recruitment, Engagement, and Access for Community Health Equity for BRAIN Next-Generation Human Neuroimaging Research and Beyond (REACH for BRAIN).

REACH for BRAIN employed mixed methods approaches combining community stakeholder engagement, modified Delphi consensus-building, qualitative and quantitative analysis, and participatory development of evidence-based tools and frameworks. The Working Group comprised 15 members representing expertise across neuroethics, neuroscience, neuroimaging, clinical radiology, community engagement, health equity, law and policy.

The guidance provides recommendations across the research arc: justification for use; operationalizing population descriptors; data analysis, including missing data; reporting; and data sharing. In addition to addressing the major questions that arise at each step of the research process, the WG proposes presumptive recommendations for answering these questions. We provide a practical, accessible framework that is both rigorous and flexible, grounded in neuroscience-specific contexts while drawing on lessons from genetics, epidemiology, and health equity research.

KEYWORDS: *Connectome; Human Neuroscience, Clinical Science, or Public Health; Neuroethics, Philosophy, Law; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Quantifying myelin using MRI and X-ray scattering

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Myelin integrity is central to healthy brain function, and its deterioration is implicated in multiple neurologic diseases. Apart from typical demyelinating diseases such as multiple sclerosis, recent evidence points to a key and early role of myelin also in neurodegenerative diseases such as Alzheimer's disease. Despite its importance, quantifying myelin has been a challenge, with the multiple proposed MRI contrasts being myelin-sensitive but not -specific, while histology methods are semi-quantitative.

We recently proposed X-ray scattering tomography as a myelin-specific tomographic method. Photons interact with the periodic myelin sheath to form diffraction (Bragg) peaks on the detector. Reconstructing this myelin-specific signal provides 3D maps of myelin levels (peak intensity) and myelin integrity (peak position = layer separation), making X-ray scattering tomography a reference method for myelin imaging for animal and human tissue.

Here, we show applications of X-ray scattering tomography to quantify myelin levels in human Alzheimer's hippocampi, in Alzheimer's mouse models, in human multiple sclerosis specimens, and in mouse diabetes models. We also use advanced myelin-sensitive MRI metrics to assess myelin in the human and mouse Alzheimer's brains, and compare these results to X-ray scattering results.

KEYWORDS: *Integrated Approaches; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics; Molecular/Cellular Neuroscience*

Automated MRI resection cavity segmentation in drug-resistant epilepsy: Deep learning and comparative traditional approaches

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Resective surgery is the standard of care for drug-resistant focal epilepsy, yet outcomes remain highly variable and difficult to predict. Accurate segmentation of the surgical cavity via magnetic resonance imaging (MRI) is essential for developing reliable outcome models. However, manual segmentation is labor-intensive and time-consuming. Artificial intelligence (AI)-mediated automatic segmentation approaches show promise, but they often fail to detect resection sites, limiting their reliability. Deep learning using multi-layered artificial neural networks simulates the human brain's processing of data and is well suited to image classification tasks, potentially providing more consistent and accurate image segmentation compared to more user-dependent approaches. Here, we introduce a deep learning-based framework for automated resection mask generation. Unlike existing pipelines that require both preoperative and postoperative imaging, our approach requires only a postoperative MPRAGE MRI as an input. To enhance robustness, we employed a combination of five distinct trained models, significantly reducing the segmentation failures previously encountered using single-model architectures. To evaluate the framework, we benchmarked its performance against other traditional approaches. We found that despite being trained on a modest dataset of 63 MRI scans, the framework achieved high-quality results, suggesting significant potential for further optimization through multi-modal data and larger cohorts. The simplicity and efficiency of this approach make it highly adaptable for integration into broader diagnostic pipelines, particularly in multidisciplinary, multi-center, and resource-limited clinical environments.

KEYWORDS: *Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Integrated Approaches*

Imaging neuronal synaptic transmission using a novel genetically encodable fMRI reporter

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The brain operates as a highly interconnected network of neurons communicating via action potentials and synaptic transmission. Understanding how these signals are coordinated remains highly challenging. Calcium indicators with optical imaging enable visualization of calcium activity in a limited field of view, while BOLD fMRI provides whole-brain coverage but lacks molecular and cellular specificity. To address this technical gap, we present a novel genetically encodable Axon-terminal-Specific Action-Potential-driven (ASAP) fMRI reporter to image synaptic transmission in defined neuronal populations.

The first-generation ASAP reporter is based on the imaging principles of hemogenetic fMRI that reports genetically targeted brain events through engineered hemodynamics. Particularly, for the novel ASAP reporter, we harness the large dense-core vesicle (LDCV) neuronal secretory machinery and neurovascular coupling mechanisms. The reporter comprises a vesicle-targeting sequence fused to the vasoactive peptide, whose presynaptic release during neuronal activation elicits MRI-detectable hemodynamic signals.

We will present the design of the reporter, validation results on (1) neuronal expression and presynaptic localization of ASAP, (2) ASAP functionality in vitro co-culture system using a luminescent assay, (3) ASAP functionality in vivo under transplantation of ASAP-N2a with stimulation, (4) ASAP functionality in vivo in CaMKII+ cortical neurons under optogenetic stimulation, and (5) no cerebral vascular disruption after 2-wk expression of ASAP in vivo.

This approach is unique because it aims to make synaptic communication visible across the intact brain with genetic specificity, presynaptic terminal specificity, and MRI-level coverage. If fully realized, this technology could help transform how we study brain function. It would allow researchers to map how genetically defined neuronal populations transmit information across distributed circuits. It can also be advanced as an imaging tool for tracking specific neuropeptide release in MRI.

KEYWORDS: *Integrated Approaches; Molecular/Cellular Neuroscience; Neuroimaging (invasive, non-invasive imaging)/Radiology; Interventional Tools*

Mapping cell-type-selective RNA targeting in the entire mammalian body

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Lipid nanoparticles (LNPs) are the leading platform for non-viral mRNA delivery; however, achieving predictable brain targeting and precise cell-type-specific translation remains a profound challenge. Here, we present PRECISE (Programmable RNA nanoparticles for Extrahepatic Cell-type-Identified Selective dELivery), an integrated, multimodal pipeline of brain-targeted LNP design, whole-brain mapping at single-cell resolution, and cell-type-specific gene therapy. First, by incorporating neuroactive small-molecule motifs into ionizable lipids, we systematically redirected LNP biodistribution toward the brain. To map brain delivery at single-cell resolution within intact anatomical contexts, we combined tissue clearing with deep-learning-based quantitative analysis. This structural mapping uncovered previously uncharacterized trafficking routes, revealing that engineered LNPs enter the brain not only by crossing the blood-brain barrier (BBB) but also through skull-to-meninges microchannels and exit via micro-lymphatic vessels at the borders of the olfactory bulb or cortex. To overcome off-target LNP accumulation and achieve true cell-type-selective delivery, we integrated the MicroSMART (MicroRNA-Sensing Modified RNA Activation and Restricted Translation) platform into our pipeline. Acting as a dual-layer biological AND gate, this system decouples physical LNP uptake from payload translation, restricting therapeutic gene expression to microglia and eliminating off-target neurotoxicity in neighboring neurons and astrocytes. Using this integrated platform to deliver therapeutic mRNAs, including the amyloid-beta-degrading enzyme neprilysin, we achieved robust therapeutic efficacy in mouse models of Alzheimer's disease. Together, PRECISE establishes a highly generalizable framework for engineering, mapping, and executing safe, brain-targeted, cell-type-specific in vivo gene therapies.

KEYWORDS: *Cell Type/Interactions; Chemistry; Neuroimaging (invasive, non-invasive imaging)/Radiology; Interventional Tools*

Visualizing neurovascular dynamics in aging via multimodal parallel imaging of brain, CSF, and retina

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Understanding the pathophysiology of neurodegenerative disease is critical in accurate and early detection, yet the ability to monitor brain health and identify early biomarkers related to neurodegenerative pathology prior to obvious symptoms is elusive. Identifying changes in retinal microcirculation and within the glymphatic system has untapped potential for biomarker detection in brain diseases, and the ability of noninvasive retinal imaging to visualize biomarkers has potential as a tool for monitoring brain health during aging.

In vivo microscopic imaging of the mouse retina and glymphatic system is a pivotal tool for exploring neurovascular structure and function, particularly in its potential as a brain-health monitor in identifying neurodegeneration biomarkers in healthy vs. diseased aging. Utilizing two-photon microscopy (2PM) and wide-field optical imaging, we measure partial oxygen pressure and blood flow non-invasively through the pupil or sclera, providing maps of microvascular morphology, blood flow & oxygenation in microvasculature and surrounding tissue. In quantifying these neurovascular changes in aging, we underscore retinal optical imaging techniques as powerful means for early detection and monitoring of neurodegeneration. Non-invasive retinal imaging approaches are underutilized despite the potential in identifying neuropathology; an integrated optical imaging approach, utilizing 2PM, PLIM/FLIM, and wide-field OISI will improve our understanding of changes in cortical oxygenation, metabolic rates, and blood flow in the healthy vs. diseased aging brain.

KEYWORDS: *Developmental/Systems Biology; Molecular/Cellular Neuroscience; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Physics or Microscopy/Optics*

Extracellular matrix anchoring enables longitudinal MRI of dopamine release

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Mapping dopamine release dynamics in vivo is critically important for understanding dopamine's roles in reward processing, learning, motor control, and goal-directed behaviors, particularly those disrupted in substance use disorder. However, current dopamine imaging technologies face major limitations. Optical imaging methods using genetically encoded sensors are limited by shallow penetration depth and restricted spatial coverage, while protein-based molecular MRI sensors cannot be expressed at micromolar concentrations and, when injected locally, undergo rapid clearance from the brain, thereby preventing longitudinal imaging studies.

Here, we present a novel extracellular matrix anchored MRI sensing platform for longitudinal dopamine imaging using the dopamine-responsive MRI sensor BM3h-9D7. This strategy combines exogenous azide-functionalized hyaluronic acid with bioorthogonal click chemistry to generate extracellular matrix-anchored sensor constructs prior to intracranial delivery. Specifically, dibenzocyclooctyne-conjugated BM3h-9D7 was linked to azide-functionalized hyaluronic acid via strain-promoted azide-alkyne cycloaddition, generating injectable sensor constructs designed to anchor within the brain extracellular matrix and prolong sensor retention while preserving dopamine sensitivity.

In vitro MRI experiments demonstrated that dopamine-responsive T1 contrast was preserved after sensor modification and extracellular matrix conjugation. Unconjugated BM3h-9D7, dibenzocyclooctyne conjugated BM3h-9D7, and hyaluronic acid anchored sensor constructs exhibited comparable dopamine sensitivity, confirming that chemical modification did not impair sensor function. In vivo mouse experiments showed that the anchored sensor exhibited prolonged retention within the brain extracellular space, with a localized MRI-detectable signal persisting for up to 4 days after intracranial injection. In contrast, free BM3h protein was retained for only hours after infusion. Postmortem immunohistochemistry confirmed sensor retention within brain tissue three days post-injection. Functional in vivo experiments in rats further demonstrated significant dopamine-responsive MRI changes compared with control infusions.

Together, these results establish extracellular matrix-anchored BM3h-9D7 as a promising platform for longitudinal, noninvasive dopamine MRI and provide a foundation for chronic monitoring of neurochemical dynamics during behavior and disease progression.

KEYWORDS: *Cell Engineering; Chemistry; Monitor Neural Activity; Integrated Approaches*

Micron-resolution fiber mapping and micro-tractography independent of sample preparation

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A primary objective in neuroscience is comprehensive mapping of neuronal trajectories. However, achieving micron-resolution over extensive areas poses significant challenges. Diffusion MRI is expensive, slow, and provides information on thousands of fibers in each voxel. Micron-resolution methods have important limitations: they either do not resolve crossings, or probe limited field-of-view, or need special sample preparations and expensive setups.

We have recently developed Computational Scattered Light Imaging to provide micron-resolution fiber orientations for any histology section independent of sample preparation.

Here, we show that we can retrieve micron-resolution fiber maps and micro-tractography for any histology section, including consecutive hippocampal sections with multiple stains, whole-human brain sections, unstained, cleared, frozen, or vibratome sections, and even sections prepared over 120 years ago. We study histology sections from healthy and diseased, animal and human brains, new or archived. We show micro-tractography changes in multiple sclerosis brain and Alzheimer's hippocampi. We compare our whole-brain results to structure tensor analysis and diffusion MRI fiber orientations.

We further extend that to 3D volumes, by leveraging our precise MR-histology coregistration pipeline. After MR-scanning human brain samples, we serial-section them and perform ComSLI on sections throughout the MR volume, producing datasets containing micron-resolution fiber orientation information across entire volumes. We showcase this in a cortical and a hippocampal human specimen, bringing MRI, histology, and ComSLI into the same space, creating 3D volumes combining MR contrasts, histological markers, and micron-resolution fiber orientations.

ComSLI is a recent low-cost, fast, and simple method to derive micron-resolution fiber orientation in histology, independent of sample preparation. Here, we showcase its capabilities and its extension to 3D datasets, coregistered with both MRI and histology, revealing unique 3D fiber architecture. This 3D micro-tractography and -connectivity information can provide new anatomic and pathologic insights, enabling detailed validation of MR-derived fiber orientations and tractography. Moreover, the combination of MRI, histology, and micron-resolution fiber orientations can shed light to multiple pathology mechanisms that involve subtle local tract degenerations.

KEYWORDS: *Circuit Diagrams; Connectome; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics; Integrated Approaches*

Voltage waveforms in terminal dendritic branches of striatal medium spiny neurons

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Striatal medium spiny neurons (SPNs) of the direct (dSPN) and indirect (iSPN) pathways constitute the major projection neurons of the basal ganglia. Their dendritic excitability and integration are fundamental to the striatal information processing. Computational studies of striatal networks are not based on real, experimentally verified dendritic signals, because SPN dendrites do not tolerate conventional electrophysiological techniques. Here, we extend the experimental characterization of dendritic electrical signaling in SPNs using ex vivo acute brain slices. dSPNs identified by green fluorescent protein expression following crossing of D1-Cre and GFP-LoxP mouse lines were loaded through a patch pipette with a red styryl voltage-sensitive dye, JPW-3028. Voltage imaging revealed robust backpropagation of somatic APs into distal and terminal dendritic segments. In many dendritic branches, APs propagated to terminal dendritic regions with little apparent attenuation or distortion of waveform shape, unlike the filtering expected from purely passive dendritic propagation. Previous studies reported that backpropagation-associated Ca^{2+} transients decline to near zero at distances of approximately 100 μm from the soma. In contrast, our calcium imaging experiments detected AP-evoked Ca^{2+} transients throughout the dendritic arbor, including terminal segments located approximately 200 μm from the cell body, providing independent support for the aforementioned VSD measurements. Importantly, both voltage and calcium imaging were performed in multiple dendritic branches from individual SPNs, increasing the robustness and generalizability of the findings. Pharmacological blockade of A-type K^+ channels with 4-aminopyridine significantly enhanced dendritic Ca^{2+} signals, indicating that local voltage-gated K^+ conductances exert strong control over dendritic excitability. Collectively, the voltage and calcium imaging data demonstrate the presence of active electrical signaling in distal SPN dendritic branches during action potential firing. These measurements provide important experimental constraints for the refinement and validation of future computational models of striatal function.

KEYWORDS: *Cell Type/Interactions; Electrophysiology; Molecular/Cellular Neuroscience; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Beyond the arousal index: Physiologically distinct microarousals differentially couple to glymphatic fluid flux

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Microarousals (MAs), brief cortical activations during sleep, are conventionally collapsed into a single arousal index treated as a uniform marker of fragmentation. In rodent studies, MAs correlate with noradrenergic surges and glymphatic activity, suggesting a beneficial physiological role. This study examines whether human MAs comprise physiologically distinct subtypes that couple differently to brain fluid dynamics—heterogeneity the conventional arousal index cannot capture.

Overnight polysomnography and prefrontal functional near-infrared spectroscopy fNIRS measured sleep and a noninvasive proxy for brain water flux. Across the cohort (13 recordings, 9 participants; mean age = 42, AHI = 3), we examined how manually scored MAs couple to stage-specific water flux using Spearman correlations, before and after removing apneic MAs. In one participant, we benchmarked three automated detectors against expert AASM scoring (Cohen's kappa). Across the cohort, we re-binned MAs by airflow and desaturation proximity to test for subtypes beyond the spontaneous-versus-apneic dichotomy.

Functionally, pooled MA-flux coupling was null (Spearman $p = 0.06$), but stage-stratified coupling was biphasic—positive in N2 ($p = 0.64$) and negative in N3 ($p = -0.39$). Removing apneic MAs preserved the N2 coupling ($p = 0.66$) and abolished the N3 trend ($p = -0.06$), localizing disruption of deep-sleep flux to respiratory rather than spontaneous events. Re-binning resolved a third subtype: desaturation-linked MAs comprised a mean 15% of N2 microarousals (range 0-30%), concealed by binary apneic/non-apneic classification. Of these, 75% carried sub-threshold oxygen drops (median 2.0%), below the 3% AASM hypopnea criterion. Lastly, MA detector agreement with expert scoring was uniformly poor (Cohen's $\kappa = 0.05$ to 0.12, “slight”); detectors were highly specific (0.97 to 0.996) but missed most expert-identified events (sensitivity 0.04 to 0.25), with arousal indices ranging from 3.3 to 16.9 per hour on the same night—the “arousal” category is not reproducibly defined across scorers.

Together, unreliable scoring, a desaturation-linked subtype, and respiratory-specific disruption of N3 glymphatic flux coupling indicate that the binary arousal index obscures physiologically distinct microarousals. These findings motivate a phenotype-first functional taxonomy of human microarousals, with relevance to sleep-dependent waste clearance.

KEYWORDS: *Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics; Software (analysis, etc.) and Engineering*

SuCor: Fast distortion correction for high-resolution brain imaging

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Susceptibility-induced geometric distortion is a long-standing obstacle to accurate diffusion and functional MRI. Magnetic field inhomogeneity stretches and compresses the image along the phase encoding direction, corrupting anatomical localization, registration, and every downstream analysis built on them. The field standard remedy is to acquire reversed phase encoding pairs and recover the distortion by an iterative nonlinear optimization. Established correctors fall into two camps, each with a cost: a) Iterative optimizers such as FSL TOPUP and PyHySCO minimize an image matching objective over many gradient steps. b) Learned methods are fast but require large labeled training sets and behave as black boxes. This process takes tens of minutes to nearly an hour per scan and depends on regularization settings that practitioners almost never adjust.

We present SuCor, which reframes correction as optimal transport along the phase-encoding axis that runs end-to-end in a matter of seconds. Because the two opposite phase-encode acquisitions are the same signal mass pushed in equal and opposite directions, matching their cumulative intensity profiles to a common midpoint recovers the displacement field in closed form in a single step. This coupled with a fully deterministic pipeline of low-rank imputation and edge-preserving anisotropic regularization gives us a realistic fieldmap that can be applied through a mass conserving pullback. No training data, no configuration files, and no manual parameter tuning are required.

Across datasets spanning multiple protocols, distortion severities, and pathology, SuCor produces fields that are smooth within tissue yet sharp at air-tissue interfaces, with correction quality similar to existing state-of-the-art. It runs roughly 55x faster end-to-end compared to the latest multithreaded version of TOPUP (~17 s versus ~950 s on matched CPU) and recovers a displacement field that agrees with the field-standard TOPUP correction and reaches comparable structural alignment at the orbitofrontal interfaces (OFC boundary agreement on normalized gradient field ≈ 0.12 , vs 0.09 uncorrected), while running ~55x faster across 1,065 subjects with no parameter tuning.

By making rigorous, guaranteed diffeomorphic distortion correction fast, automatic, and training free, SuCor removes a routine bottleneck from clinical and population scale neuroimaging.

KEYWORDS: *Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Informatics, Statistics, or Applied Mathematics*

Myomatrix array for high-resolution electromyography

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Center for Advanced Motor BioEngineering and Research

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The Center for Advanced Motor BioEngineering and Research (CAMBER) at Emory University and the Georgia Institute of Technology produces and distributes novel tools for precisely monitoring and perturbing the brain's control of the body. EMG (electromyography) measures the electrical activity of muscles and is an important technique with a wide range of applications, ranging from understanding motor control of a wide range of behaviors to evaluating muscle health and detecting neuromuscular abnormalities. CAMBER produces and distributes Myomatrix arrays, a flexible multielectrode system that can be used both acutely and chronically to record EMG across a variety of muscles, often simultaneously, within a diverse range of model systems. Traditional EMG methods are more limited—they commonly record from a single target muscle using rigid electrodes that typically cannot resolve the electrical activity of individual motor units, which consist of a single motor neuron and the muscle fibers it innervates. New advances in the development of Myomatrix arrays include the ability to combine optogenetic stimulation with EMG recordings. Thus, Myomatrix arrays allow observations of the neuronal control of muscle activity at unprecedented resolution, providing experimenters with a flexible and customizable tool for studying motor control in both research and clinical settings.

KEYWORDS: *Implantable Devices (probes, etc.)*

Active electrosensing and communication in MARL-trained weakly electric fish collectives

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We present, to our knowledge, the first biophysically grounded multi-agent reinforcement learning model of emergent communication and collective behavior in weakly electric fish. Weakly electric fish actively generate electric organ discharges to sense their environment and communicate with conspecifics, making them a powerful system for studying how sensing, signaling, and social behavior interact. Yet direct experimental access to these processes is limited by the difficulty of recording from multiple freely interacting animals while also manipulating their sensory and communication channels.

We built fish-like artificial agents that move, forage, emit electric discharges, and sense through biologically inspired mormyromast, ampullary, and knollenorgan receptor systems. Agents were trained only to maximize individual foraging success under simple ecological and social constraints. Despite the absence of explicit rewards for communication or coordination, they developed rich emergent behaviors, including active sensing, social foraging, structured electric signaling, chasing, aggression, and dominance-like asymmetries.

The trained agents qualitatively reproduce key features of real weakly electric fish, including curved electrosensory homing trajectories and heavy-tailed discharge interval statistics. Virtual perturbations reveal causal roles for short-range sensing, long-range social cues, active electrocommunication, and resource scarcity in shaping collective outcomes. Recurrent neural network analyses further show that task variables, electrosensory geometry, and social context are encoded in agent neural dynamics, with stronger shared structure during close interactions.

Together, these results establish a virtual neuroethology framework for studying social electrosensation. By combining biological constraints, closed-loop behavior, and full experimental control, this approach can generate testable hypotheses about how communication, active sensing, and neural computation give rise to flexible collective behavior.

KEYWORDS: *Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Computational Biology/Modelling*

Simple origins of complex statistical signatures in neural population activity

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The activity of large populations of neurons is apparently complex, with non-trivial statistical structure: power-law scaling, stereotyped spatiotemporal dynamics (stereotypy), and structured correlation geometry. A central question is whether these signatures require complex, finely tuned mechanisms, or emerge from simple underlying structure. Here we show that simple models based on random networks give insight into the minimal mechanisms for these observations. Beggs and Plenz first demonstrated avalanche behavior in neural activity, providing experimental evidence of criticality, with stereotypy reported in the same datasets. However, whether their co-occurrence is necessary remains unclear. We show that in random networks the two can be coupled or decoupled, while connectivity structure tightens their relationship. Networks near criticality with high stereotypy outperform others on pattern retrieval in a reservoir computing framework, showing their co-occurrence carries measurable computational benefits. Another signature observed in neural data is power-law scaling via the phenomenological renormalization group (pRG), which tracks neural statistics under iterative subsampling. Dynamical latent variable (DLV) models, where neurons couple to slowly varying stochastic latent fields, offer a principled framework for probing the minimal structure generating such scaling. Using a robust, unbiased power-law fitting approach that we developed, we show that pRG scaling emerges within a specific region of DLV parameter space defined by the number of latent variables and coupling strength, and that previously reported experimental datasets consistently fall within this region. Power-law signatures thus need not reflect precise tuning, but instead arise within a broad, biologically plausible regime of simple latent structure. Along similar lines, topological data analysis in some datasets suggests underlying hyperbolic geometry. We ask whether these signatures can emerge from simple latent structure. Applying topological data analysis to DLV-generated synthetic activity, we found such signatures follow from latent structure rather than specific geometry, indicating this model accounts for hyperbolic signatures. These signatures of apparent complexity require not complex origins but simple network structure with randomness in connectivity or coupling.

KEYWORDS: *Computational Biology/Modelling; Electrophysiology; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Physics or Microscopy/Optics; Theory & Data Analysis Tools*

Electrochemical sensing of serotonin in socially isolated crayfish

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The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been implicated as a key biomarker that regulates a range of neurobehavioral functions, including playing a prominent role in modulating social behavior across species. Here, we refined a surface-modification method to enable detection of endogenous (i.e., naturally occurring), nanomolar concentrations of 5-HT from crayfish hemolymph (i.e., blood) collected from communally housed (COMs) animals and those isolated for 1 (1-day ISOs) or 7 days (7-day ISOs). Monitoring 5-HT concentrations across social conditions provides insight into mechanisms linking isolation to neurohormones that guide behavior. Here, we utilize a three-electrode electrochemical sensor for measuring 5-HT, comprised of a carbon-fiber microelectrode (CFME) working electrode, Pt counter electrode, and Ag/AgCl reference electrode. Optimizing surface modification utilizing a carbon nanotube/Nafion dispersion and electrochemically etching (CNT-Nafion/EC) improved the signal-to-noise ratio 2.8x and maintained the limit of detection from previous fabrication (60nM), enabling successful measurements of endogenous 5-HT in vitro.

To investigate how social isolation affects serotonergic mechanisms, we measured hormonal 5-HT in hemolymph from isolated and communally housed crayfish utilizing our CNT-Nafion/EC CFME. Voltammetry results show a clear oxidation peak at 0.29 V, demonstrating detection of un-spiked, hormonal 5-HT. Our findings indicate that 5-HT levels change in response to social isolation, and these changes are species-dependent. 7-day ISOs *Procambarus* (*P. clarkii*) crayfish exhibited a major increase in 5-HT compared to COMs, whereas *Faxonius* (*F. spp*) crayfish hormonal concentrations of 5-HT peaked in 1-day ISOs. 7-day ISOs *P. clarkii* crayfish contained an average of 581.2nM 5-HT in their hemolymph, a 307.6% increase from COMs, and 1-day ISOs did not have significantly higher concentrations compared to COMs. By comparison, *F. spp* 5-HT concentrations in 1-day ISOs were 867.5nM, a 540.1% increase in hormonal 5-HT concentrations compared to COMs, and 7-day ISOs 5-HT concentrations matched COMs.

The in vitro results demonstrate the sensor's utility for studying 5-HT dynamics and exhibit results strongly suggesting an underlying effect of social isolation on hormonal 5-HT.

KEYWORDS: *Implantable Devices (probes, etc.); Integrated Approaches; Software (analysis, etc.) and Engineering*

Relearning to see following V1 damage: Lessons from artificial neural networks

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Stroke in area V1 has profound consequences. Typically, it results in a notable loss of nearly all visual function in part of the visual field. Sometimes, it also impacts visual metacognition (i.e., the ability to evaluate the quality of one's own perceptual interpretations). These conditions may or may not improve over time. It is not known which factors underlie the range, persistence, and diversity of visual deficits following V1 stroke. Here we leverage artificial neural network models to develop a biologically grounded computational hypothesis of the causes of vision loss and the prospects for recovery following V1 damage. We focus on the perceptual task of orientation discrimination and model V1 spiking activity as arising from a population of orientation-selective units that collectively operate in the information-saturated regime. Consistent with empirical estimates, sensory information in our network model is thus encoded by many more neurons than strictly required. This population activity is converted into a perceptual orientation judgement with an associated confidence report by a downstream Recurrent Neural Network (RNN) trained in an orientation-discrimination task.

Following training, the two-stage network model quantitatively resembles human psychophysical performance. To study the impacts of stroke, we silence a proportion of the V1 units. This damage leads the RNN to systematically misinterpret the stimulus, manifesting as biased perceptual judgements, accompanied by a reduced orientation sensitivity, and unreliable confidence reports. The larger the simulated damage, the more severe the resulting behavioural deficits. Critically, retraining the RNN in the same task using damaged V1 as input and trial-by-trial feedback (partially) rehabilitates the network's behavioural capabilities. This suggests that miscalibrated read-out of sensory activity by downstream circuits is partially responsible for the behavioural deficits. To further test this idea, we derived a theoretically ideal maximum likelihood decoder, which validated our hypothesis. Together, these results suggest that visual deficits following V1 stroke in part arise from miscalibrated downstream decoding operations, and they point to the potential of psychophysical training as a therapeutic tool for rehabilitation. Our framework holds promise as a practical tool to conduct large-scale in silico experiments to identify the most effective rehabilitation therapies.

KEYWORDS: *Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Neural Networks (topology, etc.); Theory & Data Analysis Tools; Informatics, Statistics, or Applied Mathematics*

Layer 6 corticothalamic neurons support cortical gain control during a tone-in-noise detection task

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Neuronal activity adapts to behavioral context, optimizing performance. Layers (L) 2/3 in the auditory cortex show attentional gain when mice are engaged in a detection task, but how this is achieved is unknown. Since L6 corticothalamic (CT) neurons play an important role in modulating cortico-thalamo-cortical activity, we hypothesize that this modulation could sharpen the tuning curves and increase the gain of neurons in L2/3 and thalamic nuclei, thereby improving sound perception in noisy environments, for example. However, it remains unclear whether L6 CT neurons contribute to the mechanisms that improve performance in such conditions. Here, we aim to investigate how L6 CT neurons respond during behavior and whether L6 CT neurons could enhance the perception of target tones embedded in a noisy background. We trained adult mice of the Ntsr1-Cre line on a fixed hearing background crossed with a reporter line expressing GCaMP6s on a tone-in-noise detection task. Constant broadband white noise (50 dB SPL) was presented together with a tone of 11.5 kHz (30 to 70 dB SPL), to obtain signal-to-noise ratios (SNRs) of -20 to +20 dB SPL. The mouse had to turn a wheel 25 degrees in either direction to receive a water reward. Mice were then imaged under 2-photon microscopy while performing the task. The pupil diameter was also recorded to assess the animal's attentional state during the task. Our findings indicate that pure-tone-responsive L6 CT neurons increase their response gain when mice successfully detect a tone embedded in a noisy background, compared to when they do not. This enhancement in response gain appears to become stronger as the SNR decreases. Our results are consistent with our hypothesis for a role of L6 CT neurons in hearing in noisy environments, suggesting that task difficulty and possibly the state of attention may be driving their responses when hearing target tones becomes more challenging.

KEYWORDS: *Cell Type/Interactions; Integrated Approaches; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Theory & Data Analysis Tools; Monitor Neural Activity*

A neural circuit for olfactory motion detection

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The direction of movement is a fundamental feature of dynamic sensory environments. In vision, neural mechanisms for extracting this variable have been studied extensively across species. Odors also arrive as spatiotemporal signals, and walking *Drosophila* use bilateral antennal sensing to respond to odor motion direction. How olfactory circuits extract this variable has remained unknown.

Here we show that the *Drosophila* antennal lobe transforms bilateral odor input into direction-selective projection neuron output. Two-photon calcium imaging first revealed direction-selective activity in the lateral horn during moving odor stimulation. Bilateral optogenetic activation of olfactory receptor neurons then isolated odor motion from wind and antennal mechanosensation, showing that sequential activation of the two antennae is sufficient to drive direction-selective responses. Antennal lobe projection neuron axons carried these signals to both the lateral horn and mushroom body, while comparison of receptor neuron terminals and projection neuron dendrites placed the earliest detected direction-selective signal at the receptor neuron to projection neuron transformation in the antennal lobe.

Direction selectivity was broad but heterogeneous across identified glomeruli, spanning channels associated with pheromones, foods, and aversive signals. In the DA1 pheromone pathway, projection neurons were sensitive to inter-antennal timing, rapid direction changes, pairwise correlations in odor intensity, and plume-like temporal signals. GABA-receptor blockade reduced DA1 direction selectivity. Connectomic, physiological, behavioral, and modeling analyses identified the inhibitory local interneuron *il3LN6* as a key component of this circuit. *il3LN6* receives contralaterally biased olfactory input, responds preferentially to the null direction for downstream DA1 projection neurons, and is required for normal behavioral orientation to odor motion. A data-driven model built from measured temporal filters showed that ipsilateral excitation and delayed contralateral inhibition are sufficient to recapitulate projection neuron direction selectivity.

These results establish odor motion direction as a circuit-level olfactory computation and show how a sensory circuit converts spatiotemporal chemical input patterns into neural signals that can guide navigation.

KEYWORDS: *Computational Biology/Modelling; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation*

Communication, coordination, and control in neuromuscular systems: Synergistic interactions

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Brains are embodied. Many fundamental questions remain unanswered: How is neural information encoded and communicated? How does the system correct for environmental perturbations? How do passive biomechanics affect the neuronal control of behavior? This leads to the foundational question: How do nervous systems control and execute interactions with the environment? Our international network of interdisciplinary research groups (IRGs), which incorporates modelers, engineers, and experimentalists, is exploring the Communication, Coordination, and Control of Neuromechanical Systems (C3NS).

As an animal's length-scale and behavioral time-scale changes, the relative importance of forms of energy also changes. We have created a framework that quantifies the changes in these forms of energy and enables us to predict control and responses to perturbations. Thus, we have chosen to study three different groups of animals that exemplify these different dominant energy regimes.

IRG1 is developing the framework as well as tools and technologies that are broadly applicable to neuromuscular modeling. IRG2, by focusing on legged locomotion in adult *Drosophila melanogaster*, investigates the effect of scale and speed in a system dominated by viscous forces. IRG3, by focusing on feeding in the soft-bodied marine mollusk *Aplysia californica*, investigates the effect of changing size in a system dominated by elastic forces. IRG4, by focusing on legged locomotion in mice, rats, cats, and dogs, investigates the effects of changing size and joint parameters on dynamic control in systems in which inertial forces increasingly dominate.

KEYWORDS: *Circuit Diagrams; Computational Biology/Modelling; Neural Networks (topology, etc.); Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering*

Dissociation between trust decisions and social inference

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Trust requires accepting vulnerability to another person's choices. This study examined how risk (potential loss if betrayed), temptation (the partner's incentive to betray), and gain/loss framing shape two stages of social decision-making: the decision to trust and the prediction of whether a partner will reciprocate—processes that may involve distinct cognitive and neural mechanisms.

Eighty-one participants completed a binary trust game as trustees during fMRI. On each trial, participants decided whether to trust, then predicted whether the partner would reciprocate. Risk and temptation varied in a 2x2 within-task design; participants were assigned to gain or loss framing conditions. Behavioral data were analyzed using GLMMs; fMRI data were preprocessed with fMRIPrep 25.1.4 and analyzed using first/second-level GLMs in SPM12 (voxelwise $p < .001$, cluster FWE $p < .05$).

Both risk and temptation significantly shaped trust decisions and reciprocity predictions. Participants trusted more under low risk and low temptation, and expected more reciprocity under low temptation. Framing interacted with risk: Frame effects on trust were larger under high-risk conditions, suggesting framing shapes social decisions most when vulnerability is high. Stage comparisons revealed a key dissociation: Risk more strongly influenced trust decisions while temptation was more strongly expressed during reciprocity predictions. This pattern suggests that predicting partner behavior requires perspective-taking on partner incentives in a way the initial trust decision does not.

Neurally, trust decisions under low temptation were associated with mPFC activity, consistent with its role in social valuation. During reciprocity prediction, a Risk x Temptation interaction emerged in left PPC, suggesting integrative processing of joint partner incentives. Cross-stage contrasts showed that temptation's neural effects reversed direction between stages: Low temptation drove mPFC and frontoparietal activation during trust decisions, while high temptation drove activation in those same regions during reciprocity predictions—directly mirroring the behavioral dissociation.

Together, these findings indicate that trust decisions and reciprocity predictions engage dissociable neural processes, with temptation as the primary driver of social inference during prediction.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology; Monitor Neural Activity*

Olfactory dysfunction and functional connectivity in a mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and synaptic dysfunction. Pathological and functional brain changes begin years before clinical symptoms emerge, including alterations in communication between distributed brain regions. Olfactory dysfunction is among the earliest and most consistent clinical features of AD, often preceding measurable cognitive decline. Although early olfactory deficits coincide with widespread network alterations, the relationship between olfactory dysfunction and functional connectivity during disease progression remains incompletely understood.

C57BL/6J (Black 6) mice were used to characterize the effects of experimentally induced olfactory dysfunction on brain functional connectivity. Olfactory dysfunction was induced using intranasal Triton X-100 lavage and confirmed with a buried food assay. Resting-state functional MRI (rs-fMRI) was then performed to assess whole-brain functional connectivity, with analyses focusing on olfactory and memory-associated networks. B6.Cg-Apptm1.1Dnli/J APP knock-in mice were used to define functional connectivity changes associated with AD pathology and disease progression in comparison with the experimentally induced model.

Optimization studies identified standard chow as the most reliable food reward for the buried food assay. Triton X-100-treated mice demonstrated transient olfactory impairment relative to controls. Preliminary rs-fMRI analyses revealed altered functional connectivity involving olfactory and memory-associated brain regions, including patterns of both hyperconnectivity and hypoconnectivity. These alterations were observed in whole-brain analyses as well as within key memory-related circuits.

These findings demonstrate that experimentally induced olfactory impairment is accompanied by measurable alterations in functional brain connectivity. Ongoing studies in APP knock-in mice will determine how these connectivity signatures compare with those observed during AD progression and may provide insight into early network changes associated with the disease.

KEYWORDS: *Behavioral Sciences/Psychology; Connectome; Monitor Neural Activity; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Integrated Approaches*

A rat hindlimb model reproduces ground reaction forces during locomotion

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We present a simplified rat hindlimb model in MuJoCo to investigate which degrees of freedom are required to reproduce ground reaction forces consistent with the animal during locomotion. The model consists of antagonistic muscle pairs at the hip, knee, and ankle with passive joint properties derived from experimental perturbation testing. The toes are modeled as independent joints with passive stiffness and damping based on the kinematics of the animal at toe-off. Joint trajectories are reproduced through kinematic replay while MuJoCo contact parameters are optimized to match the animals' ground reaction forces. When the model is limited to sagittal-plane control, it captures the overall anterior-posterior and vertical ground reaction force profiles but fails to reproduce the mediolateral force and experiences a dip in the vertical force mid-stance. Modeling the hip as a ball joint accurately reproduces the mediolateral ground reaction force but does not resolve the remaining discrepancies in the anterior-posterior and vertical forces. However, incorporating postural control of the pelvis in the pitch and yaw directions results in ground reaction forces in all three directions consistent with the animal. Despite being passively controlled, the simulated toes closely reproduce experimental toe kinematics, except for the animal's anticipatory toe extension before touchdown. These results identify the biomechanical features necessary to reproduce realistic three-dimensional ground reaction forces and provide a framework for future neuromechanical studies of walking rats.

KEYWORDS: *Computational Biology/Modelling*

The neural basis of dexterity in deer mice

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Variation in neuron number is a potential mechanism by which the nervous system evolves to support behavioral adaptation. Corticospinal neurons (CSNs) are a classic example: an expansion in the corticospinal system in the primate lineage has been hypothesized to underlie their exceptional dexterity. However, the role of CSN number in behavior has been difficult to assess due to the lack of a tractable model system. We compared two closely related subspecies of deer mice (*Peromyscus maniculatus*): forest mice, which evolved the ability to adeptly climb, presumably to support a semi-arboreal lifestyle, and prairie mice, which are less proficient climbers. We find that forest mice have about twofold larger corticospinal tracts (CSTs) driven by an increase in CSN number in secondary motor and sensory cortical areas (M2 and S2). Furthermore, forest mice display greater manual dexterity than their prairie counterparts in a reach-to-grasp task, consistent with the idea that an increase in CSN number supports more dexterous behavior. High-throughput neural recordings during this task revealed a difference in the timing of neural activity between forest and prairie mice, specifically in M2: In forest mice, the peak of activity was shifted towards the grasping phase of the behavior. Forest mice also outperform their prairie counterparts on an ecologically relevant climbing task, where they spend more time upright crossing a thin rod, move faster, and right themselves more quickly when they fall, suggesting a general difference in motor dexterity not restricted to hand use. Finally, we use F2 hybrid animals to show that CST size is correlated with climbing dexterity, providing support for the long-standing hypothesis that corticospinal system expansion supports the evolution of dexterity. Together, our work establishes the forest-prairie deer mouse system as a model to investigate the role of neuron number expansion, and CSNs in particular, in dexterous movement.

KEYWORDS: *Behavioral Sciences/Psychology; Developmental/Systems Biology; Integrated Approaches; Molecular/Cellular Neuroscience; Circuit Diagrams*

Large-scale neural Ca^{2+} imaging studies of visual perception in mice performing a visual detection task

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Sensory perception is a crucial brain function for animal survival. Although mammalian perception depends on the interactive dynamics of multiple brain regions, how these dynamics generate perceptual experience remains unknown. Here we sought to address two key challenges to studying the neurobiology of perception. First, the neural mechanisms underlying sensory perception have been difficult to isolate from those responsible for sensory encoding and downstream cognitive and behavioral processes. Second, prior recordings of the neural activity patterns that arise during perceptual processing have generally lacked the capability to span multiple brain areas within perception networks while retaining the resolution needed to sample responses of individual neurons. As a result, it has been hard to monitor the multi-scale neural activity patterns that may give rise to perceptual experience via the coordinated, inter-area interactions of cells with distinctive sensory coding properties.

Recent advances in large-scale neural Ca^{2+} imaging made by our lab now enable recordings of the Ca^{2+} dynamics of >10,000 neurons concurrently across an entire mouse cortical hemisphere. We used this technology to examine neural mechanisms of perception in mice performing a visual detection task designed to separate neural events underlying perceptual processing from those for sensory encoding, motor-driven reports, or reward processing.

We imaged somatic neural Ca^{2+} activity in cortical pyramidal cells as mice either actively reported or passively observed moving grating stimuli calibrated to be near the threshold of visual detection. Through analyses that characterized both single-cell and neural ensemble coding properties, we identified distinct subsets of cells distributed across the visual network that were selectively tuned to either stimulus encoding, motor reports and/or reward processing, or sensory perception. Perception representations arose ~120 ms after stimulus onset in higher-order visual cortical areas and then spread to motor and primary sensory regions. Neurons encoding perception generally responded just after those that encoded visual stimulus features but prior to the earliest set of cells that were sensitive to reward. Overall, these findings highlight a widely distributed network of individual neurons with activity patterns that strongly associate with visual perceptual events, in a manner that is separable from sensory information processing.

KEYWORDS: *Behavioral Sciences/Psychology; Developmental/Systems Biology; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology*

Brain-inspired spiking neural network with synaptic strength and response co-learning

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Inspired by the information processing principles of biological brains, neuromorphic computing has emerged as a promising paradigm for analyzing complex patterns in an efficient way like the brain. Spiking neural networks (SNNs), which encode and process information through discrete spike events, are particularly suitable for handling sparse and dynamic biomedical signals. However, the design and training of SNNs remain challenging due to the complex temporal behaviors of spiking neurons. In this work, we introduce a novel adaptive learning framework based on backpropagation, which can dynamically optimize the internal mechanisms of spiking neurons. The proposed method goes beyond traditional weight-only design by simultaneously adapting synaptic response dynamics, enabling more effective representation learning and improved inference accuracy. Our experiments conducted on practical biomedical signal processing tasks validate the advantages of the proposed approach. This innovative study provides a foundation for scalable and energy-efficient neuromorphic intelligence at the edge, especially for event-driven sensing and real-time precision medicine applications.

KEYWORDS: *Neural Networks (topology, etc.); Synaptic Plasticity; Computational Biology/Modelling*

Thalamocortical input reduction and microglial activity in the somatosensory cortex after sensory loss

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Throughout life the brain retains the ability to respond to changes in sensory experience. Injury to sensory systems can lead to sensory loss, triggering reorganization of sensory circuitry. Adaptive reorganization may support recovery by potentiating circuitry dedicated to processing the preserved sensory inputs, while maladaptive plasticity could impair recovery due to aberrant circuit remodeling. However, which parts of the sensory circuit and the mechanisms that drive remodeling after injury-induced sensory loss remain unknown. To determine how sensory circuit reorganization occurs, we use a mouse model of unilateral whisker denervation. Excitatory feed forward inputs arise from the whiskers, continue through the thalamus, and arrive into specialized, barrel shaped structures in layer 4 (L4) of the primary somatosensory barrel cortex (S1BC). Thalamocortical (TC) inputs from the thalamus to cortex retain capacity for plasticity after sensory deprivation, and this connection is expected to be altered after whisker denervation. Whisker denervation reduces feed forward sensory drive from the thalamus into the deprived somatosensory cortex, generating a new population of underused synapses. Microglia remove synapses in an activity dependent manner, targeting weak and underused synapses while preserving strong and active ones. This removal is known to occur in juvenile systems, but the involvement of microglia in targeted synapse removal in adults is less well studied. We hypothesize that whisker denervation in adult mice leads to a loss of TC innervation along the deprived pathway, and that this loss is mediated by microglia. The levels of VGlut2-positive thalamocortical innervation, detected by immunohistochemistry, and morphology of microglia in S1BC were measured at 7 and 28 days (D) after whisker denervation. At 7D, VGlut2 intensity in the deprived S1BC is reduced, which returns to sham levels at 28D. Microglia showed increased ramified and decreased amoeboid morphology 7D after sensory loss but returned to sham levels at 28D. This work establishes a time-dependent relationship between excitatory circuit changes and microglial activity following sensory denervation in adult circuits. A more complete understanding of the mechanisms by which neural circuitry changes after sensory loss may support future interventions to better serve people after injuries that cause sensory loss.

KEYWORDS: *Cell Type/Interactions; Developmental/Systems Biology; Molecular/Cellular Neuroscience*

Neural mechanisms underlying place-to-rate transformation

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A fundamental question in systems neuroscience is how the brain represents the external world and how it acts on it. Sensory stimuli are often represented as a place code in which the location of active neurons within a topographic map encodes the location of a stimulus. To drive behavior, this spatial representation is transformed into a rate code, in which the firing rate of motor neurons specifies the amplitude of the resulting movement. Theoretical models state that this transformation could be achieved by a readout neuron that computes a weighted sum of population activity. Because a raw weighted sum confounds stimulus location with overall activity level, models add a normalization step, an operation that pooled inhibition across the map is well-suited to implement. Although these models specify how the conversion could work in principle, the *in vivo* circuitry and mechanisms that implement them have not been identified. Recent work in our lab has established the mouse saccadic eye movement system as a powerful model for studying this transformation. A major pathway for saccade generation originates in the superior colliculus (SC), which projects to the paramedian pontine reticular formation (PPRF) in the brainstem, which in turn drives the abducens motor neurons that control the extraocular muscles. We found that air-puffs delivered at different locations and intensities evoked saccades whose endpoints depended on stimulus location but not intensity. Single-unit recordings in awake, behaving animals confirmed a topographic map of air-puff location along the SC anterior-posterior axis, with the level of activity encoding stimulus intensity, whereas excitatory PPRF neurons were tuned to stimulus location (and thus the saccade vector) but not stimulus intensity, identifying the SC→PPRF synapse as the site of place-to-rate transformation. We further found that SC neurons project to both excitatory and inhibitory populations within PPRF, the latter of which could provide the normalization needed for an intensity-invariant readout of SC activity. Ongoing work is leveraging the genetic tractability of the mouse, combined with cell-type-specific recordings and optogenetic manipulation, to determine which computational mechanism the circuit employs to convert the SC place code into the PPRF rate code.

KEYWORDS: *Circuit Diagrams; Neural Recording & Modulation; Electrophysiology*

The cervical lymph nodes and mast cells contribute to sex-dependent cognitive impairment induced by a high-fat diet

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Obesity generates a state of chronic inflammation and is associated with the development of multiple pathologies, including neurodegenerative diseases. The effects of obesity-induced chronic inflammation on the brain and the mechanisms of communication between the peripheral immune system and the brain remain poorly understood. Therefore, we aimed to determine whether changes in hippocampal function are observed in a mouse model of diet-induced obesity and whether cervical lymph nodes are involved in the development of peripheral inflammation. Consuming a high-fat diet (60% of calories from fat) generated alterations in short-term memory assessed by the novel object recognition test. Likewise, we found an increased mRNA expression of the inflammatory markers P2X4 receptors, IL-1 β , TNF- α , ITGAL, CCR1, CCR2, and CCR5 in cervical lymph nodes of obese mice. In contrast, the hippocampus shows no changes in purinergic receptor expression or in markers of neuroinflammation. However, only CCL3 mRNA expression was elevated in obese male mice compared to the control male group, indicating a possible role for mast cells, which produce CCL3 during inflammation. In this regard, only the hippocampus of male mice showed an increase in degranulated mast cells. Our observations demonstrate a clear deleterious effect of obesity on cognitive function, the involvement of myeloid immune cells in obesity-induced chronic peripheral inflammation, and the importance of the cervical lymph nodes as a communication hub linking the peripheral response and its effects on the brain. Likewise, our findings open new lines of research to understand the effects of obesity on the brain and the development of neuropathologies associated with chronic inflammation, thereby enabling the development of new therapies.

KEYWORDS: *Molecular/Cellular Neuroscience; Circuit Diagrams*

Coordinated locomotor dynamics emerge from cell-type-specific connectivity patterns

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While numerous models of the spinal locomotor circuit have emphasized the contributions of cellular- and network-level properties, the core mechanisms underlying rhythmogenesis and variable-speed control remain incompletely understood. Guided by recent results from zebrafish pointing to the importance of cell-type-specific intersegmental connectivity patterns and recruitment of speedselective subpopulations of interneurons, we developed a hierarchy of increasingly detailed models of the locomotor network. We find that coordinated locomotion emerges in an inhibition-dominated network in which connectivity is determined by intersegmental phase relationships among interneurons and variable-speed control is implemented by recruitment of speed-selective subpopulations. Further, while structured excitatory connections are not necessary for rhythmogenesis, they are useful for increasing peak locomotion frequency, albeit at the cost of smooth transitions at intermediate frequencies, suggesting a basic computational trade-off between speed and control. Together, this family of models shows that network-level interactions are sufficient to generate coordinated, variable-speed locomotion, providing new interpretations of intersegmental excitatory and inhibitory connectivity, as well as the basic, recruitment-based mechanism of speed control.

KEYWORDS: *Circuit Diagrams; Neural Networks (topology, etc.); Theory & Data Analysis Tools; Informatics, Statistics, or Applied Mathematics*

Integration of place and rate coding in the superior colliculus underlies stimulus intensity-dependent orienting behavior

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Many sensory-guided movements target the locations of stimuli. For example, catching a ball entails bringing your hand to the ball's location, and looking at a person calling your name involves directing your fovea to their location. A half-century ago, an elegant neural architecture posited to enable stimulus-targeting movements was identified in the midbrain superior colliculus (SC): SC comprises superimposed sensory and motor maps of external space whose alignment ensures that animals orient to the locations of stimuli. Here, we provide behavioral and neurophysiological evidence that head-orienting movements do not obey this model. We demonstrate that sensory stimuli in freely moving mice elicit head movements whose amplitudes depend on both the site of stimulation and its intensity. Using fiber photometry and optogenetic stimulation, we found that stimulus location and intensity are encoded in the location of active Pitx2+ neurons in SC and their level of activity, respectively, consistent with a sensory map of space in SC. In contrast, movement amplitude is a product of both the location and level of activity in SC, with many different combinations of stimulation site and intensity able to elicit identical movements, indicating that SC does not comprise a motor map of head movements. Intensity-dependent head movements that undershoot their target could be recapitulated by a model involving a Kalman filter that uses sensory input to update an internal representation of optimal heading direction. Consistent with this model, using food rewards to increase confidence in the optimality of the current heading direction decreased the amplitude of sensory-evoked head movements. These findings challenge prevailing models of sensory-guided movement generation and suggest that the brain may use a Kalman filter for head direction that facilitates exploration/exploitation tradeoffs.

KEYWORDS: *Behavioral Sciences/Psychology; Electrophysiology; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Cell Type/Interactions*

Sensorimotor integration via superior colliculus connections to the pedunculopontine nucleus

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Sensory-motor integration in the brainstem is crucial for daily functioning and ultimately survival. Two structures involved in this process are the pedunculopontine nucleus (PPN) and the superior colliculus (SC), both of which are highly interconnected with basal ganglia nuclei. The PPN is a heterogeneous structure that is critical for sleep, arousal, and motor function. Stimulation of the PPN is therapeutic in animal models of Parkinson's disease and epilepsy with a topography that is specific to cell type and location. The SC is important for integrating multisensory inputs to trigger motor responses, but the effect of SC projections to subregions and different cell types of the PPN is unknown. To address this gap in knowledge, we injected channelrhodopsin (ChR2) into the SC of ChATCre/Ai9, Vglut2-Cre/Ai9, and Vgat-Cre/Ai9 (tdTomato) mice to determine functional connectivity between SC synaptic inputs to PPN subpopulations using optogenetics and whole-cell patch clamp recordings in ex vivo brain slices. We find that almost all cholinergic and glutamatergic PPN neurons recorded receive excitatory synaptic input from the SC compared to around 75% of GABAergic PPN neurons. Since these cell types also show diverse motor effects across the rostral-caudal axis of the PPN, we separated this data into rostral and caudal subgroups. While the SC excites all three PPN cell types, the SC most strongly excites caudal cholinergic PPN neurons, as measured by the amplitude of excitatory postsynaptic currents. Furthermore, the SC drives firing in all PPN subpopulations, leading to depolarization block in a subset of glutamatergic and GABAergic neurons. Surprisingly, we also find inhibitory inputs from the SC to the PPN in around 40% of cholinergic and glutamatergic cells compared to just 26% of GABAergic cells. To determine what this means in an intact circuit, we optogenetically activated SC axons while recording from each PPN neuronal subtype using in vivo fiber photometry. We find that the PPN GABAergic calcium activity increases the most upon optogenetic stimulation of SC axons and habituates across trials. During stimulation, we find a decrease in distance traveled and mean speed and an increase in contralateral rotations. Given the important role the PPN plays in regulating arousal states and motor function, uncovering how the PPN responds to different inputs from the SC is important in understanding the modulation of movement in response to sensory stimuli.

KEYWORDS: *Cell Type/Interactions; Electrophysiology; Molecular/Cellular Neuroscience; Monitor Neural Activity*

Exploring the role of WASF3 in chemotherapy-induced cognitive dysfunction

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Chemotherapy-induced cognitive dysfunction ("chemo-brain"), typified by a number of symptoms including memory and concentration problems, is one of the most highly reported adverse side-effect in cancer survivors, but its molecular mechanism remains poorly understood. A recent study showed that endoplasmic reticulum (ER) stress elevates cellular levels of WASF3 (Wiskott-Aldrich Syndrome Protein Family Member 3), a cytosolic protein that can translocate into mitochondria and disrupt respiration as well as activate inflammatory p38 signaling. Because many chemotherapies are known to induce ER stress and WASF3 normally plays a role in actin cytoskeleton remodeling, critical for neuronal architecture and synaptic connectivity, we hypothesized that the associated induction of WASF3 may contribute to the development of chemo-brain by disrupting mitochondrial function. In this study, we demonstrate that the commonly used chemotherapeutic agent doxorubicin, highly associated with brain fog, induces ER stress, increases WASF3 expression, and activates p38 signaling, while simultaneously decreasing mitochondrial respiratory complex IV levels in mouse brain. Behavioral tests revealed that doxorubicin-treated mice exhibited significantly reduced exploratory and locomotor activity, along with impaired spatial learning and memory. Importantly, deletion of the WASF3 gene in mice prevented the downregulation of mitochondrial complex IV and the activation of p38 signaling induced by doxorubicin. Moreover, WASF3 knockout mice displayed improved memory and learning abilities compared to wild-type controls in cognitive assessments. In conclusion, our preliminary data suggest that WASF3 may play a key role in chemotherapy-induced cognitive dysfunction.

KEYWORDS: *Behavioral Sciences/Psychology; Chemistry; Genetics/Genomics; Molecular/Cellular Neuroscience; Synaptic Plasticity; Developmental/Systems Biology*

Feedback controllability is a normative theory of neural population dynamics

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The dynamics of distinct neural populations are orchestrated to produce perception, cognition, and behavior. While feedback control is a normative theory of how brains orchestrate behavioral dynamics, whether it is a normative theory of neural population dynamics is unknown. We created methods that identify directions in neural population data that are most feed-forward controllable (FFC) vs. feedback controllable (FBC), and demonstrated that those directions diverge for dynamics generated by Dale's Law connectivity. In neural population recordings across the brain, FBC directions were better decoders of task variables. Compared to FFC directions, FBC directions emerged from populations of neurons with distinct activity profiles. Finally, FBC/FFC directions emphasized different dynamic modes across brain areas in part depending on the importance of inter-neuronal interactions. These results indicate that feedback controllability is a normative theory of neural population dynamics and reveal that distinct neuronal populations produce collective dynamics underlying different modes of control.

KEYWORDS: *Informatics, Statistics, or Applied Mathematics; Theory & Data Analysis Tools; Electrophysiology*

Brain Literacy Initiative Alliance (BLIA): Advancing research-informed neuroscience education globally

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Brain Literacy (BL) refers to the capacity to understand and apply essential knowledge about the nervous system—particularly the brain—to inform decision-making and learning in a knowledge-based society. While initiatives to promote BL among the general population have emerged in recent decades, a persistent gap remains between research, educational practice, and policy implementation, particularly in regions of the Global South. Existing efforts are often fragmented, geographically uneven, and insufficiently responsive to local educational contexts. The Brain Literacy International Alliance (BLIA) emerged in 2024 as a global initiative to advance BL for non-experts through neuroeducation, fostering coordinated, evidence-based collaboration across sectors and nations. Officially launched in 2026, the Alliance brings together initiatives from diverse nations to serve as an international platform that promotes a brain-literate society, facilitates partnerships, and accelerates the translation of research into educational practice and policy. The Alliance adopts a collaborative network model that fosters South-South and South-North cooperation through regional hubs in Asia, Latin America, and Africa. Central to BLIA is supporting regional chapters to ensure equity, diversity, inclusion, and contextual relevance. This model enables knowledge exchange, capacity building, co-creation of practices, joint inquiry, and sustained engagement across research, education, and policymaking. By strengthening global networks, improving research-to-practice translation, and advancing awareness and action across education and policy, the Alliance seeks to enhance regional and global BL capacity. Thus, BLIA has the potential to advance human flourishing, strengthen brain capital, and support sustainable development by fostering and enhancing learning across diverse educational systems.

KEYWORDS: *Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health*

The brain and nerve cord connectome reveals distributed, body-wide control circuits in adult *Drosophila*

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From the processing of sensory input to the control of motor output, behavior requires coordinated signaling across the nervous system. Large-scale, comprehensive wiring diagrams that describe the connections between individual neurons at synaptic resolution—"connectomes"—provide a critical resource for identifying and understanding these neuronal circuits. For the key model organism *Drosophila melanogaster*, multiple connectomes have been generated and have provided important insight into the function of the visual system, navigational circuitry, nerve cord (the analogue of the vertebrate spinal cord), and more. However, these connectomes have been of either the brain or the nerve cord, severing the descending and ascending neurons that pass through the neck to connect these nervous system regions and that are essential for the sensorimotor transformations that underlie behavior. Here, we report the Brain And Nerve Cord (BANC), a densely reconstructed connectome of an adult female fly that spans both the brain and nerve cord. This publicly accessible resource contains the reconstructions of over 150,000 neurons as well as synapses with neurotransmitter predictions, nuclei, and mitochondria. We provide a hierarchy of annotations for each cell, including cell type-level labels for over 90% of the neurons. Furthermore, to "embody" this connectome, we focused particularly on the sensory and efferent neurons linking the central nervous system with the periphery and, based on comparisons with the literature, provide detailed annotations of targeted body parts and functions. Using the BANC, we show that efferent neurons are primarily influenced by sensory neurons in the same body part, forming local feedback loops. Long-range circuits involving ascending and descending neurons then link these local loops, and thus multiple body parts. Ascending and descending neurons can be clustered into broad behavioral groups, in which individual neurons mediate distinct but related sensorimotor transformations, suggesting a modular organization. Overall, we find a central nervous system architecture that is distributed, parallelized, and embodied, similar to distributed control architectures in engineered systems.

KEYWORDS: *Connectome*

Efficient high-throughput curation of recombinant antibodies aided by structural AI for 3D protein mapping

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Recent advances in whole mount labeling and volumetric imaging have enabled systemic neuroanatomical and cell type profiling of large brain regions in animal models and human samples. Sequence defined affinity probes (e.g., recombinant antibodies (RmAb)) are critical for whole mount immunolabeling because they are molecularly defined and easily scalable and therefore highly reproducible. We collaborated with a community of monoclonal antibody developers (NeuroMab, CDI Labs, Developmental Studies Hybridoma Bank (DSHB)) and leveraged antibody structure repositories (such as SAbDab) to curate open-source recombinant antibodies. To efficiently curate these large repositories, we utilized structure prediction tools such as AlphaFold 3 for in silico modeling and ranking, exploiting epitope-paratope interface information inferred from the predicted bound complexes. We built a scalable immunolabeling platform for screening the nominated RmAbs in both mouse and human and also benchmarked their binding with standardized validation approaches (cross-validation, paratope-epitope mutagenesis), thereby creating a high-throughput pipeline for RmAbs curation. We have completed screening of CDI-BICCN library nominated targets (~450 RmAbs covering ~100 neural targets), with ongoing efforts expanding to NeuroMab and SAbDab. In order to facilitate access to BICCN and the broad neuroscience community, we created a database infrastructure to host and share our antibody characterization efforts (<https://mab3d-atlas.com/>). The validated RmAbs will be publicly distributed by Addgene at an affordable price. Along with RmAbs curation and dissemination, we are also generating 3D whole mouse brain datasets for community reference. These efforts will provide a valuable dataset to improve current structure prediction models and facilitate efficient means to design and test molecularly defined affinity reagents. We believe a valuable resource of robust and validated affinity reagents will support diverse BRAIN initiative projects including multiplexed spatial protein mapping of cell types and fine neuroanatomical structures of the brain in 3D.

KEYWORDS: *Cell Type/Interactions; Integrated Approaches; Dissemination & Open Science/Education*

Circuit-specific neuromodulation via highly sensitive inhibitory opsin eOPN3 in a gyrencephalic brain

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Electrical neuromodulation broadly activates heterogeneous neural pathways, lacking cellular specificity. Optogenetic approaches provide cell-type-specific control but face translational barriers in gyrencephalic brains due to insufficient opsin sensitivity and the limited deep-tissue penetration of illumination. The objective of this study was to evaluate circuit-specific optogenetic neuromodulation in a large-animal model utilizing eOPN3, a Gi/o-coupled, inhibitory opsin exhibiting light sensitivity three to four orders of magnitude greater than microbial ion-pumping rhodopsins.

Adeno-associated viral vectors (AAV5/9-CaMKII-eOPN3-mScarlet) encoding eOPN3 were delivered to the hippocampus (HPC) of two Göttingen mini-pigs during MRI-guided stereotactic surgery. Green light HPC illumination was combined with electrical stimulation (0.2 Hz, 6 mA, 250 μ s) to the anterior nucleus of the thalamus (ANT) to induce single-pulse evoked response potentials (ERP) propagating to HPC through the Papez circuit. Acute epileptiform activity was induced via intracerebral kainic acid (KA) administration (1 μ g/ μ l). Statistical inference utilized Generalized Linear Models evaluating discrete temporal epochs within each subject and False Discovery Rate correction.

Two subjects survived viral induction without adverse events, with histological analysis demonstrating robust mScarlet expression in excitatory HPC neurons and axons of both subjects. Optical activation of eOPN3 in the HPC demonstrated suppression of ANT-HPC connectivity by attenuating amplitude of HPC ERP by 65.7% (95% CI [-70.8%, -59.6%]; $p < 0.001$). Extended ERP attenuation persisted for several minutes following the illumination cessation with reduction of 64.8% (95% CI [-69.5%, -59.4%]; $p < 0.001$). Illumination of HPC reduced KA-induced seizure activity by 56.2% (95% CI [-61.6%, -50.0%]; $p < 0.001$) compared to pre-illumination seizure activity.

Our preliminary study demonstrates cell-type-specific optical inhibition via eOPN3 of ANT-HPC connectivity and KA-induced HPC seizure activity in a large mammalian brain. High optical sensitivity and robust, prolonged suppression kinetics demonstrate the feasibility of this platform for precision neuromodulation. Future clinical translation necessitates validation in chronic, awake models to evaluate long-term viability, optimize viral kinetics, and assess modulatory efficacy during spontaneous seizure activity and behavioral impacts of the HPC inhibition.

KEYWORDS: *Cell Engineering; Electrophysiology; Implantable Devices (probes, etc.); Integrated Approaches; Interventional Tools; Neural Networks (topology, etc.)*

Development of presynaptic networks to distinct cortico-cortical projection neuron populations in primary visual cortex

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How cell-type-specific synaptic connectivity is established over postnatal development remains poorly understood. We addressed this question by combining monosynaptic rabies virus tracing with tissue clearing and lightsheet imaging-assisted 3D atlas registration to map presynaptic networks onto genetically defined cortico-cortical projection neurons (CCPNs) in layers 2/3 and 5 of mouse primary visual cortex at P20 and adulthood (P60+).

Both L2/3 and L5 CCPNs received higher proportions of deep-layer (L5-6) inputs at P20 than in adults, indicating postnatal refinement of laminar input profiles. Bilateral neonatal enucleation produced an intermediate phenotype in L5 CCPNs, supporting partial experience-dependent regulation of this process. Long-range connectivity also differed between timepoints in a cell-type-specific manner: L2/3 CCPNs shifted from predominantly medial to lateral higher visual area inputs and from polymodal association toward sensory-motor thalamic nuclei, while L5 CCPNs showed no comparable areal shift.

These findings indicate that postnatal maturation of cortical input networks involves coordinated refinement of both laminar and long-range connectivity, with distinct trajectories for different projection neuron populations. This work also demonstrates the utility of atlas-registered rabies tracing as a scalable approach for mapping developmental connectomes at cell-type resolution.

KEYWORDS: *Cell Type/Interactions; Circuit Diagrams; Connectome; Developmental/Systems Biology*

Transcriptomic characterization of enhancer AAVs at the whole mouse brain scale

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The mouse brain is a highly complex and heterogeneous structure comprising thousands of diverse cell types. Genetic tools that can precisely and robustly label these populations are valuable assets for researchers interested in experimentally accessing or manipulating each of them. Since specific labeling of a target population is a prerequisite for a useful genetic tool, comprehensive characterization of the labeling patterns they produce prior to their distribution to the broader scientific community is crucial. To this end, we developed a pipeline for quantitative anatomical and molecular characterization of enhancer adeno-associated viruses (AAVs) and transgenic mouse lines, consisting of three independent modalities. All enhancers are initially screened via light sheet fluorescence microscopy, which provides volumetric imaging of the whole brain and a quantitative, spatially localized readout of all cells labeled by each enhancer AAV. Next, to confirm the transcriptomic identities of the labeled cells, we employ two complementary transcriptomic methods: 1) 10x Flex, which provides high cell type resolution of labeled cells at whole brain scale, and 2) BARseq, which provides transcriptomic identity of labeled cells at fine spatial resolution across select brain slices. Here, we present BARseq and 10x Flex data from a variety of different enhancer AAVs that were screened as part of this pipeline. We show that the cell type composition of each enhancer largely agrees between these two methods, as well as with light sheet data from the same viral constructs. Taken together, these three approaches allow us to comprehensively assess both spatial localization and cell type identity of labeled cells across the brain, allowing for optimal tool selection for diverse experimental designs. These characterization datasets will be released as part of the Allen Institute's Genetic Tools Atlas in early 2027 and may serve as a ground truth for models seeking to predict cell type composition based on spatial labeling patterns.

KEYWORDS: *Cell Type/Interactions; Computational Biology/Modelling; Genetics/Genomics; Molecular/Cellular Neuroscience*

BossDB: Advancing neuroscience with a robust ecosystem for storing, accessing, and analyzing high-resolution images, annotations, and connectivity data

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The NIH BRAIN Initiative Informatics Program was established to develop data archives, community standards, and computational tools supporting analysis of increasingly large and complex neuroscience datasets. As part of this effort, the Brain Observatory Storage Service and Database (BossDB) serves as an NIH-supported data archive and ecosystem for storage, access, annotation, visualization, and analysis of high-resolution neuroimaging data, particularly those derived from electron microscopy and X-ray micro- and nanotomography. In adherence to FAIR principles, BossDB provides scalable access across multiple interfaces, managing more than five petavoxels of imaging data spanning multiple species, modalities, and research programs. BossDB supports a broad ecosystem of community tools, including Neuroglancer for 2D/3D visualization, NeuPrint for connectomic analysis, and DotMotif for motif-based graph querying, enabling researchers to move fluidly from data access through connectomic analysis. Here, we present ongoing developments that extend these capabilities within the BossDB ecosystem. Metadata and provenance extensions introduce structured dataset annotation, version tracking, and cross-linking of BRAIN CONNECTS resources, establishing traceable relationships among imaging datasets, annotations, connectivity measurements, and derived analysis products that support multimodal and comparative analyses across the broader research community. BossDB now additionally hosts a Connectome Annotation Versioning Engine (CAVE) service, providing annotation tables, dynamic segmentations, and spatially indexed annotations linked directly to source image data and segment identities. This integration supports collaborative proofreading and structural annotation at scale, while maintaining explicit provenance across curated annotations, segmentation results, and underlying imaging data. Further, new data validation workflows provide automated quality assessment and generation of derived connectivity measurements, including contactome metrics computed from large imaging volumes, with results tied to source datasets and provenance records to enhance transparency and reproducibility. Looking ahead, we are working towards creating a unified data-access layer to streamline interoperability with distributed neuroscience resources and established analysis pipelines, positioning BossDB as an increasingly cohesive infrastructure for open collaborative connectomics research.

KEYWORDS: *Circuit Diagrams; Connectome; Informatics, Statistics, or Applied Mathematics; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

A high-resolution postnatal mouse brain atlas framework for mapping spatiotemporal cellular dynamics

PRESENTER: **I.E. Bjerke**

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Developmental 3D mouse brain atlases serve as key spatial frameworks to examine spatiotemporal dynamics of region-specific cellular changes. Different tissue clearing and imaging methods introduce unique contrast and volume changes, raising the need for modality specific atlases. To address this challenge, we established a workflow to create a set of light sheet fluorescence microscopy (LSFM)-based atlases covering every other postnatal day from birth to two weeks of age (P0-P14), and the adult (P56). Brains were labelled with Sytox Deep Red nuclear stain, cleared using the SHIELD method, followed by LSFM imaging. High-resolution, multi-contrast symmetric atlas templates were generated using the ANTs registration toolkit. Region annotations were imported by registering our templates to the Allen mouse brain Common Coordinate Framework and validated using cell type markers. Using the nuclear stained datasets, we quantified spatiotemporal cellular growth patterns across the first two weeks of mouse brain development. Cell numbers reach steady state at P14 for most brain areas, except in the hindbrain, where they continuously increase until P28. Brain region volume increases were high relative to those of total cell counts, resulting in a consistent decrease in cell density across all brain regions. Our data provides the first pan-cellular, brain-wide quantification of postnatally developing mice, providing foundational insights into the dynamics of brain development.

KEYWORDS: *Developmental/Systems Biology; Neuroimaging (invasive, non-invasive imaging)/Radiology; Theory & Data Analysis Tools; Cell Type/Interactions*

CONNECTS-Proof: A scalable framework for automated connectome proofreading and validation

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Continued advances in electron microscopy (EM) imaging and automated segmentation have enabled neural circuit reconstruction at unprecedented scales, making proofreading the primary bottleneck in generating accurate connectomes. Reconstruction errors remain a significant obstacle to producing analysis-ready datasets, while manual proofreading requires substantial expert effort and does not effectively scale to increasingly large datasets, such as a whole mouse brain.

We present CONNECTS-Proof, a framework for connectome proofreading that integrates automated error detection and correction, human-in-the-loop validation, and high-throughput deployment of segmentation edits. The framework combines NEURD 2.0, machine learning-based proofreading, with NeuVue, a cloud-native validation environment, which interoperates with community infrastructure including Neuroglancer and the Connectomics Annotation Versioning Engine (CAVE). Whereas NEURD 1.0 used graph-based heuristics to identify specific classes of reconstruction errors, NEURD 2.0 employs learned classifiers trained on NEURD-derived morphology, topology, and synaptic features, enabling improved generalization and automated detection of both merge and split errors across large datasets.

The framework was evaluated on two one-cubic-millimeter mouse visual cortex datasets from the MICrONS program and AIBS, Minnie and V1DeepDive (V1DD) respectively. NEURD 2.0 achieved >95% precision for merge-error detection, producing more than 500,000 high-confidence merge corrections benchmarked against human expert proofreaders on V1DD. A complementary split-error framework achieved 93.4% top-5 recall on Minnie35. NeuVue was extended to support efficient validation of machine-generated edits through adaptive task prioritization and multi-dataset visualization.

Using this workflow, approximately 524,000 automated split edits were deployed to the V1DD dataset, removing nearly 4 million false synapses. These results demonstrate an automated proofreading workflow that substantially reduces manual effort and supports connectome reconstruction at scales required for whole-mouse-brain mapping.

KEYWORDS: *Circuit Diagrams; Connectome; Software (analysis, etc.) and Engineering*

Integrated retinal image functionality in image sensors

PRESENTER: **S. Snyder**

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The mammalian retina performs rich spatiotemporal computation before visual information reaches the brain, extracting behaviorally relevant signals such as object motion, looming threats, and motion prediction under severe bandwidth and energy constraints. Modern frame-based and event-based cameras capture portions of this process, but they separate sensing from feature computation, leaving downstream processors to infer decision-critical structure from dense and redundant data.

We present Integrated Retinal Image Functionality in Image Sensors (IRIS), a neuroscience-algorithm-hardware co-design framework that translates retinal circuits into sensor-level visual intelligence. IRIS focuses on three retinal computations with direct relevance to closed-loop behavior: object motion sensitivity, looming detection, and motion prediction. Object motion sensitivity uses center-surround suppression to distinguish independently moving objects from global ego-motion. Looming detection uses ON/OFF synaptic imbalances to identify rapidly approaching objects that may indicate potential threats. Motion prediction uses temporally offset excitatory and inhibitory pathways to estimate future object position from recent history.

These computations are implemented as compact algorithmic models and mapped to mixed-signal CMOS circuits suitable for 3D-integrated image sensors. By embedding feature extraction near the photodetector array, IRIS reduces reliance on high-bandwidth frame transfer and computationally expensive post-processing. Across representative demonstrations, the framework preserves task-relevant visual information while reducing complexity: object motion sensitivity is achieved with 80 parameters compared with a 40k-parameter neural networks, looming detection operates at 0.36 pJ per spike, and motion prediction operates at 18.56 pJ per prediction.

Together, these results suggest a pathway from retinal neuroscience to deployable neurotechnology: image sensors that compute behaviorally meaningful visual features as they acquire data. IRIS provides a modular platform for studying how biological visual circuits inspire adaptive, low-power perception for autonomous systems, neuro-inspired devices, and future brain-inspired artificial intelligence.

KEYWORDS: *Cell Type/Interactions; Circuit Diagrams; Computational Biology/Modelling; Integrated Approaches; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering*

Whole-brain quantitative anatomical and transcriptomic characterization of enhancer AAVs for cell type-specific targeting

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The mouse brain comprises hundreds of cell types, each contributing to different facets of behavior and cognition. While advanced single-cell sequencing has defined their molecular identities, understanding individual roles in brain function requires genetic tools that enable selective manipulation or activity monitoring of each cell type. To achieve cell type-specific labeling, we leveraged single-nucleus ATAC-seq (snATAC-seq) data to identify putative enhancers—cis-regulatory DNA elements driving cell type-specific gene expression—and screened for their selective activity using systemically delivered AAVs expressing a reporter. While this yielded many useful reagents, enhancer selection and characterization remained largely qualitative and limited to select brain regions.

Here, we present an improved pipeline for quantitative anatomical and molecular characterization of enhancer-driven labeling patterns. Putative enhancers were cloned into AAV backbones driving expression of the nuclear fluorophore mScarlet-H2B or the mutated recombinase iCre(R297T). Viral vectors were packaged with PHP.eB and delivered systemically to WT or H2B-EGFP cre reporter mice. After a 4-week incubation, brains were extracted, fixed, and cleared for whole-brain light-sheet fluorescence microscopy. Images were registered to the Allen CCF, with nuclear-localized signal enabling cell identification and brightness quantification. High-selectivity enhancers were further evaluated using 10xFlex or BARseq to determine the molecular identity of labeled cells.

To contextualize light-sheet data, we trained a point transformer model on Allen Brain Cell Atlas MERFISH data to infer subclass identity of CCF-registered cells, enabling estimation of enhancer specificity and completeness at early screening stages. 10xFLEX and BARseq data validated model predictions. Finally, results from ~1,400 screened enhancers were used to train a random forest classifier to predict top-performing enhancers across all 338 AiT21 subclasses. This trimodal approach with model-based prediction enables comprehensive, quantitative nomination and characterization of enhancer-AAV tools at scale, accelerating development of a complete genetic toolkit for accessing the full transcriptomic diversity of mouse brain cell types.

KEYWORDS: *Cell Type/Interactions; Genetics/Genomics; Molecular/Cellular Neuroscience; Computational Biology/Modelling*

Systemic non-viral nanovectors enable brain-targeted RNA delivery and therapeutic genome editing for Alzheimer's disease

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Efficient systemic delivery of RNA and genome-editing machinery to the brain remains a major barrier to disease-modifying therapies for neurological disorders. We developed an engineered nonviral nanovector platform for intravenous administration and evaluated its ability to cross the blood-brain barrier without exogenous disruption, distribute to the cortex and hippocampus, and deliver functional RNA cargo in vivo. In Ai14 Cre-reporter mice, systemic Cre recombinase messenger RNA delivery induced widespread tdTomato reporter activation across both hemispheres, including in neurons, microglia, and astrocytes. We then applied this platform to amyloid precursor protein (APP) C-terminal editing in APP-SAA knock-in mice, a humanized Alzheimer's disease model that preserves endogenous APP regulation. Five intravenous doses co-delivering CRISPR-associated protein 9 messenger RNA and an APP-targeting single-guide RNA induced APP editing in the cortex and hippocampus and reduced APP protein levels in both regions. In an early-intervention cohort treated at 6 weeks of age, editing and APP reduction persisted to 8 months and were accompanied by reduced amyloid-beta plaque burden, reduced tau phosphorylation, attenuated glial activation and inflammatory cytokine responses, improved neuronal preservation, and improved behavioral performance. Treatment was well tolerated, with no detectable systemic toxicity under the tested conditions. As a broader demonstration of functional RNA delivery, the platform also delivered messenger RNA to brain reward-associated regions and modulated reward-related behavioral output. These findings support systemically administered nonviral nanovectors as a modular platform for brain-targeted RNA delivery and in vivo genome editing for Alzheimer's disease and other central nervous system disorders.

KEYWORDS: *Genetics/Genomics; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Interventional Tools; Molecular/Cellular Neuroscience; Cell Engineering*

Multimodal alignments of in vivo imaging and spatial biology datasets at cellular resolution

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Parallel revolutions in intravital microscopy and spatial biology techniques have respectively enabled large-scale recordings of cellular dynamics in live animals and multi-dimensional molecular profiling at single-cell resolution. However, due to the challenges of aligning data from different modalities at cellular resolution, these two transformational approaches have generally been applied on separate biological samples, stymying the ability to link activity patterns and molecular attributes in the same exact cells. To enable routine, multimodal investigations of cells' in vivo dynamics and molecular content, we created TRU-FACT (Total Registration Under Functional Activity, Connectivity, and Transcriptomics), a broadly applicable experimental and computational pipeline for registering large populations of individual cells across intravital imaging and spatial biology datasets. The pipeline combines three key innovations: an optomechanical tissue handling and alignment method to parallelize specimen planes, a graph-theoretic method to register individual cells based on their geometric relationships to neighboring cells, and a statistical framework that provides for each cell an a posteriori probability of correct registration. We validated TRU-FACT with several preparations for imaging neural Ca^{2+} activity in cortical and deep brain areas in head-fixed and freely behaving mice, RNA-barcode-expressing viruses for labeling neural projections, and low- and high-plex spatial transcriptomic methods, yielding >10,000 total cell matches. Overall, TRU-FACT constitutes a scalable, multimodal discovery platform that is applicable to diverse tissue-types and spatial biology techniques, thereby enabling multiscale analyses of many complex biological systems.

KEYWORDS: *Cell Type/Interactions; Connectome; Informatics, Statistics, or Applied Mathematics; Molecular/Cellular Neuroscience; Monitor Neural Activity; Theory & Data Analysis Tools*

Population-level detection of subthreshold inhibition in chat-positive neurons of the septal nucleus: Ex vivo GEVI voltage imaging study

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Acetylcholine (ACh), released by neurons of the basal forebrain and septal nuclei, plays critical roles in attention and learning. Cholinergic signaling is disrupted in Alzheimer's disease and contributes to cognitive and memory deficits. To investigate how cholinergic circuits process synaptic inputs in healthy mice, we used the genetically encoded voltage indicator (GEVI) ASAP2s to monitor membrane potential dynamics in choline acetyltransferase (ChAT)-expressing neurons. Selective expression of ASAP2s was achieved by crossing TIGRE2-ASAP2s (Ai169) mice with ChAT-Cre mice, resulting in stable, brain-wide expression. In acute coronal brain slices, weak ASAP2s fluorescence was observed in the neocortex, reflecting the sparse distribution of cholinergic cells, whereas strong fluorescence was detected in the septal nuclei. Electrical stimulation of either region evoked detectable optical responses. Notably, stimulation of the medial prefrontal cortex (mPFC) produced hyperpolarizing responses in the ChAT-labeled population of the lateral septum (LS). Blockade of GABA-A receptors with gabazine (4 μ M) converted these hyperpolarizations into depolarizing responses, revealing a net excitatory drive from the mPFC to LS neurons that is normally masked by strong local inhibition. These findings suggest that afferent excitatory inputs to ChAT-expressing LS neurons are tightly regulated by local GABAergic circuitry, consistent with the predominantly inhibitory composition of the LS. Next, we investigated functional segregation within the LS using simultaneous whole-cell recordings and GEVI imaging. In response to the same afferent stimulation, non-ChAT neurons exhibited excitatory postsynaptic potentials (EPSPs), whereas neighboring ChAT-expressing neurons displayed inhibitory postsynaptic potentials (IPSPs). During EPSPs recorded from individual non-ChAT neurons, the surrounding ChAT-labeled population underwent synchronized hyperpolarization, revealing a spatially organized inhibitory network response that would be difficult to detect with conventional electrophysiology, and completely inaccessible to calcium imaging. Our findings provide new insights into information processing in lateral septal circuits and highlight the unique value of GEVIs for dissecting excitation-inhibition interactions in neuromodulatory networks.

KEYWORDS: *Cell Type/Interactions; Circuit Diagrams; Connectome; Electrophysiology; Neuroimaging (invasive, non-invasive imaging)/Radiology; Neural Networks (topology, etc.)*

Astrocytic HIF-1 α drives HIV-associated Alzheimer's-like pathology: Therapeutic targeting using extracellular vesicle-mediated siRNA delivery

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Despite the success of combination antiretroviral therapy (cART) in extending the lifespan of people with HIV (PWH), nearly 50% continue to experience HIV-associated neurocognitive disorders (HAND), frequently accompanied by Alzheimer's-like neuropathology. Accumulating evidence indicates that amyloid- β (A β) deposition occurs in a substantial proportion of middle-aged PWH receiving cART, suggesting overlapping mechanisms between HAND and AD. We previously demonstrated that HIV-1 Tat induces astrocytic amyloidogenesis by activating hypoxia-inducible factor-1 α (HIF-1 α), leading to the release of amyloid-enriched astrocyte-derived extracellular vesicles (ADEVs). Exposure of primary hippocampal neurons to Tat-ADEVs reduced dendritic complexity, spine density, synaptic protein expression, and postsynaptic currents. Silencing of astrocytic HIF-1 α reduced the release of ADEVs and their amyloid cargos and also ameliorated neuronal injury. Moreover, hippocampal administration of Tat-ADEVs in naive mice induced cognitive deficits, amyloid accumulation, and synaptic degeneration, effects that were attenuated by silencing astrocytic HIF-1 α . Building on these findings, we investigated whether therapeutic targeting of astrocytic HIF-1 α could reverse HIV-associated AD-like pathology in vivo. Using HIV-infected CD34+ NSG humanized mice, we intranasally administered ADEVs loaded with HIF-1 α -targeting siRNA to achieve non-invasive brain delivery. This intervention significantly reduced brain expression of HIF-1 α , amyloid precursor protein (APP), oligomeric A β , amyloid fibrils, and phosphorylated tau, while attenuating astrocyte and microglial activation. HIF-1 α silencing also partially restored synaptic protein expression in the hippocampus and cortex and improved deficits in spatial memory and anxiety-like behaviors. Collectively, these findings identify astrocytic HIF-1 α as a critical upstream regulator of HIV-associated amyloid pathology and neurodegeneration. Furthermore, they establish ADEV-mediated delivery of HIF-1 α siRNA as a promising, targeted, and non-invasive therapeutic approach for HAND and HIV-associated Alzheimer's-like neurodegenerative disorders.

KEYWORDS: *Behavioral Sciences/Psychology; Cell Type/Interactions; Genetics/Genomics; Integrated Approaches; Molecular/Cellular Neuroscience; Synaptic Plasticity*

AutoBIDSify: Harmonizing heterogeneous neuroimaging datasets across community standards

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Neuroimaging datasets are increasingly shared for neural network training and secondary data analysis, but many remain difficult to reuse because they are organized in study-specific schemes and contain diverse data formats with poor descriptions and insufficient metadata. Increasingly complex neuroimaging study paradigms also require multimodal scans and rich auxiliary measurements, including physiological data, facial expression and gesture tracking, head surface acquisition, and digitization. Lack of standardization in file organization greatly hampers their findability and reusability. Emerging community standards such as the Brain Imaging Data Structure (BIDS) and the Shared Near-Infrared Spectroscopy Format (SNIRF) have improved interoperability. Nonetheless, converting lab-specific datasets to standard-compliant forms can be time consuming. As standards continue to evolve, maintaining separate format-specific conversion workflows introduces additional overhead.

We have developed AutoBIDSify, a large language model (LLM)-first framework for harmonizing heterogeneous neuroimaging datasets across community standards. AutoBIDSify automatically scans metadata in diverse data files and custom file/folder naming conventions, and uses the semantic reasoning capability of the LLM to form a systematic understanding of the input datasets, including subject indexing, session, task, and measurement structure, from which it creates a dataset-adaptive conversion strategy to produce standard-compliant datasets.

To mitigate hallucination and non-deterministic outputs from LLMs, AutoBIDSify executes the final file conversion and validation steps using deterministic processes. This allows AutoBIDSify to adapt to heterogeneous datasets while maintaining reproducible and auditable outputs. AutoBIDSify can convert diverse datasets to BIDS with a fully automated pipeline, including the generation of dataset-level metadata files, participants.tsv files, and subject-level data structures. It can be extended to streamline conversion to emerging formats such as NeuroJSON, Neurodata Without Borders (NWB), and Zarr.

AutoBIDSify provides a practical pathway for reducing the burden of neuroimaging data standardization and improving interoperability across neuroscience datasets. By combining evidence-driven semantic reasoning with deterministic execution, it supports data sharing, secondary analysis, and integration across evolving neuroimaging data standards.

KEYWORDS: *Dissemination & Open Science/Education; Integrated Approaches; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Informatics, Statistics, or Applied Mathematics*

EMBER: NIH BRAIN's secure, collaborative multi-modal data ecosystem for human and animal behavioral neuroscience

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NIH BRAIN, through the Brain Behavior Quantification and Synchronization (BBQS) program, has pushed the envelope on behavioral neuroscience across human and non-human animal species. As it enters Year 3, the BBQS consortium is generating an unprecedented collection of high-fidelity brain, behavior, and physiology data concurrently collected in complex social and physical environments. To foster collaboration on these data across research teams, paradigms, and species, the BBQS program commissioned the development of the Ecosystem for Multi-modal Brain-behavior Experimentation and Research (EMBER) data archive. EMBER's core infrastructure consists of three main components: (1) an open data sharing platform (EMBER-DANDI) that leverages the BRAIN Initiative's DANDI archive, (2) a secure resource for storing sensitive human data (EMBER-Vault), and (3) a computational sandbox environment for data staging, exploration, processing, and analysis (EMBER-Hearth). Both EMBER-Vault and EMBER-Hearth are distinguishing factors from existing data archives. EMBER-Vault provides secure storage for sensitive human data while enabling controlled sharing with approved researchers. Sensitive raw data, including video and audio recordings, are protected through multiple layers of security, including multi-factor authentication, role-based permissions, and encryption during transit and storage. This approach balances data protection with scientific discovery, promoting reproducibility, secondary data use, and future discoveries within the boundaries of established IRB protocols and data-sharing constraints. Complementing these capabilities, EMBER-Hearth connects EMBER datasets to analysis tools and secure cloud computing resources. A crucial enabler of this is integration with the Pennsieve platform, a cloud-based backend for scalable execution of containerized analysis workflows. As an initial demonstration of capabilities, we have implemented a cloud-based workflow for training and deploying Social LEAP Estimates Animal Poses (SLEAP), an open-source framework for multi-animal pose tracking, on EMBER-hosted data using Pennsieve-managed AWS resources. Together, EMBER enables hosting multimodal neurobehavioral data across species, including sensitive human data, and analyzing these data with community-developed tools, advancing the BBQS vision of collaborative research to accelerate the understanding of the neural basis of behavior.

KEYWORDS: *Behavioral Sciences/Psychology; Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Neural Recording & Modulation*

AqNWB: Enabling data acquisition in the Neurodata Without Borders data standard

PRESENTER: **O. Ruebel**

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The goal of this project is to enhance the sustainability and impact of AqNWB, an open C/C++ API for enabling direct data acquisition in the Neurodata Without Borders (NWB) data standard. With the increasing adoption of NWB as the leading format for sharing neurophysiology data, there is a pressing need to support its use throughout the entire data lifecycle; from acquisition and processing to analysis, publication, and reuse. However, currently researchers typically acquire their data in acquisition-system-specific formats and then later convert their data to NWB for analysis and sharing. Recording neurophysiology data directly in NWB is crucial for enabling its adoption in laboratory research practices throughout the data lifecycle. Currently, NWB software APIs primarily target Python (PyNWB) and Matlab (MatNWB), which are widely used for data conversion, processing, analysis, and visualization. However, most data acquisition systems rely on C/C++ for high-performance integration with hardware. To address this gap, we have developed AqNWB, a lightweight and flexible C++ API for NWB. AqNWB can be integrated with data acquisition software for recording data in NWB, while maintaining the high-performance capabilities offered by C++. We will present the design and approach of AqNWB, discuss key features, and present progress towards integration of NWB with existing data acquisition software.

KEYWORDS: *Behavioral Sciences/Psychology; Dissemination & Open Science/Education; Software (analysis, etc.) and Engineering; Electrophysiology*

Ten years of NWB: Advancing standardization of neurophysiology data

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Understanding the brain requires integrating knowledge across diverse scales, species, and conditions. Technical hurdles in data sharing and integration often impede this understanding. Neurodata Without Borders (NWB) addresses this friction by providing a common data standard for neurophysiology and behavior. Over its 10-year history, NWB has evolved from a small community effort into a leading platform for reproducible, collaborative neuroscience research. The DANDI archive now hosts over 500 public datasets, comprising 500TB of data across 200,000 files from 150+ labs worldwide. Furthermore, the ecosystem has expanded significantly: 40+ community tools now integrate with NWB; 30+ extensions support new methods ranging from pose estimation to *C. elegans* volumetric imaging; and 180+ publications have reused NWB data for secondary analysis.

The NWB software stack features production-ready Python and MATLAB APIs (PyNWB and MatNWB) and NeuroConv supports conversion from 55+ proprietary formats. NWB GUIDE enables no-code conversion for non-technical users and NWB Inspector ensures compliance with the NWB standard and FAIR data practices. NWB integrates with many modern technologies (e.g., data streaming and advanced I/O via Zarr and HDF5 for efficient cloud storage and analysis and enhanced metadata for linking to ontologies and external resources). Recent innovations include LINDI, an efficient “virtual” representation of NWB data where large data chunks are accessed on demand, AqNWB, a C++ API enabling direct NWB recording during data acquisition, and a formal process for enhancing the NWB standard governed by the NWB Technical Advisory Board.

Looking ahead, support for virtual datasets will streamline conversion and enable cross-source data linking. AI systems will further lower barriers to reuse by automating data curation and generating tailored educational materials. Finally, cross-standards efforts, including BIDS BEP32, HED integration, and LinkML harmonization, will bridge neurophysiology with the broader neuroscience data ecosystems, creating analysis-ready datasets optimized for cloud computing and AI model training.

KEYWORDS: *Dissemination & Open Science/Education; Electrophysiology; Integrated Approaches; Software (analysis, etc.) and Engineering; Behavioral Sciences/Psychology*

PIASO: An atlas-scale tool to dissect cell type heterogeneity and specific enhancers

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Single-cell multiome assays jointly profile chromatin accessibility and gene expression at single-cell resolution, but analyzing atlas-scale datasets of millions of cells is constrained by the memory cost of materializing full count matrices. We present PIASO (Precise Integrative Analysis of Single-cell Omics), a streaming framework that processes single-cell multiome and scATAC-seq data from raw fragments to annotated cell types in bounded memory. Built on Cytome, a compressed, fragment-centric storage format for multimodal single-cell data, PIASO streams every downstream operation, including peak calling, peak quantification, normalization, and dimensionality reduction, without materializing the full matrix. At its core is a unified cell type specificity metric (COSG) that drives specificity-aware peak calling (PICCO), gene activity inference, and cell type prediction across modalities. PICCO weights coverage pileups by cell type specificity, enabling fully unsupervised analysis. At atlas scale, PIASO matches the accuracy of existing tools while substantially reducing memory and compute cost. Applied to the mouse brain, PIASO identified enhancers with high selectivity for distinct cortical interneuron subtypes and dopaminergic neurons, which we functionally validated with rAAV vectors, confirming their cell type-specific activity *in vivo*. Applied to human cortex multiome data, PIASO integrates chromatin and expression specificity to map disease heritability to specific cell types, resolving distinct cellular enrichment profiles for childhood-onset versus late-diagnosed attention-deficit/hyperactivity disorder (ADHD). PIASO unifies scalable computation, principled specificity scoring, and *in vivo*-validated enhancer discovery in a single framework for cell type-resolved regulatory genomics across single-cell modalities. PIASO is available at <https://piaso.org>.

KEYWORDS: *Cell Type/Interactions; Computational Biology/Modelling; Developmental/Systems Biology; Genetics/Genomics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Advancing neurodata stewardship for secondary analysis: Findings from the BRIDGE Brain Data Governance Project

PRESENTER: **M. Botes**

The University of Texas at Austin

AUTHORS: M. Botes

The rapid expansion of neuroscience data has created unprecedented opportunities for secondary analysis, data integration, and collaborative discovery. However, realizing these opportunities requires governance mechanisms that enable responsible access, sharing, and reuse of neurodata across institutions and jurisdictions. Secondary reuse remains constrained by fragmented governance frameworks, inconsistent consent requirements, uncertainty regarding de-identification standards, and limited practical guidance for researchers. As neuroscience increasingly embraces open science and data-intensive research, governance and stewardship must evolve to support both scientific innovation and trustworthy management of sensitive brain data.

This poster presents findings from the BRIDGE Brain Data Governance Project, an interdisciplinary initiative examining the legal, ethical, technical, and operational challenges associated with sharing and reusing brain data across four global regions. The project identifies barriers to secondary analysis and develops practical tools to support researchers, institutions, and data stewards throughout the research lifecycle.

The BRIDGE Project conducted a comparative legal and regulatory analysis of data protection, research governance, and cross-border data-sharing requirements across Africa, Latin America and the Caribbean, Europe, and North America. These findings informed the development of the BRIDGE Neurodata Governance Toolkit, comprising five practical tools to facilitate responsible neurodata stewardship and cross-jurisdictional data sharing.

The analysis identified five recurring challenges: (1) inconsistent consent models for future and secondary neurodata use; (2) uncertainty regarding de-identification and privacy safeguards; (3) barriers to cross-border data sharing arising from divergent legal requirements; (4) limited governance harmonization tailored to neurodata; and (5) insufficient practical guidance for responsible data access, sharing, and reuse. Together, these barriers impede FAIR and open science objectives and constrain opportunities for secondary analysis. The BRIDGE Neurodata Governance Toolkit addresses these challenges by supporting researchers in identifying governance requirements, assessing data-sharing pathways, and navigating regulatory considerations for secondary neurodata reuse.

Governance should be recognized as a core component of neuroscience research infrastructure.

KEYWORDS: *Integrated Approaches; Interventional Tools; Neuroethics, Philosophy, Law; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Dissemination & Open Science/Education*

Connectome quality converges predictably to reveal optimal stopping points during proofreading

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Volumetric electron microscopy (EM) has become a critical approach to generating high-resolution reconstructions of brain tissue. As the size of EM volumes increase, use of automated image segmentation within the reconstruction pipeline has become essential, although it generates errors that need correction. The proofreading and correcting of these errors has since become the dominant cost driver in the pipeline, but precisely estimating the sufficient number of proofreading edits to enable meaningful scientific analyses of the reconstructed neuronal networks remains a challenge. We present a fast, computationally inexpensive way to estimate the progress of a connectomic proofreading effort without requiring a priori knowledge of ground truth. We show that simple global graph invariants converge predictably to asymptotic limits with increasing numbers of proofreading edits, informing a quantitative “pencils down” criterion for proofreading completeness. We illustrate our method on two datasets in different stages of proofreading progress: a zebrafish spinal cord and the drosophila hemibrain. Our method reduces the uncertainty associated with the planning and prioritization of proofreading activities and enables data owners to accurately predict and budget the amount of proofreading necessary for their scientific questions.

KEYWORDS: *Connectome; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

ADInteractome: Discovering Alzheimer's disease-associated gene interactions from single-nucleus RNA-seq data through neural interaction states

PRESENTER: **Z. Xu**
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Alzheimer's disease (AD) is a prevalent neurodegenerative disorder characterized by amyloid beta plaques and tau tangles, yet its molecular mechanisms remain elusive. Advances in single-nucleus RNA sequencing (snRNA-seq) have provided profound insights into the cellular heterogeneity of AD-associated brains. In this study, we introduce ADInteractome, an interpretable artificial intelligence framework designed to discover gene interactions associated with AD directly from the internal state of neural networks trained on the snRNA-seq data of brain cells. The method is based on the intuition that if a neural network can accurately classify AD-associated cell types based on their snRNA-seq data, then its internal interaction states, reflecting interaction patterns within the gene expression data, are informative for identifying biologically meaningful gene interactions. Applied to a large-scale snRNA-seq dataset from the Seattle Alzheimer's Disease Brain Cell Atlas, ADInteractome reveals cell-type-specific and AD-associated gene circuits validated by existing literature. The results were further validated by our virtual knock-out and knock-in experiments, a novel concept to validate our findings through a data-driven approach. Compared to traditional co-expression network methods, it achieves higher accuracy in associating gene expression with AD and uncovers novel interaction patterns. These findings highlight the potential of interpretable AI approaches for elucidating complex molecular interactions in neurodegenerative disease.

KEYWORDS: *Computational Biology/Modelling; Genetics/Genomics; Molecular/Cellular Neuroscience; Informatics, Statistics, or Applied Mathematics*

BRAINCELL-AID: An agentic AI-created brain cell type resource for community annotation

PRESENTER: **R. Li**

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Single-cell RNA sequencing (scRNA-seq) has transformed our ability to resolve the cellular diversity of the brain. Significant breakthroughs such as the brain cell atlas of the whole mouse brain curated by the Allen Institute have introduced great potential in deciphering of the mammalian brain. However, annotating biological functions for thousands of transcriptionally defined cell clusters emerging from such large atlases remains a major bottleneck. Although we know their signature marker gene sets to infer cell type functions, existing gene set annotation methods face their limitations. Conventional enrichment-based methods depend on predefined gene sets, which are often incomplete for brain-specific contexts, and large language models (LLMs) are limited by hallucinations and weak grounding. To address this, we developed a multi-agent AI system to generate reliable, literature-grounded functional annotations for brain cell types from their defining marker gene sets. We first fine-tuned LLMs on curated gene sets from the Molecular Signatures Database (MSigDB), each linked to a Gene Ontology (GO) term, teaching principles of biological functions. The fine-tuned model will generate the initial annotations of the cell type marker genes, which is then refined by an AI agent in our system conducting retrieval-augmented generation (RAG). This grounds predictions in peer-reviewed literature from PubMed to reduce hallucinations and improve interpretability. The system takes marker gene sets derived from cell clusters and returns consolidated, literature-supported annotations. Its performance was evaluated using accuracy and semantic similarity metrics, and domain experts have validated their biological relevance.

Our task-specific fine-tuned models consistently outperformed existing methods across benchmark gene sets, and RAG further improved prediction reliability. Trained and evaluated on over 7,000 gene sets from MSigDB, our model achieved 77% accuracy on mouse and 74% accuracy on human sets with the top predictions when assisted by the RAG component. The system was applied to 5,322 mouse whole-brain clusters, and it produced biologically meaningful cell-type descriptions validated by domain experts. This open, expert-reviewed resource bridges raw scRNA-seq data and interpretable brain cell-type annotation, reducing manual curation effort and supporting community-driven construction of brain cell annotations.

KEYWORDS: *Cell Type/Interactions; Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering*

Deep multi-view graph learning of fNIRS for brain cognitive state decoding

PRESENTER: **J. Zhang**
Temple University

AUTHORS: J. Zhang, Q. Zhang

Understanding brain activity patterns is essential for revealing the underlying mechanisms of human cognition for advanced brain-computer-interaction (BCI) technologies. Recent developments in non-invasive neural sensing have created new opportunities but decoding brain states from subtle brain signals is still challenging. In this study, we present a graph-based deep learning framework to uncover informative representations from noisy brain dynamics for cognitive state analysis. Specifically, we investigate cognitive workload estimation using functional near-infrared spectroscopy (fNIRS) signals. The proposed framework leverages a hierarchical graph learning strategy, where an initial graph representation module extracts discriminative spatial relationships among brain regions, followed by a feature integration stage that learns high-level patterns for cognitive state classification. To enhance the robustness and generalization capability of the model, we incorporate a multi-view representation mechanism that combines automatically learned features with carefully designed signal descriptors. Our experiments have demonstrated that the proposed approach achieves a classification accuracy of cognitive load levels outperforming existing state-of-the-art methods. This study demonstrates the potential of graph-based representation learning for decoding complex neural signals, thereby greatly advancing intelligent, portable, and next-generation BCI systems.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Neural Networks (topology, etc.); Monitor Neural Activity*

Neuro-symbolic architectures with vector symbolic representations for scalable brain-inspired computation

PRESENTER: **S. Snyder**

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Biological intelligence combines distributed neural activity with structured reasoning, memory, and rapid adaptation under severe energy constraints. In contrast, modern artificial intelligence systems increasingly rely on large-scale models and von Neumann computing substrates that impose substantial energy, latency, and memory costs. Vector Symbolic Architectures (VSAs), also known as Hyperdimensional Computing, offer a brain-inspired alternative by representing information as high-dimensional distributed vectors and performing symbolic computation through algebraic operations such as binding, superposition, and similarity-based retrieval.

We present Neuro-Symbolic Architectures (NSAs) as a framework for unifying distributed representation, symbolic reasoning, and hardware-aware computation. Unlike conventional neuro-symbolic AI, which typically combines neural networks with external logic systems, NSAs embed symbols, uncertainty, spatial structure, and memories directly into high-dimensional representational spaces. This enables compositional reasoning while preserving robustness to noise, graceful degradation, and compatibility with neuromorphic and in-memory hardware.

We highlight three representative applications. First, in robotic perception, VSA-based occupancy grid mapping encodes spatial observations into high-dimensional vectors, enabling probabilistic spatial inference through vector operations. This approach achieves accuracy comparable to state-of-the-art mapping methods while reducing latency and memory by 45x and 400x, respectively. Second, in memory-augmented reinforcement learning, hippocampal-inspired symbolic indexing enables efficient storage and retrieval of episodic memories for contextual and sequential decision-making. Third, in scientific discovery, high-dimensional representations provide an alternative to graph neural networks for materials property prediction, potentially mitigating over smoothing while improving compatibility with hardware-efficient computation.

Together, these examples suggest that NSAs provide a computational substrate for scalable, interpretable, and energy-efficient intelligence. By connecting principles from neural coding, associative memory, symbolic abstraction, and neuromorphic hardware, NSAs offer a path toward brain-inspired AI systems that can reason, remember, and adapt under real-world resource constraints. This framework also identifies open challenges in scaling distributed operations.

KEYWORDS: *Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

BrainSTEM: A collaborative electronic lab notebook for FAIR experimental neuroscience

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Reproducible and reusable neuroscience data depend not only on standardized file formats and open repositories, but also on the quality of experimental metadata recorded at the point of data collection. Despite substantial community investment in standards such as Neurodata Without Borders (NWB) and repositories including DANDI, OpenNeuro, and CRCNS, metadata standardization prior to repository submission remains largely unresolved. Experimental details are routinely scattered across handwritten notebooks, spreadsheets, and scripts, creating fragmented records that are difficult to query, poorly interoperable, and challenging to interpret outside the originating laboratory. As a result, shared neuroscience datasets often remain insufficiently documented for discovery, interpretation, and reuse.

BrainSTEM is a web-based, collaborative electronic lab notebook (ELN) designed to address this gap. Built around a standardized relational metadata model tailored to experimental neuroscience, it provides structured capture of subjects, surgical procedures, behavioral paradigms, data acquisition sessions, and experimental manipulations across diverse modalities, from electrophysiology and optical imaging to MRI and functional ultrasound. A shared taxonomy for brain atlases, species, strains, and behavioral categories promotes terminological consistency across laboratories. At the project level, an automated STAR Methods export tool generates structured methods sections from experimental records and performs a manuscript-level audit of incomplete fields prior to author submission. Programmatic access via a REST API supports integration with Python and MATLAB workflows, and ongoing NWB import from public DANDI datasets is enabling structured contextual annotation of deposited data. Granular, object-level access controls, including configurable permission levels and group-based access requests, support collaboration within and across multi-site research groups.

BrainSTEM is currently deployed across more than 70 laboratories in multiple countries, with over 350 users. Development is guided by continuous feedback from a multi-laboratory consortium and iterative user research with neuroscientists across experimental modalities. Rather than replacing existing community infrastructure, BrainSTEM provides the structured upstream metadata layer that makes deposited data more interpretable and reusable at scale, complementing established standards and repositories.

KEYWORDS: *Computational Biology/Modelling; Dissemination & Open Science/Education; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

A multimodal NeuroAI foundation model for real-time neuroscientific discovery

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Understanding the brain demands integration across heterogeneous data streams that existing tools handle in isolation. We present a multimodal NeuroAI foundation model that unifies images, volumes, videos, time-series signals, and molecular readouts within a single inference architecture capable of real-time cross-modal reasoning and analysis.

The core architecture employs a modality-agnostic encoding strategy that projects heterogeneous inputs into a shared latent representation space, enabling joint reasoning across data types that differ fundamentally in dimensionality, sampling rate, and biological scale. Task-specific decoding heads operate over this unified representation for downstream scientific and clinical tasks, while a continual learning framework allows the model to incorporate new modalities and experimental paradigms without catastrophic forgetting of prior knowledge.

A key design principle is zero-shot generalization: The model transfers learned cross-modal structure to novel data types and disease contexts without retraining, making it extensible across the lifespan of a research program and adaptable to emerging experimental technologies as they enter the field.

We demonstrate the platform across neurological and psychiatric applications including Alzheimer's disease, stroke, autism spectrum disorder, and major depressive disorder. Across these contexts, the model identifies interpretable cross-modal biomarkers linking neural circuit dynamics, behavioral phenotypes, and molecular profiles, surfacing structure that single-modality approaches consistently miss. In basic neuroscience workflows, the architecture supports population-level connectome analysis, neural decoding, and data-driven hypothesis generation from large heterogeneous cohorts.

Inference operates in real time, enabling integration into active experimental pipelines rather than post hoc analysis alone. The system is designed to scale across data modalities, cohort sizes, and research questions without architectural modification, establishing a shared computational substrate for neuroscience that reduces redundant model development across labs and institutions.

This work positions multimodal foundation models not as narrow diagnostic classifiers but as generalizable reasoning infrastructure across the neuroscience stack, from molecular and cellular phenotypes to systems-level dynamics and behavior, accelerating discovery at each scale.

KEYWORDS: *Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Using AI to automate the detection of oncocytes in post-mortem Alzheimer's-related choroid plexus brain tissue

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The choroid plexus (CP) is a structure in the brain that secretes cerebrospinal fluid and forms part of the blood-CSF barrier. Structural changes to the CP have been documented in Alzheimer's disease (AD), including the appearance of oncocytic epithelial cells with abundant, granular, eosinophilic cytoplasm. Identifying and quantifying these cells on digitized whole-slide images (WSI) is a laborious process that can take days of manual work per image. This study applies artificial intelligence to automate the detection and classification of oncocytic CP cells. WSIs from two independent cohorts were processed using the nuclear segmentation model HoVer-Net in order to detect and segment individual nuclei. Segmented nuclei were linked to expert-drawn oncocyte annotations through an overlap-based labeling rule, producing a dataset of 77,203 nuclei from 69 slides, of which 11,361 (14.7%) were labeled oncocytic. Statistical comparison revealed that oncocyte-positive nuclei were significantly larger and rounder than negative nuclei, with higher red-channel intensity. Five classifiers were evaluated using fivefold cross-validation split by slide. XGBoost achieved the highest mean AUROC of 0.8136 ± 0.0082 . Nuclear size and shape features, specifically minor axis length and circularity, were the most informative features during oncocyte identification. Ultimately, this pipeline reduces cell counting from days of manual work to minutes of computation and lays the groundwork for linking oncocyte burden to AD pathology.

KEYWORDS: *Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Molecular/Cellular Neuroscience*

A portable brain visualization engine that lives in your web browser

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Intracranial electroencephalography (iEEG) directly records from neuronal populations in the human brain with high temporal precision and spatial resolution. A critical problem for iEEG users, cutting across neuroscience, neurology, and neurosurgery, is visualizing the myriad data types generated during even routine clinical and research studies. Common software tools are expensive and close-sourced, locking data into a single vendor ecosystem and limiting the ability to share findings with others who lack the same software. Even sharing data with departmental colleagues can be stymied by restrictive licenses limiting installation to a single computer: sharing results then requires handing off a physical laptop or sending screenshots and PowerPoint files with no interactivity.

To overcome these problems, we developed the free and open-source RAVE brain viewer. Complete installation instructions for Mac, Windows, and Linux, along with documentation and tutorial videos, are available at <https://rave.wiki>.

Our viewer offers three key advantages. First, the visualization engine lives within a single HTML file. Imaging data, electrode locations, and functional data can be viewed by anyone with a web browser, and sharing data means simply sending a file: the data remain fully interactive. Second, the viewer supports a large array of 2D and 3D data types: datasets can be displayed by dragging and dropping files directly onto the viewer, including activity or connectivity data at individual brain voxels, surface nodes, or electrode contacts. Third, the viewer supports a growing number of next-generation electrodes, such as Precision Neuroscience micro-arrays. In a common use case, users visualize brain imaging, electrophysiological monitoring, and tractography streamlines together, using only a web browser and a single downloadable HTML file.

For users requiring more advanced data manipulation, such as co-registering CT/MRI, localizing electrodes, or warping subject data to template space, we also offer free, open-source downloadable software. Importantly, these tools can generate standalone RAVE brain viewers usable by others without installing any additional software.

Our newly released brain visualization engine provides access to multiple data types without requiring any software installation, integrating easily into existing workflows.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Electrophysiology*

Toward scalable molecular connectomics using pan-expansion microscopy, automated light-sheet imaging, robotics, consumable kits, and AI-assisted tracing

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The neural basis of information storage and computation remains incompletely understood. Although large-scale connectomics has produced increasingly comprehensive wiring diagrams in model organisms and mammalian brain tissue, most dense reconstruction efforts rely on electron microscopy (EM), which provides nanometer-scale structural resolution but limited molecular specificity. As a result, current connectomic datasets primarily define anatomical connectivity, while omitting the molecular identities of synapses, cell types, organelles, and subcellular signaling compartments that may be essential for understanding neural computation, plasticity, and disease mechanisms. A scalable molecular connectome therefore requires an imaging strategy capable of resolving ultrastructural morphology and molecular composition in the same tissue volume. Expansion microscopy (ExM) provides a route to nanoscale imaging using conventional optical microscopes by physically expanding biological specimens while preserving molecular organization. Building on this framework, our group developed pan-ExM, an optical contrast strategy in which bulk protein staining provides EM-like visualization of cellular ultrastructure while remaining compatible with immunofluorescence-based molecular labeling. In brain tissue, pan-ExM enables visualization of neurites, membranes, synaptic densities, and other subcellular features at effective nanoscale resolution. Because expanded tissue is volumetrically de-crowded, molecular labels can be localized within an ultrastructural context, enabling simultaneous assessment of anatomical connectivity and synaptic protein identity, including markers such as Homer1, Bassoon, PSD-95, Synaptophysin, and related pre- and postsynaptic proteins. Here, we describe panluminate's integrated platform for scaling pan-ExM-based molecular connectomics. The platform combines four coordinated components: (i) panoptix, a high-throughput light-sheet microscope designed for volumetric imaging of expanded brain tissue; (ii) automated robotic and fluidic workflows for standardized sample processing, staining, washing, expansion, and iterative molecular labeling; (iii) consumable kits that formalize the chemistry required for reproducible pan-ExM preparation and multiplexed labeling; and (iv) tracing software for AI-assisted segmentation, proofreading, neurite reconstruction, synapse detection, and molecular annotation.

KEYWORDS: *Cell Type/Interactions; Connectome; Molecular/Cellular Neuroscience; Neuroimaging (invasive, non-invasive imaging)/Radiology; Neural Networks (topology, etc.)*

NeuroJSON.io 2.0: A scalable database for human-understandable and AI-automatable neuroimaging datasets

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As neuroimaging data sharing continues to grow in scale and complexity, researchers face increasing challenges in efficiently discovering, understanding, and accessing relevant datasets across repositories. File-oriented data dissemination approaches face challenges in rapidly searching metadata across a large number of datasets and lack relevant background information to aid in efficient data discovery.

Here, we present NeuroJSON.io 2.0, a highly scalable platform for disseminating searchable and reusable neuroimaging datasets, built upon modern NoSQL database architecture and the internationally standardized JSON format ecosystem. The platform provides (1) fine-grained cross-organization metadata search, (2) artificial intelligence (AI) enhanced dataset summaries, (3) in-browser multimodal data preview, and (4) programmable data access through a representational state transfer (REST) application programming interface (API), together with (5) a fully automated large language model (LLM) empowered data standardization pipeline.

Using the intuitive web interface at NeuroJSON.io, researchers can rapidly search both dataset-level and subject-level metadata across major public data repositories using advanced metadata filters, inspect data quality and content through interactive in-browser visualization tools, selectively download files through web and programmable interfaces, and leverage AI-generated summaries to improve dataset discoverability. NeuroJSON.io 2.0 currently hosts over 27 public data repositories (i.e., collections) comprising more than 1,500 datasets from over 58,000 subjects and 42 TB of linked data files spanning a broad range of neuroimaging modalities. The platform also integrates AutoBIDSify, an LLM-based framework that assists researchers in converting arbitrary user data into brain imaging data structure (BIDS) compliant datasets.

By combining standardized data representations, scalable database technologies, AI-enriched metadata, and interactive web-based tools, NeuroJSON.io 2.0 addresses key challenges in data sharing and provides an end-to-end infrastructure for exploring, standardizing, and reusing neuroimaging datasets.

KEYWORDS: *Dissemination & Open Science/Education; Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Resource for multiphoton characterization of genetically encoded probes

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Genetically encoded and biocompatible fluorescent probes are used in neuroscience to visualize neurons, record action potentials, and follow communication between neurons in real time in vivo. Two- or three-photon excitation of these probes provide high spatial resolution and deeper imaging as implemented in multiphoton laser scanning microscopy. To select optimum laser wavelength and pick brighter and more photo-stable probes, characterization of their multiphoton absorption spectra and cross sections is necessary. We provide the Resource for Multiphoton Characterization of Genetically-Encoded Probes for the BRAIN Initiative researchers and broader neuroscience community. We help to quantitatively characterize the 2-photon (2P) and 3-photon (3P) absorption spectra, cross sections, and molecular brightness of various probes and sensors, and measure a full set of linear absorption and fluorescence properties, including fluorescence quantum yields and lifetimes. During the last few years, we characterized the 2P spectra and cross sections of a set of functionalized rhodamine fluorophores that are used in a HaloTag and bio-compatible nanoemulsion formulations. Here we present the emerging structure—2P absorption properties relations for these molecules. We demonstrate how Si substitution in Si-Rhodamines provides the red shift of absorption spectra and strong enhancement of 2P cross sections. We also describe the effects of perfluorination at amino positions of FluoroRhodamine and the effect of counterion association with it on the 2P absorption properties. We use simple, few states approximations to describe the effects of these structural changes on the 2P properties.

KEYWORDS: *Chemistry; Dissemination & Open Science/Education; Monitor Neural Activity; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics*

The LLNL Biomedical Foundry: An ISO 13485-certified microfabrication facility for first-in-human neural interfaces

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The Biomedical Foundry at Lawrence Livermore National Laboratory, housed within the Center for Micro and Nanotechnology, is one of the only facilities in the nation that can develop chronic, long-term implantable devices and take them from concept to first-in-human prototypes. The Foundry, a microfabrication facility with an ISO 13485-certified Quality Management System, combines state-of-the-art microfabrication equipment and testing facilities to enable next-generation thin-film, polymer-based electrode arrays. The Foundry's primary focus is development and fabrication of flexible, thin-film microelectrode arrays, used in wide-ranging applications from chronic rodent studies to human implantable systems. Additionally, the Foundry includes semi-automated and long-term testing capabilities to validate functionality prior to biocompatibility testing and animal and human studies. Sponsors have included NIH, DARPA, university partners, and early-stage companies via Cooperative Research and Development Agreements (CRADAs), where applications have included minimally invasive human brain-computer interfaces (BCI) and olfactory bulb implants for odor detection in trained rodents or dogs. Here, we share prior work and devices developed with our university and industry partners to encourage broader engagement within the neural interface community to utilize this valuable resource.

KEYWORDS: *Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Monitor Neural Activity*

RNA profiling of extracellular vesicles reveals Alzheimer's disease-associated molecular signatures from iPSC-derived glutamatergic neurons

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Alzheimer's disease (AD) is a major neurodegenerative disorder affecting nearly 55 million worldwide, with cases projected to triple by 2050. Despite significant advancements, early diagnosis and effective treatment remain limited. Extracellular vesicles (EVs) are vital cell-derived nanoparticles that enhance intercellular interactions by transporting molecules between cells. We aimed to determine whether EVs released by human iPSC-derived glutamatergic neurons carry AD-related RNA signatures that more accurately reflect disease status than those in other biofluid EVs, and whether they could support future biomarker discovery. Human iPSCs derived from AD (ADiNEVs) and controls (iNEVs) were differentiated into glutamatergic neurons. Subsequently, EVs were isolated from conditioned medium using size-exclusion chromatography and characterized by NanoFCM, TEM, and SP-IRIS to assess size, morphology, and tetraspanin markers. RNA was extracted from EVs, followed by small RNA sequencing. Reads were aligned to human transcript references, including rRNA, tRNA, snRNA, snoRNA, miRNA, mRNA, lncRNA, mitochondrial RNA, and other noncoding RNA classes. Differential expression analysis between ADiNEVs and iNEVs was conducted using DESeq2 with false discovery rate correction, and selected transcripts were validated through qRT-PCR. The mean ages of ADiNEVs (n=8) and iNEVs (n=6) were 67.3±8.1 and 75±15.5 years, respectively, and 71.4% of participants were female. ADiNEVs and iNEVs showed comparable size distributions and typical EV marker profiles, supporting consistent enrichment across groups. However, ADiNEVs showed significantly reduced small nuclear RNA/RNU content, suggesting altered spliceosome-related RNA packaging. At an adjusted $p < 0.05$, a total of 57 RNA transcripts were differentially expressed, including increased MT-CO1, MT-ND4, HIST1H1A, IGSF8, and PRR32, and decreased XIST. Sex-stratified analysis identified 396 differentially expressed transcripts in female-only comparisons and confirmed disease-associated increases in MT-CO1, IGSF8, and PRR32, along with lower expression of XIST and miR-7-5p. Further qRT-PCR validation of selected DE transcripts supported the RNA-seq enrichment trends. Our findings demonstrate that RNA cargo from neuronal EVs reveals AD-associated molecular changes, including mitochondrial transcripts and noncoding RNAs. Profiling patient-derived neuronal EVs could help identify AD-specific biomarkers.

KEYWORDS: *Molecular/Cellular Neuroscience; Cell Type/Interactions*

Criterion-selective neurons in the human medial frontal cortex track decision thresholds during recognition memory

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Recognition memory judgments are thought to arise from comparing memory strength against a decision criterion. Although the decision criterion is foundational to many theories of recognition memory and decision-making, the neural mechanisms by which it is represented distinctly from memory strength remain poorly understood. To dissociate memory from decisional processes, we developed a recognition memory paradigm that manipulated memory strength and decision criteria across test blocks in a fully crossed 2x2 design, with participants rating confidence alongside recognition judgments. Memory strength was manipulated at study by presenting novel images once (weak strength) or twice (strong strength). Decision criteria were manipulated via point-based incentives, with correct responses yielding 4 points, critical errors incurring an 8-point loss and noncritical errors incurring no penalty. Across test blocks, the critical error type alternated between false alarms (encouraging a strict criterion that favored “new” responses) and misses (encouraging a lax criterion that favored “old” responses). We administered this task to 20 epilepsy patients (across 29 sessions) undergoing intracranial seizure monitoring, during which single-unit activity was recorded bilaterally from the medial temporal lobe (MTL; $n = 695$ units) and medial frontal cortex (MFC; $n = 505$ units) via Behnke-Fried depth electrodes. In the MFC, we identified a class of “criterion-selective” (CS) neurons (50/505) whose firing rates differed between favored and unfavored choices (e.g., “old” > “new” under a lax criterion but “new” > “old” under a strict criterion) during the recognition test, irrespective of underlying memory strength. The magnitude of this differential firing scaled with how extremely individuals shifted their criterion ($r(48) = .85$, $p < .001$), suggesting these neurons track the degree of criterion placement. In contrast, we identified “memory-selective” (MS) neurons in both the MTL (89/695) and MFC (80/505) that showed differential firing between hits and correct rejections, scaling with memory strength as indexed by confidence ratings, regardless of the decision criterion placement. Together, these findings reveal two functionally distinct neural populations, CS neurons that track the decision criterion regardless of memory strength and MS neurons that track memory strength regardless of the decision criterion, and their joint activity gives rise to recognition memory decisions.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation*

Neural population reinstatement and boundary cell modulation track predictive inference during event sequence learning in humans

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Memory enables us to use prior experience to anticipate what comes next. The brain learns temporal regularities (lightning→thunder) that support inference by analogy (fireworks→boom). Inference is central to adaptive human behavior; however, the underlying neural mechanisms remain poorly understood. We recorded single-neuron activity with high spatiotemporal resolution, allowing us to probe the neural basis of predictive inference. We hypothesized that successful inference is supported by reinstatement of neural population activity from prior learning, and that boundary cells, which signal unexpected transitions in an ongoing narrative, modulate responses to reflect inference.

Participants viewed naturalistic video clips involving various activities (events). Each clip contained four events (E1→E2→E3→E4) presented three times (Runs). After E2, participants predicted the next event by choosing between frames extracted from E3 and E4 (Order Prediction). After E4, participants determined if a static frame was new or old (Recognition). In Run 3, trials included repetitions, where the Run 3 clip is identical to the original clips shown in Runs 1 and 2; and generalizations, where the Run 3 clip is visually novel (e.g., live action) but preserves the same temporal structure as clips from Runs 1 and 2 (e.g., animation). We recorded 1252 neurons from 22 epilepsy patients undergoing intracranial monitoring.

Participants had high recognition accuracy (>80%) indicating engagement. Order prediction accuracy improved across Runs 1 and 2, reflecting memory-based prediction. In Run 3, order accuracy remained high for generalizations indicating successful predictive inference despite novel visuals. At the neural population level, we observed reinstatement of Run 2 activity during Run 3 generalization trials, with stronger reinstatement preceding correct predictions. At the single-neuron level, 134 boundary cells increased firing to one or more event onsets (boundaries) in Run 1. Across boundary cells, Run 3 responses attenuated for both repetitions and generalizations. Attenuations tracked order accuracy (correct > incorrect trials) and were greatest in medial temporal and prefrontal neurons.

Our findings suggest that predictive inference is supported by reinstatement of population activity and reflected by boundary cells that track event structure. These responses are modulated by inference success and anatomical region.

KEYWORDS: *Behavioral Sciences/Psychology; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Monitor Neural Activity; Neural Recording & Modulation; Integrated Approaches*

Adaptive intelligence ecosystems: Investigating human-AI-neurotechnology interactions and co-evolution in the NeuroAI era

PRESENTER: **S. Mahankali**
Shree Advisory & Consulting, LLC

AUTHORS: S. Mahankali

Advances in AI, brain-computer interfaces, neuroimaging, neural recording technologies, and adaptive neurotechnologies are transforming how humans learn, make decisions, interact with information, and engage with increasingly intelligent systems. As these technologies become integrated into cognitive environments, understanding their effects on cognition, neural adaptation, and human-machine interaction represents an emerging challenge and opportunity for neuroscience and NeuroAI.

This work introduces Adaptive Intelligence Ecosystems as an investigative approach for studying interactions among biological intelligence, artificial intelligence, and neurotechnology within interconnected cognitive environments. The approach proposes that future neuroscience research should examine not only neural systems in isolation, but also the dynamic relationships among human cognition, AI-enabled decision systems, neural interfaces, neural data ecosystems, and adaptive information environments.

Several domains for investigation include human-AI decision-making, cognitive adaptation to AI-mediated environments, neural responses to adaptive technologies, closed-loop human-machine interactions, and the effects of AI-enabled systems on learning, expertise, and cognitive performance. These interactions create opportunities to study how neural activity, behavior, neuroplasticity, learning trajectories, and cognitive resilience may change as humans increasingly interact with adaptive intelligent systems.

Because these interactions emerge across coupled biological, computational, and neurotechnological systems, they may not be fully captured by existing neuroscience, artificial intelligence, or neurotechnology models examined independently.

By integrating perspectives from neuroscience, NeuroAI, neurotechnology, informatics, and neuroethics, this work identifies opportunities to investigate intelligence as an ecosystem-level phenomenon spanning biological and artificial domains. The approach highlights future research directions involving neural adaptation, cognitive resilience, adaptive learning, interpretability, human-machine collaboration, neural data ecosystems, and responsible neurotechnology integration.

Aligned with the 2026 BRAIN Initiative Conference theme, *Inventing the Future*, this work proposes a research agenda for understanding how intelligence systems interact and co-evolve across brains, machines, and increasingly integrated neurotechnological environments.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Neural Networks (topology, etc.); Neuroethics, Philosophy, Law; Software (analysis, etc.) and Engineering*

Early quantitative EEG biomarkers for electrographic seizure prediction in newborns with hypoxic ischemic encephalopathy

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Seizures in newborns during early hours of life are among the most common manifestations of acute neurological dysfunction and are associated with increased risks of brain injury, mortality, and neurodevelopmental impairment. Newborns with hypoxic-ischemic encephalopathy (HIE) are particularly vulnerable, accounting for a substantial proportion of neonatal seizures. Importantly, many seizures in this population are subclinical, characterized by electrographic seizure activity without observable clinical signs. Early identification of high-risk infants could facilitate enhanced monitoring and timely therapeutic intervention during a critical period of brain vulnerability. The objective of this study was to investigate differences in spectral EEG characteristics during early hours of life between newborns with and without electrographically confirmed seizures (SZ) anytime during their hospital stay.

A total of 205 full-term newborns (gestational age 39 [38, 40] weeks) with mild to severe HIE were included, comprising 167 newborns in the No SZ group and 38 newborns in the SZ group. The first artifact-free 2-hour EEG interval selected for analysis began at 7 ± 3 hours after birth across the cohort. Central-Parietal bipolar montage (C3ñC4, C3ñP3, C4ñP4, and P3-P4) was considered for predicting seizures. Quantitative EEG biomarkers were calculated using area under the Power spectral density (PSD) curve within conventional frequency bands, including delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-20 Hz), and total power (0.5-20 Hz). Additional biomarkers included the delta/alpha ratio (DAR), the (delta+theta)/alpha ratio (DTAR), and spectral edge frequency at 90% power (SEF90).

Univariate logistic regression models demonstrated that higher slow delta, fast delta, delta, theta, alpha, beta, and total power were each associated with lower odds of seizures. In contrast, DAR, DTAR, and SEF90 were not significantly associated with seizure status. Overall, these findings support the feasibility of automated quantitative EEG spectral analysis for identifying early EEG features associated with seizure risk in newborns with HIE. Future multivariable modeling that combines quantitative EEG biomarkers with clinical variables may improve early seizure-risk stratification and support timely bedside monitoring and early therapeutic interventions.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology*

EEG-Based Neonatal Encephalopathy Score (ENES) for objective and real-time assessment of neonatal hypoxic-ischemic encephalopathy severity

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AUTHORS: S. Kota, S. Desai, E. Bhandari, S. Montazeri, S. Vanhatalo, L. Chalak

Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal mortality and morbidity. Repeated neurological exams can be subjective and not practical due to evolving encephalopathy. Mild HIE management has remained divisive due to evolving encephalopathy progression. At present, we lack tools to objectively assess severity of HIE using continuous EEG monitoring in real-time at the bedside. To address this gap, we developed a fully automated cloud, deep learning and EEG-based Neonatal Encephalopathy Score (ENES) algorithm for objective assessment of HIE severity using amplitude-integrated EEG (aEEG) from central-parietal bipolar derivations (C3-C4, P3-P4, C3-P3, and C4-P4) on the first day of life.

A total of 205 full-term newborns (≥ 36 weeks' gestation) with mild to severe HIE were included. Severity of HIE was determined using a modified Sarnat exam within 6 hours of life and the total Sarnat scores were obtained from medical records. Therapeutic Hypothermia (TH) was initiated for newborns with moderate-to-severe HIE group ($n = 115$) while the mild ($n = 90$) group did not receive TH. Thirteen newborns in the moderate-to-severe group were initially classified as mild but progressed clinically within 6-24 hours of life and subsequently met criteria for late TH.

Newborns with moderate-to-severe HIE had lower birth weights and lower Apgar scores at 1, 5, and 10 minutes. Abnormal EEG background activity was more prevalent in the moderate-to-severe HIE group than in the mild HIE group (30% vs. 6%). Electrographic seizures, longer hospital stays and infant mortality were observed among newborns with moderate-to-severe HIE.

EEG monitoring was initiated at 6 ± 4 hours of life across the cohort. ENES demonstrated strong differentiation of HIE severity across the first 24 hours of life. Linear regression analysis demonstrated a significant association between ENES and total Sarnat score, indicating that ENES reflected the severity of HIE ($R^2 = 0.32$, $P < 0.0001$). These findings support the potential of ENES to provide objective and timely assessment of HIE severity, facilitating early identification of newborns who may benefit from neuroprotective interventions.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Intracranial recordings reveal temporo-parietal junction as the earliest site sensitive to linguistic constituency structure

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How the brain builds meaning from basic phrases remains mostly unknown. Models differ on the cortical contributions to this. We performed an intracranial study of phrase reading in 25 epilepsy participants. We implemented a “Minimal Structure” paradigm of 3-word phrases presented in RSVP (500ms per word) involving Function/Content manipulations, with violations created by intentionally misplaced/nonsense function words. Content words contained a mix of categories. Phrases with Function-Function pairs were used to trigger syntactic inferences without strong semantic demands. Combinations of these words preceded a third phrase-completing word. Participants made acceptability judgments. Behavioral performance was high (>90%) and only correct trials were analyzed. We contrasted grammatical trials (“to the car,” “the fast car,” “drive the car,” “drive quickly now”) with agrammatical (“they the car”) and asemanic (“ti the car”) trials. We analyzed structure-sensitive electrodes in high gamma power (70-150Hz). For grammatical vs. ungrammatical Function-Function trials, a region in temporoparietal junction (TPJ) showed greater activity for violations as early as second word presentation, while posterior IFG showed a decrease but only during third word presentation. To more conservatively isolate phrase structure effects, we contrasted all acceptable vs unacceptable phrase types (regardless of lexical category). The only region to survive this contrast was a narrower strip of the previously mentioned TPJ—portions of the most posterior extent of pSTS bordering parietal cortex—aligning with recent lesion-symptom mapping research that has “pushed back” the core causally derived syntax site from previously-believed MTG. This suggests that this posterior syntax hub generates structural properties of phrases, while in parallel pIFG engages in integration, repair, or lexical-semantic control. In three patients, we used a separate paradigm to isolate visual recursive processing using a series of increasingly complex geometric shapes that either violated or adhered to a recursive rule. We discovered that all of the cortical sites sensitive to visual recursion in TPJ were immediately neighboring but distinct from linguistic sites, but in frontal cortex there was partial overlap, suggesting that the pSTS-TPJ syntax hub contains cortical patches more focally dedicated to linguistic structure vs. domain-general control.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

American Brain Coalition 2026 BRAIN Initiative educational and advocacy efforts

PRESENTER: **K. Sale**
American Brain Coalition

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The American Brain Coalition (ABC) is a nonprofit organization that unites patient advocacy groups, professional societies, researchers, clinicians, academic institutions, industry partners, and other stakeholders to advance brain health. Through collaboration, education, advocacy, and support for research and innovation, ABC works to improve the lives of individuals and families affected by brain diseases and disorders.

ABC actively advocates for robust federal funding of the BRAIN Initiative. We equip patient advocacy organizations and professionals with the tools and resources needed to engage Congress and communicate the importance of the BRAIN Initiative through ongoing advocacy and public engagement efforts.

KEYWORDS: *Behavioral Sciences/Psychology; Neural Networks (topology, etc.); Neuroethics, Philosophy, Law; Informatics, Statistics, or Applied Mathematics*

Analyzing the internal representations of a generalist muscle transformer policy

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Humans excel at diverse motor tasks, but the neural representations supporting this flexibility remain poorly understood. Specialist policies for human-like musculoskeletal control on single tasks have advanced in recent years, but current approaches require retraining from scratch to learn new tasks, and are thus poor models of humans' motor generality. We introduce Arnold, a generalist muscle policy that masters 14 tasks across multiple embodiments, spanning finger reaching, object manipulation, and locomotion. Arnold is an encoder-decoder transformer trained with behavioral cloning and proximal policy optimization, using a compositional sensorimotor vocabulary to handle variable-length sensory inputs and motor outputs across tasks. Arnold achieves expert-level performance on all tasks and learns novel tasks significantly faster than randomly initialized networks, suggesting the acquisition of transferable motor representations.

To probe how Arnold can learn multiple tasks, we analyze its internal and output activations. We find that post-encoder contextual embeddings of sensory tokens are strongly clustered by task identity, suggesting that Arnold's success in each task may come from compartmentalizing its representations and using non-overlapping strategies. However, linear decoders trained to predict muscle identity from embeddings of one task set generalize above chance to held-out tasks, and performance improves with the number of training tasks, indicating partial reuse of representational structure across tasks. Additionally, semantically similar task pairs exhibit lower projected variance difference and principal angle difference in their contextual embedding spaces, reflecting meaningful encoding structure. We also find that each of the principal components of Arnold's action space accounts for performance in multiple tasks rather than specializing in a single task, meaning representations are not fully compartmentalized. Finally, transferring contextual embeddings of target tokens between similar tasks produces negligible performance drops, suggesting that despite strong task-level organization in embedding space, the decoder can exploit transferred information when given correct actuator tokens. Together, these findings reveal that multi-task training in Arnold promotes a representational organization that is strongly task-structured but permits some generalization—a balance that may parallel strategies in biological motor control.

KEYWORDS: *Computational Biology/Modelling; Integrated Approaches; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering; Informatics, Statistics, or Applied Mathematics*

Mechanistic investigation of gymnemic acid-I (GA-1) in differentiated SH-SY5Y cells

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Nearly 1 out of 8 individuals in the United States is affected by diabetes mellitus (DM), of which approximately 90-95% of cases are attributed to Type 2 (T2DM), a major metabolic disorder resulting from impaired insulin production and/or reduced insulin sensitivity. T2DM causes chronic hyperglycemia and dysregulated energy metabolism, ultimately contributing to long-term cellular and tissue damage across multiple organ systems. Diabetic neuropathy, characterized by progressive neuronal damage and pain, is among the most debilitating complications.

Gymnema sylvestre, an anti-diabetic medicinal plant traditionally used in Ayurvedic medicine for glucose regulation, has emerged as a potential neuroprotective candidate. Previous studies conducted in our laboratory demonstrated the neuroprotective potential of gymnemic acid-I (GA-1), a major bioactive constituent of *Gymnema sylvestre*, in undifferentiated SH-SY5Y cells. Building upon these findings, the present study provides a mechanistic evaluation of GA-1 in differentiated neuronal SH-SY5Y cells, thereby offering a more physiologically relevant in vitro model for investigating diabetic neuropathy.

To further validate the therapeutic potential of GA-1, its cytotoxic profile and neuroprotective efficacy were evaluated in differentiated SH-SY5Y neuronal cells. GA-1 (10 μ M-80 μ M) exhibited no significant decrease in cell viability, confirming the absence of inherent toxicity. Neurotoxicity was induced using 6-hydroxydopamine (6-OHDA) and streptozotocin (STZ), which model oxidative stress-mediated neuronal damage and diabetic neuropathy, respectively. The IC₅₀ value for 6-OHDA was determined to be 40 μ M and that of STZ was 3.5 nM through one way ANOVA followed by Bonferroni post hoc test. Considering the established role of GA-1 in glucose homeostasis, insulin production was investigated as a potential mechanism using an insulin ELISA initially in undifferentiated SH-SY5Y cells. GA-1 treatment groups did not exhibit insulin levels above control, indicating that GA-1's neuroprotection is not insulin-mediated in this cell line. Consequently, this investigation was not extended to differentiated SH-SY5Y cells. Current studies are focused on evaluating oxidative stress and the involvement of advanced glycation end products (RAGE) signaling pathway. These studies aim to further elucidate the molecular mechanisms underlying the neuroprotective effects of GA-1 in differentiated SH-SY5Y neuronal cells.

KEYWORDS: *Molecular/Cellular Neuroscience*

Childhood trauma severity predicts reduced left amygdala-dACC resting-state functional connectivity in midlife

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Childhood trauma is associated with long-term neural circuitry changes, particularly disrupted connectivity patterns across fronto-limbic circuitry involved in salience, threat detection and emotional processing. It has been proposed that top-down regulatory processes involving the dorsal anterior cingulate cortex (dACC) may recruit ventral anterior cingulate cortex regions such as the subgenual anterior cingulate cortex to dampen limbic reactivity. This study examined amygdala seed-based resting-state functional connectivity (rs-fc) in a sample of middle-aged adults in the United States (N = 214). Our findings demonstrate that higher levels of childhood trauma severity are associated with reduced resting-state functional coupling between the left amygdala and ddAC. Exploratory analyses suggest that reduced left amygdala-dACC rs-fc is more strongly associated with childhood abuse than neglect. These findings support the notion that childhood trauma is associated with persistent fronto-limbic disruptions, potentially involving aberrant dACC-associated top-down regulation, and suggest that individuals experiencing childhood abuse may be particularly vulnerable to such disruptions.

KEYWORDS: *Behavioral Sciences/Psychology; Circuit Diagrams; Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology*

BICAN data infrastructure: Enabling community re-use of the basal ganglia atlas

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The goal of the NIH BRAIN Initiative Cell Atlas Network (BICAN) is to generate a standardized, integrated cell atlas of the human, macaque, marmoset, and mouse brain that can serve as a foundational community reference for the classification and study of brain cell types. The initial stage of analysis and cell atlasing incorporated a joint anatomic sampling plan focused on creation of a cross-species, multimodal atlas of the basal ganglia, a set of subcortical nuclei central to motor control and implicated in a wide range of neurological disorders. The cell atlas is based on a transcriptomic classification of single cells that are integrated with epigenomic and spatial genomic mapping, supported by parallel sampling and harmonized analysis across species. A federated set of atlases, browsers, and analysis tools support access to the basal ganglia data and cell types, including data archives, metadata management, and knowledgebase. These resources may be accessed via the BICAN website (brain-bican.org). Realization of this resource has required the development of data standards, harmonized donor metadata across brain banks, and unified anatomical reference systems. Analogous to standardization achieved in genome sciences, these data resources, tools, and collaborative infrastructure form a FAIR (findable, accessible, interoperable, and reusable) framework that enables researchers to map, compare, and interpret diverse datasets against a shared reference and associated knowledge base.

KEYWORDS: *Cell Type/Interactions; Dissemination & Open Science/Education; Software (analysis, etc.) and Engineering; Molecular/Cellular Neuroscience*

Single-cell CUT&Tag+RNA reveals region-specific epigenetic dysfunction in Alzheimer's disease

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AUTHORS: C. Hartl, C. Saldanha, N. Chapin, P. Lin, H. Ishii

Alzheimer's disease (AD) impacts over 55 million people globally, including 1 million sufferers living in the UK. Despite intense research, the only strategy to have achieved moderate success has been directly targeting amyloid plaques rather than cellular processes leading to their generation and propagation. Understanding the molecular mechanisms that drive AD pathology is critical to devising effective treatment strategies. Genome-wide association studies (GWAS) have begun to unravel the genetic basis of late onset AD (LOAD), the most prevalent form of AD, and has found thousands of sequence variants associated with LOAD. Translating this knowledge into a mechanistic understanding of AD pathogenesis remains challenging. Two key hurdles are that (i) most AD risk variants are non-protein-coding and lack functional annotation, and (ii) the effects of non-genetic risk factors on cellular mechanisms—particularly neuronal mechanisms proximal to cell death—are not well-understood. Recent advances in single cell epigenomics assays have enabled the generation of cell type-resolved maps of the epigenome and accelerated annotation of gene regulatory elements in the human genome, improving our ability to interpret the genetic basis of multigenic diseases. We present a pilot multi-regional single-cell epigenetic atlas of the human brain in matched AD donors and controls. We examine the epigenetic footprint of Alzheimer's disease across hippocampus, white matter, and cerebellum and explore epigenetic changes across glial and neuronal populations, identifying signatures of epigenetic erosion that potentially contribute to neuronal loss.

KEYWORDS: *Genetics/Genomics; Human Neuroscience, Clinical Science, or Public Health; Molecular/Cellular Neuroscience; Computational Biology/Modelling*

Stimulus-specific recruitment of human amygdala neurons predicts episodic memory encoding success

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Our daily experiences are filled with a constant flow of sensory information, yet only a small subset is encoded into long-lasting episodic memory. The neural mechanisms that determine which events are preserved in memory and which are forgotten remain poorly understood.

Using intracranial recordings from neurosurgical patients, we examined single-neuron activity and local field potentials in the human brain during memory encoding and retrieval. Participants viewed novel visual stimuli from five categories and later performed recognition with confidence ratings.

We first identified category-selective neurons by testing for different responses across stimulus categories (1x5 ANOVA). Category neurons were observed above chance levels in four regions: ventral temporal cortex (VTC), amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC). In the amygdala, category-selective neurons showed enhanced firing during encoding for items that were subsequently remembered compared to those later forgotten. This difference was observed in the amygdala at around 350 ms after stimulus onset, preceding a weaker hippocampal effect at approximately 1300 ms. Cells in the VTC and vmPFC, while strongly category selective, did not predict memory encoding success, highlighting the specificity of this effect to the amygdala.

Critically, amygdala firing rates tracked memory strength in a graded manner, with highest activity for high-confidence remembered items, intermediate responses for low-confidence remembered items, and lowest responses for forgotten items. These results indicate that amygdala category neurons encode not only whether an item will be remembered, but also the strength of the resulting memory.

One potential mechanism linking stronger category-cell responses to enhanced memory formation is increased coordination with ongoing network oscillations. Consistent with this, spike-field coherence within the amygdala was significantly stronger for subsequently remembered than forgotten items. Successful memory formation was also accompanied by enhanced spike-field coherence between the activity of category cells in the amygdala and hippocampal field potentials.

Together, our findings demonstrate that recruitment of stimulus-specific representations in the amygdala predicts episodic memory formation. This data suggests that category cells in the amygdala may be a potential target for interventions to treat disorders affecting episodic memory.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation*

Divergent strategies in implicit and explicit representations of inferred latent dynamics

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Decision-making in dynamic and uncertain environments requires integrating recent observations with beliefs about the latent environmental state and updating those beliefs when the environment changes. Although humans can effectively adapt their behavior under such conditions, how they learn, represent, and use environmental change rates to guide decisions remains an active area of investigation. To examine these processes, we developed a probabilistic two-alternative forced-choice (2AFC) task in which the correct choice switches according to a latent change rate. Following sequences of noisy observations, participants ($n=37$) performed two tasks: a report task, in which they select the environmental state of the final observation, and a prediction task, in which they predict the subsequent state. Participants displayed distinct behavioral patterns across the report and prediction tasks. They were substantially more accurate in the report task, with estimates of the current environmental state broadly consistent with a Bayesian ideal observer model. In contrast, a large subset of participants exhibited a systematic bias in future-state predictions toward overestimating the latent change rate in stable environments. This systematic bias was persistent across many noise levels and task structures, but prediction accuracy improved as the total amount of evidence was reduced, suggesting that these participants applied a non-Bayesian strategy that becomes more apparent with increasing amounts of evidence. In tandem, we trained recurrent neural networks (RNNs) to investigate the computational mechanisms behind these behavioral patterns. The networks were trained on the same joint report-prediction task and displayed a staged learning trajectory, first acquiring a simple heuristic solution for the report task before gradually developing more Bayesian-like behavior. Before this transition toward Bayesian-like performance, the networks produced prediction biases, supporting the hypothesis that humans' predictive biases may arise from computationally simpler intermediate strategies encountered during learning. Together, these findings indicate that differences between current state estimation and future state prediction behavior in humans are not a reflection of task difficulty, but may instead arise from more fundamental differences in how the brain explicitly represents environmental change rates compared to implicit use of change rates.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics*

Spatiotemporal activity modification as an intervention in people with mild-moderate Parkinson's disease

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Individuals with Parkinson's disease (PD) experience disrupted motor-cognitive integration. Heterogeneous neuropathology and motor-cognitive limitations in PD manifest as varied movement deficits, especially during gait, necessitating comprehensive classification and curated rehabilitation to maximally restore function.

This randomized controlled trial tests a novel rehabilitation strategy targeting gait modulation and motor-cognitive function in people with PD (PwP).

We developed Spatiotemporal Activity Modification (STEAM), an effective treatment and assessment tool that uses movement patterns varying in spatial (joint coordination), temporal (stepping rhythm), or combined features. STEAM treatment was administered in 2 formats, where spatial and temporal instructions were taught either separately (ISO class) or simultaneously (COU class). Rates of Physical and Cognitive Perceived Exertion (RPE and RCPE) were rated on a 10-point Likert scale at the start, halftime, and end of each 90-min STEAM class. People with mild-moderate PD completed 10 STEAM classes over 3 weeks to assess improvement in gait modulation and its relationship to musical and dance affinity.

22 PwP were randomized to ISO classes and 17 PwP to COU classes (age= 71.80±7.2 years, sex = female (13), male (26); Hoehn & Yahr stage 1=16; stage 2=20, stage 3=2, stage 4=1). Of 39 randomized participants, 34 completed 10 classes (ISO=20, COU=14), 3 completed ≥8 classes, and 2 attended <5 classes. The attrition rates were 4.5% and 5.9% for the ISO and COU groups respectively. A total of 375 classes were completed (214 ISO, 161 COU) over 48 weeks. Completion of clinical outcome measures had ≤2.5% missing across key assessments, and all participants provided complete motion capture data. Exit surveys (n=32) showed high enjoyment (93.8%) and positive feedback for ISO (71.4%) and COU (76.2%) classes. Average RPE and RCPE increased in ISO and COU groups, starting at light to moderate by the end of class. COU showed higher RPE and RCPE at halftime and end of the 90-min class.

STEAM is a feasible and acceptable intervention with flexible levels of difficulty and a dual-tasking component for PwP with mild to moderate symptoms. Both ISO and COU format of STEAM intervention showed moderately challenging difficulty. Further analyses of motor, cognitive, and patient-reported outcomes will determine the optimal STEAM format in this population.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Interventional Tools; Behavioral Sciences/Psychology*

The Brain Stress Test: A new framework for quantifying neural resilience through recovery dynamics

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Stress tests are widely used in medicine to reveal latent vulnerabilities by challenging a system beyond its resting state. We propose a Brain Stress Test (BST) framework that applies a standardized cognitive challenge and quantifies subsequent changes in resting-state EEG (the resting-state EEG Task Aftereffect), as indicators of neural resilience, network recovery, and cognitive vulnerability. Analogous to cardiac stress testing, BST shifts assessment from static at rest-state measurement to dynamic evaluation of how effectively brain networks respond to and recover from challenge. We further propose a mechanistic model, dynamic EEG Network Reconfiguration (dENR), to characterize the magnitude, trajectory, and efficiency of post-task recovery.

We synthesized findings from eight EEG studies spanning cognitively normal older adults and individuals with mild cognitive impairment (MCI). Across studies, participants completed cognitively demanding tasks along with pre- and post-EEG recordings. BST metrics included post-task perturbation magnitude, spectral power changes, theta/beta ratio, functional connectivity, graph-theoretical indices of network organization, and recovery-related changes.

Across studies, MCI participants consistently exhibited enhanced post-task EEG responses relative to cognitively normal controls, including greater spectral slowing, elevated theta/beta ratios, altered frontal asymmetry, and larger reductions in EEG current density. Network analyses revealed increased post-task integration in MCI, whereas healthy individuals generally showed transient reductions in integration followed by recovery toward baseline. Importantly, combining EEG network metrics with cognitive measures yielded classification accuracies approaching 86.5% for distinguishing MCI from healthy aging.

We propose the Brain Stress Test, a dynamic EEG framework that quantifies neural resilience by measuring post-task recovery following cognitive challenge. Rather than assessing the brain solely at rest, BST evaluates the capacity of neural systems to recover following perturbation, providing a dynamic measure of reserve and adaptability. Across eight studies, BST consistently differentiated healthy aging from MCI through altered recovery dynamics, spectral changes, and network reorganization. BST introduces a scalable, non-invasive biomarker framework for early detection of cognitive decline and neurodegenerative disease.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation*

Could improving neural probe targeting accuracy and reducing tissue damage improve clinical outcomes?

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Previous studies have shown that the insertion process for neural tools (preclinical or clinical systems) can affect device function, promote tissue inflammation, cause neural cell death and glial scarring, and contribute to device failure. Targeting accuracy may further affect device function and failure risk through off-target electrical stimulation. In some studies, up to 80% of deep brain stimulation (DBS) probes deflect during insertion, and up to 8% deviate several millimeters from the intended target, requiring repositioning or an additional procedure. The work of Dr. C. Wu and Dr. Q. Wu indicates that probe deflection can arise at intraparenchymal interfaces, where differences in tissue density and stiffness alter probe trajectory. Stereoelectroencephalography (sEEG) probes may similarly deflect during placement, resulting in missed targets, repeat insertions, and increased revision risk.

Damage during insertion is also a concern. In preclinical studies, mechanically induced tissue damage can be detected within hours to days after implantation of electrodes by elevated intracellular calcium levels and axonal blebbing, both indicators of neuronal injury. Insert-and-remove array studies suggest that insertion trauma alone can produce significant inflammation and neuronal loss. A major question is whether this damage is impacting clinical outcomes and neural deficits.

We hypothesize that probe deflection during DBS and sEEG placement is a key determinant of targeting accuracy, and that the NeuralGlider® Inserter (NeuralGlider, Actuated Medical, Inc.), a micron-scale ultrasonic vibration system, can improve targeting accuracy and resultant clinical outcomes. Preclinical studies have shown that NeuralGlider can improve accuracy and reduce acute tissue damage during probe insertion. Ongoing studies are evaluating whether reducing insertion-related tissue damage and probe deflection can be translated to clinical systems and improve outcomes, including initial positioning success, neurological deficits, foreign body response, and long-term probe patency, in procedures requiring neural probes or cannulas to traverse multiple brain structures en route to the target.

These findings may extend beyond electrode implantation to infusion therapies, including adeno-associated virus (AAV) delivery. Although smaller diameter cannulas may minimize insertion-tract size, they can deflect when traversing brain regions with differing stiffness.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Interventional Tools; Neural Recording & Modulation*

Reflexive inhibition of eye movements relies on intact visual cortical processing

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Motor circuits in the brain have privileged access to visual information, allowing humans to respond to external signals with minimal delays. Whether such rapid visuomotor behaviors are mediated via cortical or subcortical pathways is debated. Here we study oculomotor freezing, the reflexive cessation of saccadic eye movements in response to the sudden onset of visual or auditory stimuli, to test whether this short-latency oculomotor behavior relies on intact visual cortical processing. We recorded eye movements of two patients (p01: 65-year-old male, p02: 42-year-old female) with unilateral stroke-induced damage to early visual cortex. The patients continuously fixated on the center of a screen while we presented visual gratings, auditory white noise bursts, or both combined. The gratings were either presented inside the patients' blind field (p01: [-18,-5], p02: [7,5]) or at a corresponding location within the patients' intact visual hemifield. In both patients, stimulus-locked microsaccade rates exhibited a rapid decrease in response to the onset of the peripheral grating presented in the intact hemifield (indicating oculomotor freezing). Conversely, when gratings were presented inside the blind field, we did not observe oculomotor freezing. In trials where gratings were paired with the auditory stimulus, oculomotor freezing was enhanced for stimulus presentation in the intact hemifield, compared to auditory-only trials. No enhancement was observed when gratings were presented inside the blind field, indicating that multisensory response enhancement only occurred when the visual stimulus was presented inside the intact field. An analysis of the microsaccade direction revealed that the few microsaccades that occurred during oculomotor freezing were biased towards stimuli presented inside the intact field. Conversely, microsaccades were not biased towards stimuli presented inside the blind field. Our results provide neuropsychological evidence that intact visual cortical processing of stimulus onset is necessary to elicit oculomotor freezing. These findings are consistent with lesion studies in monkeys, questioning the functional relevance of direct retinal projections to motor structures via subcortical pathways. By extending previous reports of oculomotor abnormalities in cortically blind patients, we propose a new way in which eye movements can serve as an easily measured, objective biomarker of visual cortical function in occipital stroke patients.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Behavioral Sciences/Psychology*

Development of an implantable electrochemical sensing probe for biomarkers screening in cerebrospinal fluid

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We propose a novel microelectrode array (MEA)-based probe intended for sensitive and localized detection of key biomarkers present in cerebrospinal fluid (CSF) implicated in sepsis-associated encephalopathy (SAE). The device was manufactured as a flex circuit embedding a 2x2+2 MEA and is electrochemically characterized by electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV). A biocompatible phase-change sheath enables tissue penetration in its path towards the brain ventricles while preserving probe flexibility in the brain tissue. Noise baseline, signal-to-noise ratio (SNR), insertion force, electrode surface profile and roughness were also obtained. This promising step forward holds significant potential for advancing both basic sepsis research and future clinical applications.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Interventional Tools*

Normalization-based population receptive field (pRF) modeling captures recovery-associated changes in human cortical blindness

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National Institute of Mental Health

AUTHORS: J. Ahn, E. Merriam

Recovery from cortical blindness after V1 damage is associated with plasticity in spared perilesional visual cortex. Prior work from our group showed that visual discrimination training improves luminance detection sensitivity in chronic cortical blindness, and that recovery is predicted by spared pre-training V1 activity representing blind-field locations. That study further showed that training enlarges population receptive fields (pRFs) in perilesional V1 and increases coverage of the blind field. However, conventional pRF models describe these changes phenomenologically and do not specify how altered inputs from spared neural populations give rise to estimated changes in pRF size or coverage.

Here we developed a normalization-based pRF model to characterize recovery-associated pRF changes after cortical injury. The model assumes that each voxel contains a remaining pool of visually responsive neural populations. Inputs within this pool contribute to the response-driving signal and are also pooled into a divisive normalization term. By explicitly modeling how activity from the remaining neural pool is weighted and summed into the surround normalization pool, the model predicts BOLD responses from the effective input structure of spared visual cortex rather than from excitatory spatial tuning alone.

We tested whether changes in surround-pool weights within the remaining neural population can produce pRF size changes similar to those observed after visual training. The model captured increases in estimated pRF size and visual-field coverage without requiring a literal expansion of the underlying receptive field structure. In the model, pRF enlargement emerged when the weights governing summation into the normalization pool changed within the spared neural population.

These results suggest that recovery-associated pRF enlargement may reflect altered weighting of surround inputs into the normalization pool within spared perilesional cortex, rather than a literal expansion of the underlying receptive field structure. This framework extends prior evidence that perilesional V1 supports training-induced recovery by providing a mechanistic account of pRF changes after cortical injury. A normalization-based pRF model may help interpret pre- and post-training patient fMRI data by linking observed pRF changes to altered normalization weights in the remaining neural population.

KEYWORDS: *Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Social well-being predicts slower whole-body aging estimated from a single brain MRI scan: Prospective evidence from MIDUS

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Subjective well-being is a robust predictor of health and longevity in mid-to-late adulthood. Yet whether separable dimensions of well-being, such as hedonic (e.g., pleasure), eudaimonic (e.g., purpose), and social well-being (e.g., belonging), are differentially associated with biological aging remains unclear. This study addresses this gap by modeling the multi-faceted structure of subjective well-being and examining its relationships with DunedinPACNI, a novel brain biomarker trained to estimate the multi-system pace of aging.

Using data from the Midlife in the United States (MIDUS) study (N = 213; age = 56.2±13.7; female N = 118), we modeled eudaimonic (Ryff Psychological Well-Being Scale), social (Keyes Social Well-Being Scale), and hedonic well-being (Positive/negative affect, Life Satisfaction Scale) via confirmatory factor analysis performed on the validated self-report questionnaires. The three-factor model showed acceptable fit, supporting the separability of these dimensions. A pace-of-aging (PACNI) was estimated per participant from an MRI scan acquired on average 3.6±2.7 years after the survey measurement. We fit three separate hierarchical regression models, testing whether each dimension of well-being predicted PACNI, controlling for demographics (Block 1: age, sex, race, socioeconomic status), health and lifestyle (Block 2: chronic conditions, body mass index, perceived stress, exercise, smoking, drinking, everyday cognitive activity), and social integration (Block 3: marital status, social network size).

While body mass index, chronic conditions, socioeconomic status, and age predicted PACNI in theoretically expected directions, only social well-being was consistently associated with a lower PACNI across all blocks (Fully model: $\beta = -.18$, $p = .03$). Neither eudaimonic nor hedonic well-being significantly predicted PACNI (All Ps = .21). A global index averaging all well-being measures was also non-significant after multiple-comparison correction ($p = .14$), showing that the association was most pronounced for the social dimension.

These results suggest that a fine-grained characterization of subjective well-being may yield unique insights into the psychosocial correlates of healthy aging. They also point to the utility of DunedinPACNI as a scalable, biospecimen-free index of whole-body aging. Our findings have implications for designing interventions that promote individual flourishing and public health.

KEYWORDS: *Behavioral Sciences/Psychology; Neuroimaging (invasive, non-invasive imaging)/Radiology; Human Neuroscience, Clinical Science, or Public Health*

BrainRISE: A cloud-based ecosystem for personalized adaptive neurostimulation

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Mayo Clinic

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A major barrier to personalized neurostimulation is integrating continuous neural data with real-world patient behavior and clinical outcomes. To address this challenge, we developed BrainRISE (Brain Restoration, Intelligent Stimulation Ecosystem), a secure, cloud-based, disease- and device-agnostic platform that enables scalable data integration, analysis, and adaptive therapy. BrainRISE currently supports multiple investigational device studies, including Medtronic Summit RC+S™, Cadence™ Neuroscience system, CorTec Brain Interchange and UNEEG sub-scalp device.

BrainRISE provides a bidirectional interface through device application programming interfaces (API), integrating continuous data streams from implantable neurostimulators, smartphones and wearable sensors. Artificial intelligence algorithms identify disease-specific biomarkers including epileptiform activity, beta-band oscillations, and sleep-wake states, to support personalized therapy. A core feature of BrainRISE is its ability to trigger remote cognitive and behavioral assessments on a patient's mobile device—either scheduled or based on detected neural events—enabling dense, brain-state-dependent phenotyping in natural environments.

BrainRISE has been successfully deployed in feasibility studies for several brain disorders, including epilepsy, Parkinson's disease, and chronic pain. In epilepsy, the platform enabled a direct comparison of deep brain stimulation (DBS) paradigms by linking chronic neural data with remotely acquired measures of cognition, sleep, and awareness collected via smartphones and smartwatches. These multimodal data identified stimulation settings that optimized not only seizure control but also cognitive performance and sleep quality.

By unifying chronic neural sensing, digital phenotyping, and adaptive neuromodulation within a single ecosystem, BrainRISE provides a scalable framework for developing personalized, data-driven therapies across a broad range of neurological and psychiatric disorders.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Software (analysis, etc.) and Engineering*

The intracortical visual prosthesis (ICVP): Multi-year results from the clinical trial

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The intracortical visual prosthesis (ICVP) has been in development for over 25 years and uses 16-channel wireless 5mm-diameter fully-untethered floating microelectrode arrays (WFMA) for intracortical stimulation of the visual cortex. The intended application is providing artificial vision for people with profound blindness. Each WFMA has a unique address for controlling the 16 electrodes with an extracorporeal telemetry controller.

As part of a five-subject clinical trial, the first three participants were implanted in February 2022, October 2024, and April 2026. The three participants received 25 WFMA/400 electrodes, 32 WFMA/512 electrodes, and 34 WFMA/544 electrodes, respectively, each into the right occipital lobe on the dorso-lateral surface. Following DSMB approval, testing of the implanted WFMA began in March of 2022 (for participant #1) and has continued through July of 2026 for all three participants. Electrode voltage transients for 30 μ A/200 μ sec stimulation were recorded via the wireless telemetry. Percepts produced by the electrodes were catalogued and mapped in the visual field. A visible/infrared camera was interfaced to the ICVP system and visual task performance was assessed. The ICVP was also paired with a commercial image-to-speech device to combine the ICVP visual targeting capability with the commercial-device image recognition capability. EEGs were recorded for most of the testing sessions. For the third implant, presurgical planning was used to strategically place the WFMA in targeted visual areas, outside of striate cortex.

The implanted technology has shown high reliability, with only a few of the electrodes showing an electrical disconnection in the first participant. Electrode voltage transients show high electrode stability and perceptual thresholds have been highly stable since the onset of testing. While the artificial vision provided by the ICVP is crude, relative to biological vision, visual task testing with the camera interface has shown some surprising tasks which all the participants can easily accomplish. EEG recordings have shown after-discharges following stimulation, raising concerns about potential seizures.

The ICVP with its WFMA cortical interface has been validated in three participants as being reliable and able to produce crude artificial vision. The chronic nature of the interface is a significant advantage.

KEYWORDS: *Implantable Devices (probes, etc.); Integrated Approaches; Interventional Tools; Human Neuroscience, Clinical Science, or Public Health*

Clinical validation of an in-ear neural interface platform for continuous autonomic monitoring in critically ill patients

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Ear canal represents an emerging anatomical site for unobtrusive neural interfaces, offering proximity to brain while enabling continuous monitoring without disrupting clinical care. NeuroPulse platform is an in-ear neural interface designed to capture multimodal physiological signals, including electroencephalography and autonomic nervous system activity. Before deploying this platform for neural recording applications, validation of its electrophysiological signal acquisition is essential. Auricular cardiography (ACG) provides a testbed for assessing device's ability to reliably detect biological electrical signals, as cardiac waveforms offer well-defined morphological features and established reference standards.

Objective: To validate electrophysiological signal acquisition performance of NeuroPulse in-ear neural interface by assessing agreement between device-derived cardiac parameters and standard Lead II ECG in ICU patients.

In this prospective validation study, NeuroPulse device was deployed in 10 neurocritical ICU patients for up to 3 hours. ACG signals were acquired at 6.5 kHz and processed using bandpass filtering (0.5-45 Hz). Heart rate, heart rate variability (HRV) via Poincaré analysis with DBSCAN clustering, and interval measurements (QTc, PR, QRS) were extracted. Agreement with simultaneous Lead II ECG was assessed using correlation, intraclass correlation coefficients, and Bland-Altman analysis.

NeuroPulse platform demonstrated robust signal acquisition across critically ill patients (median recording: 133.5 minutes; ~8,000 cardiac cycles per patient). Device-derived heart rate showed strong agreement with reference ECG ($r=0.75\pm0.12$; bias: -0.32 bpm; 95% limits of agreement: -9.79 to +9.15 bpm). Autonomic metrics were preserved, with comparable HRV cluster detection (device: 3.6 ± 1.5 vs. ECG: 3.1 ± 1.9 clusters) and minimal cluster-center error (0.03 ± 0.05 s). Waveform morphology showed high concordance: QTc ($R^2=0.991$), PR ($R^2=0.993$), QRS ($R^2=0.983$). Notably, device maintained reliable signal acquisition in a mechanically supported patient where pulse-based monitoring failed.

NeuroPulse in-ear neural interface demonstrates reliable electrophysiological signal acquisition in challenging clinical environments. These findings establish foundational validation supporting future applications in multimodal neural monitoring, brain-heart interaction studies, and closed-loop neuromodulation.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Neural Recording & Modulation*

Deep-penetrating amorphous silicon carbide microelectrode arrays with ruthenium oxide electrodes

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High-density intracortical microelectrode arrays enable single-unit recording and spatially selective stimulation, but their long-term performance is limited by tissue reactivity, material degradation, and implantation challenges. Conventional probes can induce insertion trauma, micromotion, glial encapsulation, neuronal loss, fluid ingress, electrode corrosion, and progressive channel failure. Although thinner, more flexible implants may reduce the foreign-body response, they often require insertion shuttles, temporary stiffeners, or robotic systems. We have developed high-density, ultrathin microelectrode arrays using amorphous silicon carbide (a-SiC) as the substrate and encapsulation material and sputtered ruthenium oxide (RuOx) as a low-impedance, high-charge-storage-capacity electrode coating. Our objective is to create self-inserting neural interfaces that combine subcellular-scale dimensions, high channel counts, long-term reliability, and selective recording and stimulation.

We expanded the a-SiC platform from 1.5-2 mm cortical probes to deep-penetrating devices with 5 mm shanks for rodents and 20 mm shanks for potential macaque applications, while maintaining sub-10 μm thicknesses and shank widths of 70-80 μm . To support dense routing within these narrow geometries, we developed a multilayer architecture comprising two patterned metal layers separated by 500 nm a-SiC dielectric films, with 5 μm bottom and 2.5 μm top a-SiC structural layers. Metal traces were patterned with 2 μm lines and spaces. Layer-by-layer stress characterization and process optimization produced planar, mechanically stable devices with minimal out-of-plane deformation. A 1 μm polyimide layer enabled device release from silicon substrates. We also developed a reactive sputtering process for RuOx using oxygen and hydrogen as reactive gases. Films deposited at 15 mTorr with a 3:2:1 Ar:O₂:H₂ gas ratio exhibited low impedance and high charge-storage capacity suitable for neural recording and stimulation.

To support system-level operation, we developed Iris-128, an open-source 128-channel recording and stimulation headstage built from off-the-shelf components. Benchtop characterization and acute rat studies demonstrated noise below 10 μV RMS, reliable impedance monitoring, and robust neural signal acquisition. Finally, a solder-reflow interconnection process enabled accurate alignment and reliable bonding between thin-film arrays and printed circuit boards.

KEYWORDS: *Implantable Devices (probes, etc.)*

Burst frequency dependent modulation of evoked resonant neural activity by DBS

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Deep brain stimulation (DBS) is a neuromodulation therapy that electrically stimulates key basal ganglia structures to improve abnormal movements in patients with Parkinson's disease and related disorders. Symptom reduction depends on many variables such electrode placement, stimulation configuration, and stimulus amplitude and frequency. Conventionally, DBS at >100 Hz is required to improve tremor, but the mechanistic basis for this phenomenon is unclear. ERNA, or the evoked resonant neural activity, is a local neural response found approximately 3-4 ms after electric stimulation in the subthalamic nucleus and globus pallidus interna. Its amplitude is larger in STN than in GPi but shows paired pulse facilitation at both sites. How these responses evolve in the context of bursts and/or continuous stimulation is unclear. Here we sought to contrast changes in ERNA in response to 200 ms stimulus bursts at effective and ineffective stimulation frequencies (e.g., 30 versus 130 Hz). Biphasic stimuli were delivered at a therapeutic amplitude determined by a neurologist performing brain mapping for electrode targeting with pulse width of 60 μ sec. DBS bursts at therapeutic frequencies initially increase the amplitude and shorten the latency of ERNA, however this facilitation often diminishes by the conclusion of the 200 ms burst. In contrast, bursts at an ineffective frequency (30 Hz) do not significantly alter ERNA amplitude or latency. Our findings suggest that DBS synchronizes activity in the basal ganglia circuitry and that ERNA short-term facilitation may relate to its therapeutic effects. Future studies require similar recordings over longer time intervals to better understand the potential relevance of ERNA as a biomarker to guide both open- and closed-loop approaches to DBS therapy.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Monitor Neural Activity; Neural Recording & Modulation*

Low-channel EEG classification of Parkinson's disease under implant constraints

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Parkinson's disease (PD) is widely known as a progressive neurodegenerative disorder. It has been traditionally diagnosed through clinical observations, including motor symptoms that emerge after a great loss of neural signals. Machine Learning that utilizes electroencephalography (EEG) signals has given hope for identifying computational biomarkers of PD. However, many approaches still rely heavily on lab-grade EEG systems that are impractical for wearable or implantable neurotechnology. Wearable and implantable neurotechnology are largely restricted by their power, bandwidth, and hardware constraints.

This work explores the ability of reliably classifying resting-state EEG from PD using reduced electrode configurations, which are compatible with low-powered neural systems. A publicly available dataset by the University of New Mexico was used to analyze EEG recordings that consisted of PD patients demographically paired with healthy controls. This data was analyzed using Support Vector Machine (SVM), Random Forest (RF), and Convolutional Neural Network (CNN) classifiers. Frequency bands delta, theta, alpha, beta, and gamma are spectral bandpower features that provide the foundation of feature extraction. Spectral ratios were also derived. To prevent biased generalization, evaluation was performed using Leave-One-Pair-Out Cross-Validation.

A process of backward elimination helped us to evaluate how implant architectures impact diagnostic performance. Reducing to a minimal number of channels maintains robust classification capability. A balanced accuracy of 85.2% was achieved by our SVM model, at 5 channels. A balanced accuracy of 82.4% was achieved at 4 channels. Channel reduction did not universally decrease model performance, indicating that subsets can simplify sensing while improving generalization.

Our research demonstrates that accurately detecting PD can be done from simplified EEG setups, which is ideal for wearable devices. The research contributes to scalable and limited-resource neural diagnostic platforms capable of operating under realistic telemetry and embedded-system limitations.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Theory & Data Analysis Tools; Electrophysiology*

A 144-channel multiregion implant system designed for use in freely moving rats with stimulation and recording capability

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Understanding large-scale neural dynamics requires interfaces that can both record and stimulate neural activity across distributed brain regions. However, existing devices are limited by their low channel counts, large form factors, and restricted bidirectional (recording and stimulation) capabilities. To address limitations in size and channel count of existing neural recording and stimulation systems, we propose the development and implantation of a multishank thinfilm electrode array, paired with a higher channel count headstage capable of neural recording and stimulation in freely moving rodents. The implant consist of a flexible, amorphous silicon carbide based thinfilm microelectrode array and a custom designed headstage using Intan integrated circuits. The array is packaged to integrate with the open-source, and lightweight headstage intended for chronic implantation in rats, consisting of 128 recording-only and 16 bidirectional (recording and stimulation) channels. We show preliminary acute recordings in addition to in vitro characterization of the headstage and thinfilm. This platform addresses key limitations of existing commercial systems by combining high channel count, bidirectional functionality, and size.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Neural Recording & Modulation*

A genetically encoded optical sensor for real-time detection of GLP-1 signaling in vivo

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Glucagon-like peptide-1 (GLP-1) is a proglucagon-derived neuropeptide produced primarily by intestinal L-cells and brainstem nucleus tractus solitarius (NTS) preproglucagon neurons, where it signals satiety following food intake. GLP-1 signals through the GLP-1 receptor (GLP-1R), a G protein-coupled receptor, rendering conventional electrophysiological approaches insufficient for resolving GLP-1 release dynamics with high spatial and temporal resolution. Here, we describe the development and validation of a novel genetically encoded optical sensor (i.e., the Reporter for Transmission mediated by G-protein-coupled receptor (RTGR)) for GLP-1. GLP-1 RTGR was engineered by inserting a circularly permuted GFP (cpGFP) into the stalk domain, a segment linking the extracellular domain to the transmembrane region, of GLP-1R, enabling robust, real-time fluorescence responses to GLP-1. In vitro characterization in a heterologous expression system shows that GLP-1 RTGR localizes to the plasma membrane and exhibits high sensitivity and specificity for GLP-1 relative to other proglucagon-derived peptides. In paraventricular nucleus (PVN) brain slices expressing GLP-1 RTGR, trains of high-frequency electrical stimulation increased fluorescence signal, with no responses observed under control conditions. Using fiber photometry in vivo, GLP-1 RTGR signals were detected in the PVN during prolonged high-frequency optogenetic stimulation of NTS GLP-1 neurons in *Gcg-Cre::GLP-1R-Cre* mice expressing GLP-1 RTGR in the PVN and a red-shifted opsin in the NTS. No responses were observed under control conditions or following brief stimulation, suggesting sustained neuronal activity is required for GLP-1 release in vivo. In freely moving mice, overnight photometry recordings revealed prandial state-dependent changes in GLP-1 signaling in the PVN, with GLP-1 RTGR fluorescence increasing following each eating bout. Preproglucagon knockout mice showed disrupted feeding and lacked signaling dynamics observed in control animals. These findings support a role for GLP-1 signaling in satiety and refeeding, consistent with previous studies. In summary, these results indicate GLP-1 RTGR as a powerful and validated tool for tracking real-time GLP-1 dynamics in vivo, providing new insight into the neuroendocrine mechanisms underlying appetite regulation. Future work will define in vivo spatiotemporal GLP-1 release patterns and mechanisms governing hypothalamic neuropeptide release.

KEYWORDS: *Developmental/Systems Biology; Integrated Approaches; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Single-unit activity patterns during brief synchronized bursts from acute human cortical slices

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In vivo UP states are associated with sleep and memory processes. In vitro correlates of UP states, observed as brief spontaneous bursts, have been reported in mouse cortex, human brain organoids, and acute human cortical slices. However, in human cortex, these events have primarily been characterized using local field potential (LFP) recordings.

We sought to investigate the spatiotemporal structure of neuronal activity during spontaneous burst events in acute human cortical tissue at single-neuron resolution across a large cortical area.

Acute human cortical slices obtained from surgical resections were recorded using a high-density microelectrode array (HD-MEA) in a submerged chamber.

Spontaneous burst events were observed in acute human cortical slices from a subset of resections (4 of 6). Within individual bursts, neurons exhibited structured temporal firing patterns (sequences). Burst frequency was modulated by carbachol and 4-aminopyridine (4-AP). The activity patterns of spontaneous bursts differed from the seizure-like activity induced by a high concentration of 4-AP (100 μ M), which exhibited less temporal structure and greater synchronization around the burst peak.

Acute human cortical tissue exhibits spontaneous burst activity resembling the UP-state-like events previously described in mouse cortex and human brain organoids. These findings provide a foundation for investigating the role of local cortical circuits in UP-state-related human memory processing.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Synaptic Plasticity; Monitor Neural Activity*

Taking EEG source localization models to new frontiers of realism

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The distribution of EEG waves, from its neurogenesis on the cortex to their recording on the scalp, is heavily affected by the contrasts in conductivity among the different tissues in the human head.

Latest segmentation software from MRI can produce meshes of over 50 different tissues of the head involving millions of triangles.

Forward modeling—the most computationally expensive part of source localization—can be very challenging to perform with such complex models if one applies traditional methods like BEM or FEM.

We demonstrate that these models can be easily solved by combining reciprocity with the boundary element fast multipole method (BEM-FMM), which is a forward solver that uses surface elements like BEM but whose speed rivals that of FEM.

This enables source localization with models of an unparalleled accuracy, whose application can have far reaching consequences in clinical screening, brain-computer interfaces, and basic research in neuroscience.

KEYWORDS: *Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Neural Recording & Modulation*

Acetylcholine release in hippocampal CA1 encodes spatial novelty and correlates with movement speed

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In the hippocampus, acetylcholine (ACh) has been implicated in memory encoding, retrieval, and consolidation, with elevated ACh levels proposed to facilitate the encoding of new information and novel experiences, whereas lower ACh levels support memory retrieval and consolidation. Consistent with this framework, human studies have shown that muscarinic receptor blockade impairs memory encoding, disrupts hippocampal theta oscillations during learning, and compromises spatial navigation efficiency, resulting in longer paths to goal locations in real-world mazes. In parallel, animal studies have demonstrated that the activity of cholinergic projection neurons in the medial septum/diagonal band of Broca is strongly correlated, on behaviorally relevant timescales, with locomotion and the exploration of novel object locations. However, these studies did not directly measure hippocampal acetylcholine (ACh) release in CA1, leaving unanswered to what extent sub-second ACh release dynamics are correlated with animal movement, and spatial novelty encoding. Here, we used a genetically encoded ACh sensor (GRAB-ACh3.0) combined with fiber photometry to record ACh release dynamics in CA1 of 3- to 7-month-old female mice. Simultaneously, mice were video tracked, and deep learning-based behavioral analyses were used to quantify correlations between sub-second ACh release dynamics and behavior during free foraging, novel environment exposure, and an object location memory task. Consistent with previous GCaMP studies, CA1 ACh release was strongly correlated with the logarithm of running speed. Furthermore, ACh release increased during novel object exploration and was higher for objects in novel locations than for those in familiar locations. Finally, exploration of a novel arena induced a sustained increase in CA1 ACh release across the entire running speed range. Notably, the positive correlation between ACh release and movement speed was preserved under both conditions, indicating that environmental novelty enhances cholinergic activity independent of locomotion speed. Together, these findings demonstrate that hippocampal ACh release is dynamically correlated with exploratory behavior and spatial novelty encoding and provide insight into how cholinergic dysfunction may contribute to memory impairment in disorders such as Alzheimer's disease.

KEYWORDS: *Behavioral Sciences/Psychology; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation; Integrated Approaches*

Expanding the two-photon voltage imaging toolkit with functionally tuned multicolor GEVIs

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Voltage imaging with genetically encoded voltage indicators (GEVIs) enables cell-type-specific optical recording of neuronal membrane potential with high spatiotemporal resolution. However, neuronal voltage signals span a wide range of amplitudes and temporal dynamics, from slow subthreshold fluctuations to fast action potentials. At the same time, diverse two-photon imaging modalities impose distinct constraints on speed, sensitivity, and spectral compatibility. These combined demands create a broad and often conflicting design space that no single GEVI can fully address.

Here, we present a palette of GEVIs optimized for two-photon microscopy and designed to meet the needs of diverse experimental regimes. The toolkit comprises five GEVIs spanning complementary signal regimes and imaging constraints: two green negative-going JEDI3 sensors, two green positive-going FORCE indicators and one red positive-going VADER1 sensor. JEDI3hyp and JEDI3sub are optimized to detect millivolt-scale subthreshold dynamics in awake behaving mice, with JEDI3hyp tuned for hyperpolarizations and JEDI3sub for both subthreshold fluctuations and spike detection. The FORCE family targets robust spike detection across imaging conditions. FORCE1s, with prolonged responses to spikes, enables reliable single-spike resolution across larger imaging areas and cell populations via subkilohertz sampling rates using conventional resonant-scanning microscopy. In contrast, FORCE1f features faster kinetics, enabling temporally accurate tracking of rapid voltage transients during high-speed acquisition. Complementing green GEVIs is VADER1, a red-shifted GEVI that expands experimental capability by enabling spectrally multiplexed imaging with green sensors and all-optical integration of optogenetics and voltage imaging.

Together, JEDI3hyp, JEDI3sub, FORCE1s, FORCE1f, and VADER1 constitute a multicolor multifunctional GEVI palette spanning subthreshold dynamics, population spike imaging, ultrafast spike reporting, and spectrally multiplexed recordings. By tailoring sensitivity, kinetics, and spectral properties to distinct experimental demands, this toolkit substantially expands the capabilities of in vivo voltage imaging and enables deep-tissue, large-scale, and multimodal interrogation of neural circuit dynamics across diverse behavioral and physiological contexts.

KEYWORDS: *Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Linking genetic and neural signatures of stimulation in the human cortex *ex vivo* and *in vivo*

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Deep brain stimulation has seen had adoption in the previous decades, with emerging indications being tested for affective and cognitive conditions including stimulation of the temporal cortex for enhancing learning and memory in the face of cognitive impairment. Despite the potential of such therapies, the neural and genetic mechanisms underlying the effect of stimulation on human brain circuits are not understood. To explicate direct mechanisms of neural modulation elicited by brain stimulation, we developed an *ex vivo* approach utilizing microelectrode array stimulation and recording of resected temporal cortex from epilepsy patients. Our data indicate that stimulation enhances pyramidal cell firing rate which correlates with the activation of gene networks controlling synaptic plasticity in the same cell types. We show that stimulation strengthens and activates memory-associated cell assemblies. We detail cell type-specific gene regulatory networks that indicate preferential involvement of specific excitatory neuron subtypes and a potential role for non-neurons including astrocytes. Finally, we show that the genetic effects of *ex vivo* stimulation are concordant with those of *in vivo* stimulation in the human prefrontal cortex. We conclude that the overall impact of stimulation on the human cortex is activation of specific excitatory neurons and enhanced cell assembly activity and that these changes are supported by gene networks involving immediate early, synaptic, and ion channel genes. The results presented here support the synaptic plasticity and circuit modulation hypotheses of stimulation. Our findings establish a foundation to identify targetable cell type-specific genetic signatures that may be harnessed for therapeutic benefit in future neuromodulation strategies.

KEYWORDS: *Electrophysiology; Genetics/Genomics; Integrated Approaches; Neural Recording & Modulation; Synaptic Plasticity*

Brain-controlled spinal stimulation enables immediate upper-limb functional assistance after chronic tetraplegia

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Volitional motor intent and spinal circuit excitability must be temporally coordinated for effective motor control, yet this coupling is disrupted after cervical spinal cord injury (SCI). Epidural spinal cord stimulation (ESCS) can increase the excitability of residual spinal sensorimotor circuits. We tested whether an implantable brain-computer interface (BCI) that triggers cervical ESCS from decoded motor imagery could provide immediate upper-limb assistance. Three individuals with chronic cervical SCI (n=3; C3-C5 neurological levels; AIS A-D) underwent percutaneous implantation of epidural leads targeting dorsal rootlets spanning C5-T1. Stimulation contacts were selected using spinal mapping sessions in which candidate electrode configurations were tested to identify patterns that preferentially facilitated functional components of upper-limb movement, including pinch, grasp, and reaching. During activity-based therapy, primary motor cortex signals were decoded in real time via event related desynchronization to detect motor intent and trigger ESCS, thereby pairing endogenous cortical drive with exogenous activation of task-relevant cervical spinal circuits. BCI decoding success was $83.8 \pm 4.2\%$. Assistive effects were assessed by comparing grip force, EMG activity, and 3D reaching kinematics across no-stimulation, tonic ESCS, and BCI-ESCS conditions. Immediate neurophysiological effects were assessed before and after each session using motor evoked potentials (MEPs) and posterior root muscle (PRM) reflexes to evaluate corticospinal and spinal circuit excitability. BCI-ESCS improved grip force and reaching smoothness and accuracy beyond tonic ESCS. Immediately after single sessions, BCI-ESCS was associated with increased neural excitability, whereas tonic ESCS produced limited neurophysiological change under matched conditions. These findings suggest that ESCS may be most effective when stimulation is both anatomically targeted through spinal mapping and temporally coupled to volitional intent. BCI-driven cervical ESCS may therefore provide neuroprosthetic assistance by engaging residual corticospinal circuits after chronic tetraplegia.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Interventional Tools; Neural Recording & Modulation; Software (analysis, etc.) and Engineering; Synaptic Plasticity*

A Ca²⁺-selective channelrhodopsin for direct optical control of intracellular calcium and synaptic transmission

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While optogenetics has revolutionized neuroscience by enabling light-driven control of neuronal activity, direct, temporally precise optical control of intracellular Ca²⁺—a central regulator of cellular function—remains a key capability gap. Cation-conducting channelrhodopsins can elevate intracellular Ca²⁺ indirectly by depolarizing the membrane and activating endogenous voltage-gated Ca²⁺ channels. However, this strategy lacks precise control over Ca²⁺ dynamics and does not apply to cell types that lack such channels, including astrocytes. Despite long-standing interest in developing Ca²⁺-selective channelrhodopsins, naturally occurring examples have not been identified, and existing engineered approaches (e.g., CapChR2) suffer from limited conductance and spectral crosstalk with red-shifted optical reporters. Achieving robust, precise, light-driven control of Ca²⁺ would transform the ability to study and manipulate Ca²⁺-dependent processes in normal brain function and in neurological disorders such as Parkinson's disease.

Here, we report a naturally occurring Ca²⁺-selective channelrhodopsin (CaCR) that generates large, fast, and low-desensitizing photocurrents with markedly enhanced relative Ca²⁺ permeability compared with existing engineered channelrhodopsin. We demonstrate that this CaCR can be multiplexed with red-shifted, genetically encoded Ca²⁺ indicators, allowing all-optical control and visualization of intracellular Ca²⁺ dynamics. In acute cortical brain slices, CaCR activation was sufficient to trigger synaptic transmission even in the absence of voltage-gated Ca²⁺ channel activity, enabling direct interrogation of presynaptic Ca²⁺-dependent processes without relying on action potential generation. Finally, structure-guided mutagenesis identified residues that tune Ca²⁺ selectivity and conductance, providing a framework for rational engineering of CaCRs with improved and alternative properties.

Together, these results establish natural Ca²⁺-selective channelrhodopsins as a promising new avenue for direct, single-component control of intracellular Ca²⁺. This capability enables the dissection of Ca²⁺-dependent signaling and dynamics across diverse cellular contexts, and provides a foundation for strategies targeting Ca²⁺ dysregulation in disease.

KEYWORDS: *Electrophysiology; Molecular/Cellular Neuroscience; Neural Recording & Modulation; Physics or Microscopy/Optics; Synaptic Plasticity; Cell Type/Interactions*

Adaptive stimulation and response modeling of neural latent dynamics in real time

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Neural latent dynamics are a widely used framework for modeling the time evolution of low-dimensional neural data. These models have been established for neural decoding, for example, to translate from latent neural activity to ongoing kinematics in a motor task. To understand how such latent variables causally encode behaviors and to subsequently use these factors to modify external outputs would require methods for stimulating neural dynamics during an experiment. Tools to drive neural dynamics remain limited, however, due to the need to continually track ongoing changes in neural activity, to account for variation in neural responses under stimulation, and to select useful stimulations to apply from an extensive set of possibilities.

We developed a real-time method for stimulation-response modeling in smooth latent spaces, and an optimization framework for selecting high-dimensional stimulation patterns to drive low-dimensional dynamics. We package these as a tool to analyze and manipulate neural dynamics on the sub-second timescale. Our method combines streaming latent space construction, a stimulus-aware kernel regression model of perturbed dynamics, and projection maximization under feasibility constraints (such as sparsity and non-negativity) to determine stimuli that move dynamics along a desired vector. We demonstrated our approach on both simulated and real neural data (calcium fluorescence images, intracortical electrophysiological recordings). In simulations, we demonstrate that our method can regress and design stimulations correcting for nonlinear stimulation-response regimes. Our method is freely available as an open-source Python module, providing both immediately useful analyses as well as an extendable framework for new analysis. The tool's reliability and correctness is checked through extensive automated test coverage. We additionally collected preliminary data designing closed-loop stimulations in larval zebrafish, showing a proof-of-concept in real closed-loop experiments. Our method provides a novel end-to-end framework for stimulation of neural latent dynamics in real time, offering a promising avenue for both better understanding the causal relationship between neural activity and evoked behaviors, and for future brain-machine interface applications.

KEYWORDS: *Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Interventional Tools; Neural Recording & Modulation; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Opening the clinical trial door: Bench and intraoperative testing of an auditory nerve implant

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Cochlear implants are the most successful and well-known neural prosthetic to date and have restored meaningful hearing and communications to >1 million patients. CIs are implanted in hearing impaired infants to aid in language development, necessitating a decades-long device and performance lifetime. Despite this success, CI performance for speech in noise, low-frequency percepts, and enabling more independent channels has been stagnant for more than two decades. Stimulating spiral ganglion neurons through the bony cochlear wall with intracochlear electrodes immersed in relatively conductive perilymph and inability to place electrodes in the apical cochlea are the putative factors limiting performance advancements. We aim to demonstrate a higher performance hearing prostheses using a Blackrock Neurotech penetrating microelectrode array in the auditory nerve driven by a MEDEL Synchrony 2 cochlear stimulator forming the Auditory Nerve Interface (ANI) device to achieve direct and focal auditory nerve microstimulation in human subject perceptual studies in Hannover Germany. A cohort of 5 devices was tested for stimulation stability using 6.3 billion biphasic pulses at 100 μ A (clinical max) and 1200 μ A (stimulator max). Impedances over time with optical and electron microscopy observed the electrodes tolerated stimulation without degradation. First-in-human intraoperative studies under Ethics Committee approval with nine volunteers were performed at the Hannover Medical School. Study participants scheduled for translabyrinthine auditory nerve tumor resections, agreed to intraoperative placement of a wire ANI electrode array. We evaluated the surgical approach, electrode placement, evoked auditory brainstem responses (eABRs), and electrode impedances. Stimulation thresholds between 20 and 40 μ A were measured for evoked responses supporting viability of the surgical approach and technology. A forward masking paradigm was used evaluate independence of percepts evoked for each electrode. Outcomes suggest each electrode recruits distinct nerve fiber populations. Pre-clinical 3-month cat model studies using periodic intense stimulation, evaluation eABRs, and electrode impedance measurements were also completed. Sustained eABRs and electrode impedances <70 k Ω suggest the auditory nerve remains healthy and device remains functional. In conclusion, these data support the ANI device is sufficiently safe and effective to open the door for clinical trial.

KEYWORDS: *Implantable Devices (probes, etc.); Interventional Tools; Neural Recording & Modulation; Electrophysiology*

Enabling new insights into the living brain metabolome using LC-MS/MS and untargeted chemometrics

PRESENTER: **C. Cain**

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Central to advancing neuroscience is characterizing and monitoring the chemical composition of the brain extracellular space. Neurotransmitters, neuromodulators, and other metabolites within this microenvironment reflect several physiological functions occurring simultaneously on different spatiotemporal scales. Elucidating the role that these metabolites play in normal and diseased brains can improve our understanding of neurological disorders, thereby providing potential new drug targets and therapies. This presentation will demonstrate how analytical advances in liquid chromatography-tandem mass spectrometry and untargeted chemometrics can enable a deeper annotation of the living brain metabolome. Using in vivo microdialysis sampling, we can routinely monitor hundreds of compounds present in the brain metabolome. These compounds not only represent a wide range of chemical functionalities but also exhibit diverse biological functions. Leveraging this sampling framework, we define baseline and cocaine-induced differences in neurochemistry between two behavioral phenotypes in a rodent model of addiction. These differences were found to be associated with several metabolic pathways such as stress, neuroinflammation, energy usage, and neurotransmission. Ultimately, these findings broaden our understanding of addiction's impact on the brain and serve as the basis for ongoing efforts to better characterize neurochemical adaptations.

KEYWORDS: *Behavioral Sciences/Psychology; Chemistry; Developmental/Systems Biology; Implantable Devices (probes, etc.); Theory & Data Analysis Tools; Informatics, Statistics, or Applied Mathematics*

Bioinspired electronics for brain-machine interface

PRESENTER: **X. Yang**
Johns Hopkins University

AUTHORS: X. Yang

Bioelectronic devices have been very important as fundamental research tools for probing and understanding the brain with high spatiotemporal resolution, and as therapeutic avenues for treating brain diseases, disorders, and injuries. We draw inspiration from biological systems and art forms to design and develop a series of bio-inspired and art-inspired bioelectronics for broad applications in brain-machine interfaces, regenerative medicine, and the study of human neural development and diseases. Our studies encompass neural probes for in vivo brain-machine interface, electronic scaffolds for brain repair, and platforms for detecting human genetic diseases and tracking human neural development using human brain organoids.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation*

A low-cost flexible probe platform for stable chronic cortical single-unit recordings across weeks in mice

PRESENTER: **R. Bain**

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Chronic extracellular recordings in mice are limited by probe cost, implant weight, tissue response, and loss of single-unit identity across days. These constraints are especially problematic in cortical areas where acute probes can yield many units but stable chronic unit tracking is difficult. We developed a low-cost chronic electrophysiology platform built around ultra-flexible polyimide probes, compact Intan-based headstages, and lightweight resin-printed headcaps for long-duration recordings in freely moving and head-fixed mice. The recording interface consists of 64-channel flexible polyimide probes with gold traces and PEDOT-coated recording sites. Probes are fabricated using standard cleanroom processes and assembled onto compact PCBs with 64-channel SlimStack connectors. During implantation, each probe is inserted using a removable fine shuttle threaded through a distal loop, allowing placement without leaving a rigid insertion element or glue in the brain. After hydration, the probe forms a compact three-dimensional braid-like structure that provides local multichannel recording neighborhoods while minimizing residual implant volume. Custom 128-channel headstages containing Intan RHD2164 chips support two 64-channel probes per headstage, and two headstages can be used for 256-channel recordings with a total implant mass of approximately 4 g, including headcap, probes, connectors, and electronics. We tested this platform in posterior parietal cortex across chronic recording sessions. At week 6 after implantation, high-quality single units remained detectable with stable waveforms across multi-day intervals. In one dataset, 71 putative single units were matched across a 48-hour gap from W6D2 to W6D4 without volume-conduction modeling or probe-drift correction. In a separate analysis combining recordings from W6D1 and W8D4, many units remained recognizable across a 17-day interval, indicating that the flexible interface can preserve single-unit identity over timescales that are challenging for many acute or semi-chronic approaches. Together, these results demonstrate a scalable chronic recording platform combining low probe cost, low implant mass, removable insertion hardware, and long-term unit stability. This platform enables repeated high-channel-count recordings from the same cortical circuits across days to weeks and provides a practical foundation for longitudinal studies of neural population stability, learning, sleep, and circuit dynamics.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Software (analysis, etc.) and Engineering*

Acute tremor suppression and potential carryover benefits with thalamic coordinated reset deep brain stimulation in essential tremor

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Essential tremor (ET) is the most common movement disorder affecting millions in the US. While thalamic traditional deep brain stimulation (T-DBS) is a well-established therapy for medication-refractory ET, limitations remain, including current spread related side effects, high energy demands and variable long-term efficacy. Coordinated reset DBS (CR-DBS) has been proposed as an alternative strategy that delivers low-amplitude, spatially and temporally patterned stimulation across multiple contacts of a DBS lead to desynchronize pathological neural synchrony, with effects persisting beyond stimulation (carryover effect). Here, we present preliminary results ($n = 5$) from an ongoing proof-of-principle clinical study evaluating the feasibility, safety and efficacy of unilateral thalamic CR-DBS for ET. In a within-subject design, participants underwent one week of CR-DBS or T-DBS, followed by up to two weeks of wash out period to monitor carryover effects, with treatment order pseudorandomized for each participant. Both the participant and outcome assessor were blinded to the treatment order. The frequency (i.e., cycle rate) and stimulation contacts for CR-DBS were determined based on the tremor related neural oscillatory activity in thalamus as well as the relative location of DBS contacts to the ventral intermediate nucleus (VIM). Tremor severity was assessed using the Essential Tremor Rating Assessment Scale (TETRAS), including the Performance (TETRAS-P) and Activities of Daily Living (TETRAS-ADL) subscales. CR-DBS produced significant reductions in the TETRAS-P score at the 1st and 2nd hour of stimulation (Wilcoxon signed-rank test, one-sided, $p < 0.05$, $n = 5$). However, substantial inter-subject variability was observed at one week on and after CR-DBS in TETRAS-P as well as CR-DBS related TETRAS-ADL scores. One participant demonstrated long-term carryover benefits, with TETRAS-P score reduced by $>50\%$ during the two weeks after CR-DBS was ended. In contrast, another participant exhibited limited carryover reductions in the TETRAS-P score (6-9%). These preliminary findings suggest that thalamic CR-DBS can acutely reduce tremors in ET and may produce long-term carryover benefits. Studies in more subjects are needed to confirm the acute effects of CR-DBS, characterize sources of inter-subject variability and optimize CR-DBS stimulation parameters to maximize clinical benefits for each participant.

KEYWORDS: *Electrophysiology; Neural Recording & Modulation; Human Neuroscience, Clinical Science, or Public Health*

Cortex-wide patterned optogenetics

PRESENTER: **M. Rynes**
University of Chicago

AUTHORS: M. Rynes, M. Kolb, P. Salvino, L. Pinto

Distributed brain activity is thought to underlie cognitive behaviors. For example, decision-making tasks involve cortex-wide spatiotemporal activity patterns. However, what exact patterns of activity and co-activity are causal to different aspects of cognitive behavior is still poorly understood. A major remaining challenge to accomplish this is the fact that techniques to perturb activity at these scales remain limited. Here, we developed an open-source Digital Micromirror Device (DMD) based apparatus and accompanying software for spatiotemporally patterned optogenetic perturbation at a ~1-cm scale, with a resolution of ~25 μm . We used this apparatus for optogenetic inhibition through the intact cleared skull of mice transgenically expressing Channelrhodopsin-2 in inhibitory interneurons (VGAT-ChR2-EYFP), while they ran spontaneously on a wheel. We first used extracellular electrophysiology with laminar silicon probe to characterize the spatial pattern and amount of inhibition. Compatible with results from laser-scanning systems, we achieved inhibition across all cortical layers with a lateral spread of ~1 mm. We then used this apparatus to generate spatiotemporally stochastic (white-noise) patterns of optogenetic inhibition, while recording from the retrosplenial (RSP) or secondary motor cortex (MOs). Using systems identification (e.g., spike-triggered averaging/reverse-correlation analysis), we inferred large-scale functional interactions between single-unit spiking in these regions and the rest of the dorsal cortex. Crucially, these functional-interaction maps mirrored known features of anatomical connectivity. We have thus developed a new method for cortex-wide patterned optogenetics, offering the possibility of the causal contributions of investigating distributed neural dynamics to cognitive behaviors.

KEYWORDS: *Electrophysiology; Neural Recording & Modulation; Software (analysis, etc.) and Engineering*

Neural mass modeling of local field potentials to probe neuromodulatory mechanism of subcallosal cingulate deep brain stimulation

PRESENTER: **P. Sarikhani**
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AUTHORS: P. Sarikhani, E. Fitoz, H. Mayberg, R. Butera, C. Rozell, S. Alagapan

Deep brain stimulation (DBS) targeting the subcallosal cingulate cortex (SCC) white matter has shown promise as a therapeutic intervention for treatment-resistant depression (TRD). Recent neurotechnological advances allow for longitudinal recording of local field potentials (LFPs) during DBS, revealing acute modulation of beta-band activity consistent with previous intraoperatively and post-implantation experiments. Prior evidence suggests that SCC DBS may exert its acute effects through projections to downstream dopaminergic and serotonergic systems, leading to changes in neurotransmitter levels that influence neural dynamics. Dopamine, in particular, has been shown to modulate beta band oscillations. However, the inability to simultaneously measure neurochemical and electrophysiological signals in vivo limits direct validation of these mechanisms. Neural mass models (NMMs) provide a biophysically informed generative framework to address this gap by linking measurable neural activity to interpretable parameters. When combined with modern inference techniques, NMMs fitted to LFP data enable quantification of DBS-induced circuit-level changes and facilitate hypothesis-driven investigation of neuromodulatory processes. In this study, we introduce a computational framework that integrates an extended Jansen-Rit NMM with stochastic variational inference (SVI) for Bayesian parameter estimation from LFP power spectral densities (PSDs). The model consists of three interacting neural populations, with neuromodulatory effects incorporated as concentration-dependent changes in excitatory and inhibitory postsynaptic gains, as well as in the sigmoid transformation governing the membrane potential-to-firing rate relationship. Simulations demonstrate that serotonin and dopamine jointly modulate oscillatory power in a nonlinear and interdependent manner, where the effect of each neuromodulator depends on the level of the other. The framework was implemented in PyTorch, and parameter estimation was performed by maximizing the evidence lower bound (ELBO), using a likelihood defined by the log mean squared error between simulated and observed PSDs. Validation on synthetic data generated from the Jansen-Rit model showed accurate recovery of PSDs, achieving $R^2 = 0.99 \pm 0.005$ across five runs. When applied to experimental LFP data, the posterior mean PSD closely matched the empirical PSD, with $R^2 = 0.88 \pm 0.02$ and mean 95% interval coverage of 0.99.

KEYWORDS: *Computational Biology/Modelling; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation; Software (analysis, etc.) and Engineering*

Genetically encoded assembly recorder temporally resolves cellular history

PRESENTER: **Y. Yan**

Johns Hopkins University

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Cells dynamically transform molecular and transcriptional states in response to sensory experience, internal brain states, pathological insults, and pharmacological perturbations. Mapping these activity-dependent cellular histories with both anatomical coverage and temporal precision is essential for understanding brain function and dysfunction. However, current approaches face a fundamental trade-off. Real-time electrophysiology and optical imaging provide high temporal resolution but are typically restricted to limited fields of view and sparse cell populations. In contrast, post hoc histology methods enable brain-wide cellular phenotyping, but they largely collapse activity histories into static snapshots.

Here we introduce Granularly Expanding Memory for Intracellular Narrative Integration (GEMINI), a genetically encoded recording platform that enables retrospective reconstruction of cellular activity histories from fixed samples. GEMINI leverages a computationally designed protein assembly that grows predictably inside living cells, functioning as an intracellular memory device. As the assembly expands, activities are captured as tree-ring-like fluorescent patterns, allowing temporal information to be decoded post hoc. Using HaloTag-based pulse labelling, we demonstrate that GEMINI can recover absolute chronological information with hour-level accuracy. In cultured cells, GEMINI maps NF- κ B-mediated transcriptional responses to tumor necrosis factor, resolving brief stimulation windows as short as 15 minutes and distinguishing differences in signal amplitude, duration, and repeated activation.

To establish GEMINI as a tool for the neuroscience community, we performed AAV-based gene delivery to the mouse brain, demonstrating that GEMINI particle formation minimally perturbs neuronal physiology, brain anatomy, and behaviours. In vivo, GEMINI resolves transcriptional changes and activity-dependent neuronal histories, including immediate early gene responses associated with seizure induction. GEMINI enables brain-wide spatiotemporal mapping of activity-dependent molecular events. We envision that GEMINI would introduce a paradigm shift to the existing neuronal recording technologies by bridging dynamic recording with histological analysis.

Together, GEMINI provides a scalable and generalizable platform for reconstructing organ-wide cellular dynamics underlying brain physiology, pathology, and responses to perturbation.

KEYWORDS: *Genetics/Genomics; Integrated Approaches; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Use of the NeuralGlider insertion system to lower the insertion of microelectrode arrays, Neuropixels probes, optics, and chemogenetic delivery needles

PRESENTER: **K. Snook**

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Development of microelectrode arrays (MEA), Neuropixels probes, optics, and chemogenetic delivery needles has propelled neuroscience research. However, despite efforts to minimize tissue damage through design optimization, the physiological response following device insertion continues to limit research. Minimizing mechanical forces during insertion can mitigate this response and improve experimental and physiological outcomes, such as neural activity and reactive gliosis. Use of NeuralGlider® Inserter (NeuralGlider, Actuated Medical, Inc.), a micron-scale ultrasonic vibration system, reduces insertion force and cortical dimpling during device placement. In vivo, acute recordings of NeuralGlider-implanted MEAs into porcine cortex showed higher single unit yield. Herein, we investigated vibrated placement of Neuropixels, gradient-index (GRIN) lenses, and infusion cannulas/needles on bench and in vivo models. NeuralGlider lowered the force for Neuropixels probes to penetrate an agarose model—77% for Neuropixels 1.0 single-shank (SS) probes and by 73% for Neuropixels 2.0 probes—reducing probe buckling and dimpling. In vivo, vibration-assisted cortical insertions reduced tissue buckling and enabled insertion depths of up to 10 mm with Neuropixels 1.0 NHP SS probes. Neuropixels 2.0 multi-shank and SS probes were also successfully inserted into the cortex of large and small preclinical models, respectively, without buckling. Vibration-assisted insertions of 0.5 mm GRIN lenses and 1.0 mm optical lenses into ex vivo porcine brain tissue reduced pial puncture force by >50% and resultant tissue compression ($p < 0.01$, Student's T-test). In vivo NeuralGlider GRIN lens insertions (mouse medial prefrontal cortex) were completed utilizing controlled insertion speed, omitting tissue aspiration, and demonstrating improved implantation success, offering a reliable GRIN lens implantation procedure for deep-brain calcium imaging. Puncture force of vibrated infusion needles was reduced by >75% from control at speeds up to 500 micron/s and enabled puncture of porcine dura with 33G needles. In vivo testing showed smaller gauge infusion needles reduced aliquot backflow along needle tracks. Infusion sites showed higher cellular density (less damage) with vibrated insertion after 6 weeks. NeuralGlider's micron-scale, ultrasonic vibration allows for insertion in vivo and ex vivo, while reducing probe buckling, tissue dimpling and allowing entry into difficult tissue types.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Physics or Microscopy/Optics*

An analysis of stakeholder perspectives on the principal risks and existing regulatory gaps in consumer EEG-based neurotechnology

PRESENTER: **J. Moonga**
King's College London

AUTHORS: J. Moonga, L. Soo, S. Ayis

Consumer electroencephalography (EEG)-based brain-computer interfaces are increasingly marketed for cognitive enhancement, self-monitoring and entertainment. These devices not only collect sensitive and contextual neural data, but they also generate health-adjacent interpretations. Increasingly, concerns are raised on the risks and harms surrounding neurotechnologies since many fall outside conventional medical-device pathways, creating regulatory inefficiency. In addition, the lack of appropriate policy instrument and governance framework understates manufacturers' ethical responsibility. We conducted qualitative research consisting of ethnographic evaluation and semi-structured interviews with 22 experts working across clinical neuroscience, neurology, neuropsychiatry, neuroengineering, manufacturing, data science, medical ethics, law and regulation in North America, Europe, and Latin America. The interviews examined perceived benefits, risks and harms of EEG-based neurotechnologies, and limitations of regulation and governance. The collected data was analysed using thematic approaches to identify recurring patterns and interconnected themes. Firstly, participants described substantial regulatory ambiguity at the boundary between medical, wellness and consumer applications. Secondly, they raised concerns about safety extended beyond direct physical harm to include inaccurate outputs, unsupported health claims, psychological consequences and the vulnerability of users seeking clinical benefit. Thirdly, participants highlighted privacy mechanisms are insufficient to address issues around data safeguard, storage and interference. Lastly, the participants did not generally support the reliance on a single regulatory instrument. In addition, differing opinions are identified on the distribution of responsibility among manufacturers, regulators, professional bodies and users. Based on these findings, a layered governance approach is proposed with risk-proportionate statutory oversight, consumer-protection measures, technical standards, and lifecycle monitoring of devices. This research suggests existing governance challenge is not simply an absence of policy and regulation, but a mismatch between regulatory instruments and the hybrid functions of EEG-based neurotechnology. Efficient governance will require a combination of regulatory frameworks and anticipatory approaches with ethical considerations throughout the lifecycle of consumer neurotechnologies.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Interventional Tools; Monitor Neural Activity; Neural Recording & Modulation; Neuroethics, Philosophy, Law; Software (analysis, etc.) and Engineering*

Development of an implantable brain-computer interface question prompt list (QPL) for clinical trials: Preliminary results of a modified Delphi study

PRESENTER: **E. Klein**
Oregon Health and Science University

AUTHORS: E. Klein, A. Brown, S. Goering

Implantable brain-computer interface (iBCI) clinical trials are ethically complex and there are few tools available to help research participants and researchers navigate these complexities. We describe preliminary results of development of a shared decision-making tool—a question prompt list (QPL) for clinical trials—that can help facilitate dialogue about best practices between iBCI researchers and participants. We have conducted two of three planned modified Delphi rounds. First, qualitative interviews were conducted with implantable neurotechnology participants and their caregivers (n=11) to understand participant experiences and needs, and to identify candidate best practices of support for participants enrolled in clinical trials. From those interviews, we created categories of support and drafted a tool for facilitating dialogue on those areas. Second, qualitative interviews were conducted with implantable neurotechnology researchers (n=21) to understand their perspectives on best support practices, and to obtain feedback on the idea and content of the QPL. Third, a draft version of the QPL tool will be refined through an additional round of feedback from BCI researchers and iBCI participant community members. Our analysis of interview data from the first two Delphi rounds identified candidate best practices of support for iBCI participants, including topics not typically covered in informed consent discussion or documentation, such as managing expectations over the long period of the study, navigating social relationships built during the study, and support for the eventual transition out of the study. Researchers expressed favorable attitudes toward the idea of a QPL tool that could be provided to participants during the enrollment phase of clinical trials to facilitate dialogue about best practices of support and how to implement them. Here we report preliminary findings of the first two rounds of the modified Delphi study to be presented to BCI researchers and iBCI community members in the final Delphi round.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Neuroethics, Philosophy, Law*

Public expectations for post-trial responsibilities following experimental deep brain stimulation

PRESENTER: **A.R. Merner**

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DBS systems are being explored as treatments for a growing number of neurological and treatment-resistant psychiatric conditions. Although many participants experience an improvement in symptoms, these devices are considered experimental and continued access is not guaranteed after trials end. Participants who cannot secure continued access to the device may experience recurrence of severe symptoms, while those who are able to maintain the device may experience significant financial burden, as insurance companies are not required to cover the costs associated with an experimental device. Patient, care partner, and researcher views on these issues have been explored; however, there is little information regarding the public's views on responsibilities for post-trial device access and maintenance. Given that many of these trials are at least partially funded by public tax dollars, and these devices are being tested on members of the public, it is critical to gain their insights on post-trial obligations. We surveyed a nationally representative sample of the U.S. public (n=1200) regarding their views on post-trial access and maintenance responsibilities. Participants were presented with a description of DBS, a timeline of a DBS trial for treatment resistant depression, information on the stakeholders involved in these trials (e.g., TRD participants, device manufacturers, funders, researchers), and a vignette describing the typical patient-participant experience in an experimental DBS trial. Participants completed open-ended and single-selection questions regarding responsibility for device maintenance/repair (e.g., battery replacement), stimulation adjustments, and mental health support costs. Most respondents believed participants should not be responsible for device maintenance/repair (84.7%) or stimulation adjustments (68.3%), instead assigning responsibility to device manufacturers and insurance providers. Qualitative responses highlighted themes of duty of care, fair compensation, long-term commitment, informed consent, societal responsibility, equity, and reciprocity. Additional findings will be discussed. Our data suggest that the public views post-trial responsibilities as shared obligations rather than the sole responsibility of research participants. As investigational DBS expands to new indications, these perspectives can help inform ethical guidance and policy surrounding post-trial access and long-term device support.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neuroethics, Philosophy, Law*

The ambiguously experimental position of Argus II recipients

PRESENTER: **W. Chiong**

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AUTHORS: V. Black, M. Hunt, W. Chiong

While the closure of neurotechnology company Second Sight is often cited as a cautionary tale, focusing solely on its abrupt dissolution risks obscuring the systemic conditions that shaped users' experience of abandonment. Drawing on interviews with Argus II recipients, this project examines how they initially received a device that inadequately incorporated blind user input but were later engaged to provide feedback that shaped the next iteration of external components. Yet when Second Sight ceased operations, these same contributors were abruptly cut off—including from access to components they'd helped improve. This highlights a deeper issue: the lack of obligation to ensure disabled users share in the benefits of their contributions. While post-trial ethical reforms aim to better protect research participants, they may not apply to those who—like these users—were not enrolled in formal trials. This reveals an ethical gray zone: internal product testing and clinical care can blur together without triggering the obligations of formal study enrollment. These recipients occupied shifting roles—user, patient, participant, and consumer—reflecting a broader pattern of fragmented responsibility in implanted device design and implementation. Preventing disabled users from being rendered “ambiguously experimental” requires recognizing that feedback incorporation, while important, does not necessarily fulfill ethical obligations to them.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neuroethics, Philosophy, Law*

Ethical issues in multimodal data collection studies for identification of emotions: Accuracy, trust, and privacy

PRESENTER: **N. Dorfman**
University of Washington

AUTHORS: N. Dorfman, E. Klein, S. Goering

The NIH's Brain and Behavior Quantification and Synchronization (BBQS) grant program funds research to create new tools for understanding the neural basis of behavior. Our BBQS parent study integrates multiple synchronized physiological data streams to identify emotional states. Participants view videos and complete an interview with a virtual agent while wearing EEG, heart rate, sweat, eye-tracking, and other sensors. To understand the ethical issues associated with this kind of research, we plan to interview participants to ask about their experiences in the study, their use of self-tracking technologies, and their perspectives on a hypothetical emotion sensing device that relies on similar multimodal data. This poster presents preliminary findings from four participant interviews.

We developed a semi-structured interview guide informed by a literature review on the ethics of wearable technologies. Interviews were conducted via Zoom (30-50 minutes), transcribed, de-identified, and analyzed using grounded theory methods.

Three preliminary themes emerged: accuracy, trust, and privacy. Participants viewed accuracy as essential for emotion-sensing technologies. Most participants expressed skepticism that synchronized physiological data can currently determine emotional states, while expecting future technological advances to improve performance. One participant believed that only implantable devices would be able to accurately infer emotional states, while another participant questioned whether emotional experience, given its complexity and context-sensitivity, could ever be adequately captured through biodata measurement. When discussing a hypothetical device that could infer and report users' emotional states, three participants reported they would trust their own self-assessments over the device's output, whereas one believed the device would be more accurate than their own perceptions. Finally, all participants had privacy concerns about any kind of multi-modal data collection, noting that emotional data is particularly sensitive. Participants expressed that data sharing should be opt-in only, and users should have significant control over who has access to their data.

Multimodal data collection to identify emotional states raises ethical issues related to accuracy, trust, and privacy. Our next steps include conducting interviews with more study participants to better understand the associated ethical issues.

KEYWORDS: *Neuroethics, Philosophy, Law; Neural Recording & Modulation*

Multi-scale imaging of chandelier cell development reveals region-specific circuit alterations in the autism-associated 16p11.2 microdeletion mouse model

PRESENTER: **A. Benn**

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AUTHORS: A. Benn, C. Munn, N. Blaha, S. Manjila, Y. Kim, A. Paul

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition marked by sensory abnormalities, social and communication deficits, and restricted or repetitive behaviors. Although ASD etiology remains unclear, genetic risk factors are substantial, and recurrent copy number variants at human 16p11.2 locus are among the strongest contributors. Notably, 16p11.2 microdeletion is strongly associated with ASD, developmental delay, and obesity. Symptom onset coincides with cortical circuit maturation, a period when inhibitory interneurons establish connectivity. One proposed mechanism is that genetic risk disrupts cortical interneurons, producing excitation-inhibition imbalance and downstream behavioral deficits. Chandelier cells (ChCs) are especially relevant because they selectively innervate the axon initial segments (AISs) of hundreds of pyramidal neurons (PyNs), inhibiting action potential generation at this critical site. Indirect combinatorial immunostaining of human post-mortem ASD prefrontal cortex samples has suggested alterations in putative ChCs. Hence, we examine whether a mouse model carrying a heterozygous syntenic deletion corresponding to human 16p11.2 disrupts ChC connectivity and cortical distribution. This study uses a genetically labeled mouse line to enable robust visualization across a critical window of ChC development at postnatal days (P) 7, 12, 17, and 28-31. Super-resolution confocal microscopy with an automated image-analysis pipeline quantified ChC bouton density and morphology at the AIS of PyNs across cortical regions. Whole-brain light-sheet fluorescence microscopy (LSFM) was used to visualize and quantify ChC cell bodies and their regional and laminar cortical distributions. Preliminary estimates indicate that subtle differences emerge by P12, whereas the strongest ChC connectivity changes occur at P28-31, when region-specific differences in ChC bouton density and morphology at AISs of PyNs are most apparent relative to wild type. Whole-brain LSFM further reveals altered regional and laminar distributions of ChCs. Ongoing work is probing potential non-cell-autonomous influences that may contribute to altered ChC bouton development and maintenance. Together, this study establishes a cell type-resolved framework integrating genetic access, multiscale imaging, and automated quantification. This framework may clarify how ASD-associated risk reshapes connectivity and guide strategies for modulating cortical circuits.

KEYWORDS: *Cell Type/Interactions; Developmental/Systems Biology; Molecular/Cellular Neuroscience; Neuroimaging (invasive, non-invasive imaging)/Radiology; Synaptic Plasticity; Genetics/Genomics*

Optimization of genetically encoded indicators for multiwavelength in vivo analysis of brain circuits

PRESENTER: **A. Andreoni**

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AUTHORS: A. Andreoni, S. Li, J. Yu, M. Martin, V. Mensah, Y. Wang, Y. Hua, L. Tian

The brain is remarkably dynamic, adaptive, and flexible in response to environmental changes. These capacities are enabled by diverse cell types which communicate with an array of chemical neurotransmitters (NTs) or neuromodulators (NMs) and receptors. To understand the logic by which multiple convergent inputs shape neuronal activity, it is essential to record the timing and location of NT and NM release and the dynamic changes in membrane voltage that result. Our team has developed genetically encoded indicators, as well as high-speed and resolution microscopy, to allow simultaneous optical measurement of various NT/NM release and diffusion and post-synaptic activity in vivo with cell-type and circuit specificity.

Despite these successes, significant headroom exists to optimize these indicators to enable sensitive imaging in small structures, higher throughput, and measurements in sparsely innervated brain areas. Moreover, existing NT and voltage indicators are nearly all green in color, and optimization of other colors is needed to enable multiplexing, along with hardware to perform such recordings and algorithms to process them. Finally, these new tools must be rigorously and systematically benchmarked in vivo to allow the large community of users to better design and interpret measurements in behavioral experiments. With available technology, we have yet to address the diversity of chemical neurotransmission at scales crucial to understanding brain circuit function.

KEYWORDS: *Molecular/Cellular Neuroscience; Monitor Neural Activity; Neuroimaging (invasive, non-invasive imaging)/Radiology; Chemistry*

BundleAtlasing: A tool for population-specific white matter bundle atlas creation

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White-matter (WM) tract atlases are essential for bundle extraction, tractometry, population studies, and cohort-specific comparisons. Many atlas-building workflows begin from voxel-space templates, averaged diffusion models, or whole-brain tractogram clustering, and are not optimized for the common setting in which corresponding bundles have already been segmented across subjects. We introduce BundleAtlasing, a framework for constructing population-specific WM atlases directly in streamline space from pre-segmented bundles.

BundleAtlasing builds on Streamline-based Linear Registration (SLR; Garyfallidis 2015), a well-established streamline-space registration framework, but adapts it from pairwise target-to-reference alignment to unbiased population atlas estimation. The key advance is a geometry-preserving halfway registration strategy (Halfway SLR) that estimates a population centered space for each bundle rather than forcing all subjects toward one fixed reference. A groupwise bundle-combination strategy then distills population consistent bundle anatomy while suppressing subject specific and noisy streamlines. This makes the method better suited for atlasing, where the goal is to recover a representative population bundle rather than to maximize apparent overlap through shrinkage or nonlinear overwarping.

We evaluated BundleAtlasing using Human Connectome Project young-adult data and Parkinson's Progression Markers Initiative—918 and 64 subjects, respectively—data across association, commissural, projection, brainstem, and cerebellar tracts. Performance was assessed at two levels: pairwise registration accuracy and final atlas quality. We used different quantitative metrics to measure streamline-space similarity, voxel-space coverage, and geometry preservation, allowing us to distinguish true anatomical agreement from apparent improvements caused by shrinkage or deformation depending on the registration method. In registration experiments, Halfway SLR provided robust alignment while better preserving bundle geometry than alternative streamline-based linear and nonlinear methods. In atlas comparisons, BundleAtlasing produced compact, anatomically coherent atlases that were closer to target populations than existing reference atlases and alternative registration-based atlasing strategies. BundleAtlasing provides a practical framework for building unbiased, population-specific streamline atlases for reproducible WM bundle analysis and tractometry.

KEYWORDS: *Connectome; Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering*

Direct decay-location reconstruction for gamma-positron brain imaging

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Prompt-gamma positron emitters can provide more information than conventional PET because each decay may produce two 511-keV annihilation photons and a coincident higher-energy gamma ray. In a dedicated brain-imaging system, this mixed signal creates an opportunity to estimate the radionuclide decay spatial distribution directly, rather than relying only on the positron annihilation location. We present a GPU-accelerated list-mode reconstruction framework for gamma-positron brain imaging that jointly models PET coincidences, prompt-gamma Compton events, and triple events containing both event classes from the same decay.

The framework uses UAMonteCarlo emission and detector simulations to generate sorted list-mode data and voxelized sensitivity maps for an edge-on crossed-strip cadmium-zinc-telluride (CZT) geometry. The initial brain-imaging configuration contains 690 detectors in a 30-cm-diameter ring surrounding a 24-cm water sphere and models scandium-44, including a 1474-keV maximum-energy positron and a 1157-keV prompt gamma. For each event, GPU kernels evaluate the probability of the measured detector data over candidate decay voxels. PET likelihoods include annihilation-photon attenuation and positron range effects; prompt-gamma likelihoods include Compton kinematics, energy deposition, detector interaction type, and attenuation; and triple-event likelihoods combine PET line-of-response support with prompt Compton-cone support. Event kernels are incorporated into a list-mode maximum-likelihood expectation-maximization update normalized by event-type-specific sensitivity.

Initial consistency studies with simulated scandium-44 point-source data show that PET-only and prompt-only reconstructions recover the expected source location after three iterations using 2000 events per mode. Representative likelihood images and independently generated sensitivity maps show the anticipated tradeoff between higher-sensitivity PET and prompt-only data and lower-sensitivity triple events with greater localization weight per event. These results establish the reconstruction machinery needed for combined gamma-positron brain imaging and motivate ongoing studies of triple-event reconstruction, mixed-event-type updates, and spatial resolution characterization in task-relevant phantoms.

KEYWORDS: *Informatics, Statistics, or Applied Mathematics; Neuroimaging (invasive, non-invasive imaging)/ Radiology; Physics or Microscopy/Optics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Transcranial acoustoelectric imaging of the cortical hand knob in a realistic head phantom

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Transcranial Acoustoelectric (AE) Imaging has been proposed as a new modality for mapping neuronal currents at high spatial and temporal resolution. As ultrasound (US) pulses are steered in the brain and interact with physiologic currents, generating a weak radiofrequency interaction signal, while recording electrodes detect AE-induced voltages. The measured AE signals are used to form cross-sectional or volumetric movies proportional to local currents. Previous limited AE imaging head phantoms used simple currents without user interaction or feedback. The this study aimed to demonstrate feasibility of AE imaging using realistic currents combined with interactive feedback from a subject performing a hand pumping task, serving as a unique testbed that pushes the limits of AE imaging technology towards in vivo proof-of-concept studies in humans with cross validation using scalp EEG and fMRI.

A human skull filled with conductive agarose gel was implanted with a 5x4 ECoG grid array over the hand knob region of the motor cortex. A bipolar waveform consistent with cortical currents generated by median nerve stimulation were passed through two ECoG contacts separated by 10 mm, producing a time-varying dipole. US pulses were rapidly focused and steered through the skull as AE signals were recorded by EEG electrodes on the skull surface connected to a broadband MHz amplifier, producing M mode and B mode AE current maps through the skull. A closed-loop feedback system using an Arduino was setup such that the amplitude of the dipole inside the head phantom varied depending on the pumping pressure exerted by the subject and reflected in the subject's forearm electromyogram (EMG).

We successfully demonstrated real-time AE imaging of cortical currents (0.1 mA) in the head phantom and dependent on the subject's squeeze pressure and EMG recordings. Trials with the highest to lowest squeeze pressures produced peak AE signals of 90, 50 and 27 μV , respectively, and highly correlated ($R^2 = 0.96$) with the induced cortical current. The AE imaging system with motor-controlled feedback serves as an ideal testbed for optimizing tABI towards in vivo validation of this new modality for mapping neuronal currents in healthy volunteers.

KEYWORDS: *Electrophysiology; Monitor Neural Activity; Neuroimaging (invasive, non-invasive imaging)/Radiology*

NexGen 7 T MRI: A BRAIN Initiative resource for human mesoscale neuroimaging

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Understanding the structural and functional organization of human brain circuits requires imaging technologies capable of resolving cortical architecture and connectivity at the sub-millimeter, mesoscale. To address this need, our team, supported by the NIH BRAIN Initiative, established the Next-Generation (NexGen) 7 T MRI platform as a national resource integrating state-of-the-art hardware, pulse sequence development, image reconstruction, and collaborative user support to advance non-invasive human neuroimaging.

The NexGen 7 T scanner combines an innovative asymmetric head-only gradient system (200 mT/m, 900 T/m/s), high-density 64- and 96-channel receive arrays, a 16-channel parallel transmit system, and advanced EPI, 3D GRASE, and spiral imaging methods to substantially improve spatial resolution, acquisition efficiency, and image uniformity. Together, these technologies enable routine human neuroimaging at spatial scales previously inaccessible with conventional MRI platforms.

An important milestone achieved with the NexGen 7T was sub-0.1 μ L voxel functional MRI using CBV-weighted VASO at 0.39 mm isotropic resolution, permitting layer-specific mapping of human cortical activation. In parallel, the combination of ultra-high field strength and high-performance gradients enables diffusion MRI with unprecedented spatial-angular resolution tradeoffs, supporting high-resolution cortical tractography, structural connectomics, quantitative microstructural imaging, and improved characterization of human cytoarchitecture. By integrating structural and functional measurements on a common platform, the NexGen 7 T resource enables multimodal investigations of cortical circuitry and mesoscale connectomics across the entire brain.

Beyond technology development, the U24 resource has supported dozens of collaborative pilot projects from around the world spanning basic, translational, and clinical neuroscience. These projects disseminate advanced imaging methods to the broader research community through shared protocols, training, and user support. By lowering barriers to access and fostering interdisciplinary collaboration, the NexGen 7 T platform establishes a foundation for community-driven advances in human mesoscale neuroimaging and next-generation structural and functional connectomics that were previously inaccessible with existing MRI technology.

KEYWORDS: *Connectome; Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Physics or Microscopy/Optics*

Cloud-based miniscopes enable continuous 24-hour “neurosurveillance” of brain health and disease in freely behaving animals

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Miniaturized microscopes called “miniscopes” have forged a new frontier in neuroscience by making it feasible to capture images of brain function in freely behaving animals. While most miniscopes are designed to image neuronal activity at high speed for a short duration (e.g., >10 Hz for 15 minutes), they are unsuitable for probing the brain’s neuro-vascular function across longer time scales (e.g., >24 hours), for applications such as monitoring circadian rhythms or tracking neuropathologies in vivo. For example, characterizing the dynamic remodeling of the microvascular landscape within the brain tumor microenvironment, a potent drug target, would be impossible if miniscopes only recorded short spurts of neuronal activity. Such limitations compelled us to define a new imaging paradigm called “neurosurveillance,” in which miniscopes are harnessed for long-term, multimodality imaging of brain health and disease. To transcend this neuroimaging time barrier and enable neurosurveillance, we developed the CloudScope, a miniature microscope capable of continuous, multimodal neuroimaging in freely behaving animals for >24 hours. It connects to the cloud via Wi-Fi and is autonomously controlled. CloudScopes can be accessed via the internet from anywhere in the world, and allow imaging of neuronal activity (NeuACT, via fluorescence or FL of GCaMP-bound Ca^{2+} in neurons), changes in cerebral blood volume and oxygenation (via intrinsic optical signals), and cerebral blood flow (CBF, via laser speckle contrast), every 5 seconds. The FL channel can also be used to track fluorescently labeled entities such as brain tumor cells. Images are acquired at a resolution of 5-7 microns over a 3x3 mm² field of view. Here we demonstrate CloudScope’s ability to (i) quantify the co-localization of NeuACT and CBF dynamics over 24 hours, (ii) disentangle hemodynamic alterations from their neuronal counterparts during spontaneous seizures, and (iii) characterize the migration of individual tumor cells over 72 hours in the brain of a freely behaving animal. With its 24-hour, multimodal imaging capabilities and global accessibility, we believe that the CloudScope heralds an exciting new era of neuroscientific discoveries in the healthy and diseased brain.

KEYWORDS: *Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics; Software (analysis, etc.) and Engineering*

Modeling behavior and functional connectivity in a mouse model of tauopathy

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Tauopathies are neurodegenerative diseases defined by the accumulation of tau protein, which drives network dysfunction and cognitive decline. Alzheimer's disease, the most common tauopathy, shows a close correlation between tau pathology and cognitive impairment. Magnetic resonance imaging (MRI) enables non-invasive measurement of brain functional connectivity (FC), making it well-suited to track how tau pathology alters network function and behavior over time and to identify early biomarkers and therapeutic targets. This study investigated the relationship between FC and cognitive performance in the rTg4510 mouse model of tauopathy. Mice were assessed at 3, 6, and 10 months of age, corresponding to pre-tangle, early tangle, and advanced tangle stages. Spatial learning and memory were evaluated using the Morris Water Maze, and FC between 30 brain regions was mapped in awake mice using resting-state functional MRI (rsfMRI) to avoid anesthetic confounds. Machine learning was used to model the relationship between FC and spatial learning and memory performance, identifying the connections most predictive of cognitive performance. Spatial learning deficits appeared as early as 3 months, before tau tangle formation, and worsened with age. FC analysis revealed widespread hyperconnectivity at 3 months, particularly in hippocampal and cortical networks, shifting toward mixed hyper- and hypo-connectivity by 10 months. Predictive modeling identified specific connections, including those involving the prefrontal cortex, anterior cingulate, and striatum, that were strongly associated with cognitive performance across time points. These findings demonstrate that functional connectivity disruptions can predict cognitive decline in tauopathy. The machine learning models successfully identified key functional connections predictive of spatial learning performance, marking them as central vulnerabilities in network connectivity. Together, the results highlight the potential of FC-based modeling for pinpointing circuit-level biomarkers that detect early connectivity dysfunction and inform targeted interventions in tau-related neurodegenerative disease.

KEYWORDS: *Connectome; Integrated Approaches; Monitor Neural Activity; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Theory & Data Analysis Tools*

Comparing functional connectivity changes in amyloid and tauopathy models

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Alzheimer's disease (AD) is characterized by the accumulation of amyloid- β (A β) plaques and tau tangles. Resting-state functional MRI (rs-fMRI) provides a non-invasive measure of functional connectivity (FC). Human PET studies have demonstrated associations of A β with hyperconnectivity and tau with hypoconnectivity. However, PET tracers selectively detect insoluble A β plaques and tau tangles, limiting their ability to characterize earlier pathological stages. It is poorly understood how FC changes throughout AD progression. Furthermore, it is unclear whether early FC alterations predict subsequent cognitive decline. To address these questions, we characterized FC changes in mouse models of A β and tau pathology across disease progression.

APP/PS1 and rTg4510 mouse models were studied. Spatial learning and memory were assessed using the Morris water maze. Functional connectivity was evaluated using awake rs-fMRI, eliminating the confounding effects of anesthesia on neural activity. Imaging and behavioral assessments were performed at 3, 6, and 10 months of age.

APP/PS1 mice exhibited progressive network hyperconnectivity, with 47 significantly altered connections identified at 3 months of age, increasing to 84 connections by 10 months. Notably, these FC abnormalities emerged prior to deficits in spatial learning and memory, indicating that network dysfunction preceded measurable cognitive decline. In contrast, rTg4510 mice exhibited early hyperconnectivity at 3 months that evolved into a mixed pattern of hyperconnectivity and hypoconnectivity by 10 months. Spatial learning and memory deficits were present by 3 months and worsened with age.

These findings extend prior PET observations linking A β pathology to hyperconnectivity by demonstrating that these alterations emerge during pre-plaque stages of disease. We observed that tau-associated hypoconnectivity is preceded by a hyperconnective phase not detectable with tau PET, which is limited to insoluble tau aggregates. Thus, the hypoconnective phenotype commonly associated with tau pathology may represent a later stage of disease progression rather than its initial manifestation. By capturing dynamic network changes across the continuum of AD pathology, rs-fMRI offers unique potential as an early biomarker for detecting disease progression before the emergence of overt pathological deposits and cognitive impairment.

KEYWORDS: *Connectome; Monitor Neural Activity; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Theory & Data Analysis Tools; Integrated Approaches*

Modeling functional connectomics with cognitive deficits in a knock-in mouse model of Alzheimer's disease

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Alzheimer's disease (AD) pathology consists of cytotoxic aggregates composed of β -amyloid ($A\beta$) plaques and hyperphosphorylated tau tangles. Functional connectivity (FC)—the correlation of activity that occurs between spatially distinct brain regions—is assessed through the measurement of blood oxygen level detection (BOLD) using the task dependent MRI technique, resting state functional MRI (rs-fMRI). Together they have become a promising diagnostic tool, as studies have demonstrated rs-fMRI's ability to detect FC changes in brain regions that participate in memory function in both animal models and human AD patients. Several studies have demonstrated that in animal models, these changes in FC occur prior to the emergence of cognitive deficits. Previous work by our group used machine learning to characterize alterations in FC and associate these alterations with changes in cognition throughout disease progression in multiple mouse models of AD (i.e., APP/PS1, rTg4510). Across models, we have consistently observed that perturbations in FC precede the manifestation of deficits in spatial learning and memory, and that these connectivity changes are dynamic over the course of disease. Altogether, this suggests rs-fMRI has the potential to broaden the current diagnostic repertoire and support earlier detection of AD. This work builds upon these efforts through characterization of the APPSAA mouse model of AD. APPSAA mice express a humanized $A\beta$ sequence within the App gene, along with three familial AD mutations (Arctic, Austrian, and Swedish) to model early-onset AD. In 4-month-old mice, we performed the Morris water maze assay along with a battery of behavioral assays to evaluate spatial learning, memory and other facets of cognition. Next, we measured FC between several regions of interest known to be affected in AD pathogenesis using rs-fMRI. Finally, we employed machine learning to correlate alterations in FC to disruptions observed in cognition and other behavioral dysfunction. Preliminary results are consistent with what would be expected given our previous findings. Future work will include spatial transcriptomics and the assessment of additional timepoints to comprehensively characterize changes across the AD continuum.

KEYWORDS: *Computational Biology/Modelling; Connectome; Integrated Approaches; Neural Networks (topology, etc.); Neuroimaging (invasive, non-invasive imaging)/Radiology; Developmental/Systems Biology*

Obstruction counting provides evidence for a low-dimensional topographic hyperbolic structure of early olfactory neural population responses

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Two of the open questions in olfactory representations are whether they are continuous and, if so, what the dimensionality and parameters of the corresponding manifold are. The same questions also pertain to high-level and abstract representations such as memory. Here we present a new approach based on topological methods where a given set of neural responses is consistent with encoding of stimuli in some contiguous space, without knowing the parameters of that space. We tested the method on neural responses in both fly and mouse olfactory stimuli. We find that these responses are not consistent with a non-topographic maximum entropy model, even when this model is adjusted to have the same mean activity levels and pairwise correlation structure as in real data. Instead, the obstruction count was consistent with a low-dimensional topographic representation in either Euclidean or a negatively curved low dimensional space, with negatively curved space providing a better fit of the two. Together, these results illustrate that topological methods based on obstruction counts can provide traction on longstanding problems in sensory coding. Because these methods are abstract and do not require knowledge of input space parameters, they can be applied to investigate the properties of latent spaces in non-sensory and cognitive areas of the brain.

KEYWORDS: *Theory & Data Analysis Tools*

Long-term dynamics of dendrites and inhibitory neurons in mouse CA3

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Neurons maintain large dendritic arbors supporting non-linear input integration which can greatly boost their computational power. Recent work suggests that synaptic plasticity induced by dendritic plateau potentials underlies new place field formation in the hippocampus, highlighting the functional relevance of dendrites to memory formation. But the modulation of hippocampal dendritic activity supporting memories over long timescales has not been characterized. Are there dendritic compartment-level differences in the stability and flexibility of spatial representations? How does inhibition targeted to specific compartments affect the way in which different inputs affect somatic output?

To address these questions, we imaged calcium activity of dendrites and soma of pyramidal neurons and dendrite-targeting somatostatin expressing (SST) neurons in area CA3 of headfixed mice. We virally expressed GCaMP in either population, allowing simultaneous imaging of soma and dendrites of labeled neurons. Mice performed a random foraging task on a linear treadmill belt with different tactile cues defining position in two environments (A and B). Neurons were longitudinally imaged for one week during familiarization with environment A. Imaging continued for another week with sessions switching between environments A and B. This longitudinal imaging allows us to examine the stability of spatial representations.

In pyramidal neurons, we observed that apical dendrites had higher levels of stability compared to basal dendrites, with better position decoding across days. SST+ INs showed a variety of response properties. Roughly 2/3 showed positive modulation by reward. 2/3 showed speed modulation, having elevated activity during movement. Roughly 1/3 of neurons showed overall activity modulation by the environment, preferring one environment over the other, without specific spatial modulation. A subset of cells also showed spatial modulation like the traditional place cell activity observed in pyramidal neurons. A minority were silent the majority of the time but were active when the environment changed. Response properties were highly stable and repeatable across days, far more stable than typical pyramidal neuron responses. This quantification demonstrates the varied roles that SST+ INs can play in spatial memory, particularly in discriminating between different environments in wild-type mice.

KEYWORDS: *Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation; Cell Type/Interactions*

A connectome-wide survey of somatostatin interneuron subtypes reveals distinct contributions to surround suppression in mouse visual cortex

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Surround suppression is a core computation of primary visual cortex (V1), and somatostatin (SST) interneurons have been implicated in it across cortical layers. But SST cells are a heterogeneous family spanning multiple transcriptomic subtypes, and which subtypes implement surround suppression, through what wiring motifs, and at what cortical depths, remains unknown.

To address this, we used MICrONS functional connectomics and the VORTEX reconstruction effort to cluster 120 proofread Martinotti cells (MCs) into eight emergent SST subtypes (c1-c8) from their connectivity features alone. We then used morpho-electric-transcriptomic (MET) reference cells to anchor these clusters to known SST types. For each subtype we asked how its synaptic wiring to pyramidal cells (PCs) relates to those PCs' orientation tuning, predicted by a functional digital twin of the same volume.

The subtypes made distinct contributions. c4, which contained the curated MET-8 reference cells, formed a like-to-like recurrent motif: At less than 200 microns, reciprocal PC-MC pairs were more iso-oriented than unidirectional PC-to-MC pairs, a deep-layer counterpart of the Hendricks L2/3 motif. Two Calb2-family subtypes wired their MC-to-PC output onto iso-oriented PCs: c3 (L4-soma), a candidate substrate for the L4-local orientation-tuned surround documented by Self et al. 2014, and c5 (L5-soma), extending the rule into deeper layers. In striking contrast, c6 (a layer-5 projection-target type) wired its output onto orientation-DISSIMILAR PCs, a candidate substrate for Adesnik 2010/2012's broadly-tuned Martinotti surround onto layer-5 output neurons. The remaining subtypes showed no significant orientation-similarity bias, indicating these are subtype-specific rules rather than general SST properties.

Together, these results indicate that surround suppression is not the role of a single SST type but is distributed across the family as a multi-channel inhibitory toolkit: distinct subtypes supply orientation-tuned recurrent inhibition, iso-oriented surround inhibition across layers 4 and 5, and broadly tuned cross-orientation surround onto deep output neurons. Connectomics thus resolves the SST contribution to surround suppression at subtype precision.

KEYWORDS: *Cell Type/Interactions; Circuit Diagrams; Connectome*

Reward aligns dominant population modes with task-relevant information

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Learning changes sensory representations through both repeated exposure to environmental statistics and reinforcement by behavioral outcomes. However, how these processes differentially shape population activity remains still unclear. Here, we analyzed calcium-imaging recordings from visual cortex in mice exposed to identical virtual-reality environments either with reward contingent on a sensory context or without reward. Using tensor component analysis to separate within-trial dynamics from across-trial learning-related changes, we found that rewarded learning induced a characteristic reorganization of population geometry that was not apparent in unrewarded mice. After learning, population activity was captured by fewer latent components, with variance concentrated in dominant activity modes. This reduction in latent dimensionality was aligned with the task, rather than resulting from a non-specific variability change. In rewarded animals, the components explaining the largest fraction of population variance also carried the strongest discrimination between the rewarded and unrewarded visual stimuli. In contrast, after unrewarded exposure, stimulus-selective activity remained distributed across lower-variance components.

To identify candidate circuit mechanisms, we trained recurrent neural networks on an analogous visual-discrimination task using either reward-gated local synaptic plasticity or unsupervised local plasticity driven by correlated pre- and postsynaptic activity. Both learning rules generate changes in stimulus selectivity through repeated exposure. However, reward-gated plasticity selectively reorganizes recurrent dynamics such that task-relevant stimulus differences become embedded in the dominant activity subspace, reproducing the concentration of variance and selectivity observed in rewarded animals. Unsupervised plasticity produces stimulus-specific changes without the same systematic alignment between the leading population modes and task-relevant information.

Together, these results indicate that reward selectively reshapes recurrent dynamics so that information relevant for behavior is preferentially represented in the dominant activity modes. This provides a mechanistic link between local reward-gated synaptic plasticity and the emergence of population codes organized around task-relevant variables.

KEYWORDS: *Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Monitor Neural Activity; Synaptic Plasticity; Theory & Data Analysis Tools; Neural Networks (topology, etc.)*

Embodied solutions recapitulate key dynamical features of motor cortical population activity

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Neural populations display complex response patterns with marked transitions between distinct underlying computational strategies on very short timescales during motor tasks. Such complex yet structured dynamical strategies may reflect computational needs of neural systems, shaped by optimal feedback and autonomous mechanisms, in addition to biological and embodied constraints. A representative example of this occurs during the delayed reaching tasks. During the preparatory period, cortical activity converges to condition-specific fixed points. During movement-period, it transitions into rotational dynamics emerging from these states. Preparatory and movement-related computations occupy orthogonal subspaces, further characterized by marked changes in correlation structure across epochs. Importantly, this orthogonality is not captured by existing representational or dynamical systems models of motor cortex. Here, we explore the hypothesis that computational strategies underlying neural population response represent embodied solutions to the control of musculoskeletal dynamics for goal-directed movements. We test this hypothesis using muSim, a framework that trains RNNs via deep reinforcement learning to control musculoskeletal models under simulated feedback. Here, an RNN controls an anatomically accurate model of the macaque forelimb during a delayed reaching task. In a closed loop with the musculoskeletal dynamics (simulated in MuJoCo), the RNN converts multimodal sensory feedback—proprioception (muscle lengths and velocities), vision, and a go-cue signal—into the muscle excitations that drive the body. RNNs trained under these embodied constraints reproduce the orthogonal structure observed across preparatory and movement epochs in neural recordings. Sensory feedback ablation studies suggest that proprioception may be important for the emergence of orthogonality across the two epochs, in addition to driving the actual movement as captured by kinematic accuracy on the task. Collectively, these results suggest that the neural dynamics may be more strongly modulated by embodiment and associated feedback than previously appreciated.

KEYWORDS: *Neural Networks (topology, etc.); Computational Biology/Modelling*

Learning to learn with reward-gated local plasticity

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AUTHORS: D. Maoutsa

Task-trained recurrent neural networks (RNNs) are widely used in neuroscience to generate hypotheses about circuit computation. Yet gradient-trained RNNs often exhibit a simplicity bias, converging to low-dimensional solutions that may reflect the inductive bias of the training algorithm rather than the space of computations accessible to synaptic plasticity. Biological circuits, by contrast, modify recurrent interactions through local synaptic variables gated by delayed, global reinforcement signals. Existing approaches for discovering plasticity rules that fit behavioral or neural data mostly consider two-factor rules or continuous feedback, leaving reward-modulated learning underexplored. This raises the question: Which reward-gated local learning rules can generate task-appropriate recurrent dynamics?

We address this question by meta-optimising a family of local three-factor plasticity rules in recurrent networks trained on delayed-reward tasks. Each synapse carries an eligibility trace that accumulates pre-post synaptic co-activity and allows for punctuated changes of neuronal interactions upon reward delivery. Rule parameters shape the eligibility dynamics, thereby controlling how co-activation patterns drive plasticity. We factorise the meta-optimisation objective into two parts: a behavioural sensitivity, capturing how infinitesimal changes in the connectivity influence task outcome; and a plasticity sensitivity, capturing how infinitesimal changes of the rule parameters influence the connectivity. We approximate the former by a scalar analysis functional that correlates with task performance, and compute the latter by forward-mode differentiation on a random projection subspace.

Applying this procedure to standard delayed-reward tasks used in systems neuroscience, we find that the meta-optimised rules consistently learn the task faster than the canonical reward-modulated cubic rule. Our work provides a practical procedure to search for local three-factor rules that support learning common neuroscience tasks from delayed rewards.

KEYWORDS: *Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Synaptic Plasticity; Theory & Data Analysis Tools; Computational Biology/Modelling*

Tracking flow of attention in visual circuits across the brain

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The overall goal of this project is to reveal how spatial attention enhances neural information processing across the mouse brain to improve visual task performance. Our aims are to define cellular and circuit-level details about these processes in mice, with comparisons to principles of attentional modulation in other species. We pair multi-area, high-density Neuropixels recordings with a well-controlled behavioral task that enables replicable and high-throughput attentional behavior. Expert mice performed psychometric detection of small, static stimuli that varied in contrast and appeared in discrete portions of the visual field. The behavioral protocol efficiently trains naive mice to become experts in 18 days (median; $n=36$ mice), and elicits several behavioral signatures of spatial attention: improvements in detection speed, accuracy, and contrast sensitivity across consecutive trials at the relevant spatial location task. We then asked if attentional modulation of neural activity is most prominent in higher-order visual areas (HVAs) of cortex, as seen in monkeys, and if both excitatory and inhibitory neurons show attentional modulation across the mouse visual cortical hierarchy. We recorded during task performance in primary and secondary visual thalamus (LGN, LP), primary visual cortex (V1), and 5 HVAs during the task (20 mice; 171 recording days; $n=4655$ neurons). Cortical recording sites were retinotopically targeted via hemodynamic imaging. V1 putative excitatory and inhibitory neuron firing rates, pairwise spike count correlations and local field potential (LFP) responses showed significant modulation to both task-relevant and task-irrelevant stimuli, largely consistent with spatial attention effects seen in primates. Surprisingly, LFP and putative excitatory neurons in V1 and the lowest order HVA showed the strongest modulation, while putative inhibitory neurons showed more prominent modulation throughout early and mid-level HVAs. These preliminary findings suggest early visual cortical areas may play a larger role for spatial attentional effects in mice. We are currently investigating how the degree of neural modulation is related to the extent of behavioral improvement, and how retinotopic preferences within cortical areas relate to the magnitude and sign of neural activity modulation.

KEYWORDS: *Cell Type/Interactions; Circuit Diagrams; Electrophysiology; Monitor Neural Activity; Integrated Approaches*

Ultraflexible spinal cord electrodes uncover shared and context-specific neural substrates underlying multiple hindlimb behaviors

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The spinal cord comprises genetically and functionally heterogeneous cell types that are highly interconnected to generate diverse limb movements. Genetic, molecular, and imaging approaches have advanced our understanding of spinal circuits through cell-type-specific interrogation and time-resolved activity measurements. However, capturing millisecond-scale spiking dynamics across distributed spinal populations during natural behavior remains challenging. In vivo electrophysiology is uniquely suited to address this gap, but tissue motion has historically limited stable single-unit recordings in freely behaving animals. Using ultraflexible nanoelectronic threads (NETs) with 128 electrodes spanning the mediolateral and dorsoventral axes on both hemicords, we recorded spinal neuronal activity in awake mice during sensory-evoked reflex and rhythmic locomotion, including walking and trotting. The ultraflexible design minimizes tissue-electrode displacement, enabling stable, high-quality single-unit isolation during free movement. Implanted NETs were co-sectioned with spinal tissue for postmortem verification of electrode locations within the spinal laminae.

To identify shared and behavior-specific neural representations, we first used an encoding model to identify behaviorally tuned units. Across walking and trotting, we observed units that were exclusively tuned in a specific gait, units with gait-invariant tuning, as well as multiplexed units whose tuning curve changed with gait. Low-dimensional population analyses revealed both shared and behavior-specific latent subspaces, each explaining a substantial fraction of spiking variance. Notably, neural representations were less strongly shared between rhythmic locomotion and evoked responses than between walking and trotting, which is congruent with the relative similarity between the three behaviors. Network connectivity analyses likewise identified conserved and behavior-specific structures. Together, these findings suggest that flexible sensorimotor control arises from both shared motifs and dynamic reconfiguration across behaviors.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Networks (topology, etc.); Neural Recording & Modulation; Synaptic Plasticity*

A transcriptomic axis aligns with in vivo functional dynamics in hippocampal inhibitory circuits

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Linking molecular identity to function in vivo at single-cell resolution remains an outstanding challenge in neuroscience. Here, we bridge this gap in the mouse hippocampus with an end-to-end pipeline of cell-resolved two-photon imaging and spatial transcriptomics. CA1 interneurons exhibiting heterogeneous physiological responses during a virtual-reality navigation task were post hoc clustered by gene expression into 5 GABAergic subclasses and 14 types. Physiological responses of individual cells aligned with a transcriptomic axis, and a classifier trained on physiological features alone recovered the same ordered organization. Our approach establishes a direct, scalable framework for linking in vivo circuit dynamics to constituent cell identity, revealing a transcriptomic axis that encompasses the structural and functional diversity of hippocampal inhibitory neurons.

KEYWORDS: *Cell Type/Interactions; Molecular/Cellular Neuroscience; Neuroimaging (invasive, non-invasive imaging)/Radiology; Integrated Approaches*

Intranasal dantrolene nanoparticles for treatment of amyotrophic lateral sclerosis

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The study investigates the therapeutic efficacy of intranasal dantrolene nanoparticles (IN-DAN) formulated in Ryanodex to inhibit motor neuron degeneration and improve motor function, muscle strength, body weight, and survival in SOD1-G93A amyotrophic lateral sclerosis (ALS) transgenic mice. Male and female C57BL/6SJLF1 wild-type (WT) and SOD1-G93A mice received daily intranasal dantrolene nanoparticles (IN-DAN, 5 mg/kg), Ryanodex vehicle (IN-VEH), or no treatment (NO TX) from 90-120 days of age. Motor function was assessed weekly using the rotarod test, while body weight and survival were monitored daily. At treatment completion, neurological and motor function were evaluated using standardized neurological scoring, the balance beam, grip strength, and rotarod test. Blood, brain, and spinal cord tissues were collected for biomarker and histological analyses. Blood levels of neurofilament light chain (NFL), a sensitive and selective biomarker of neurodegeneration, were measured. Motor neuron degeneration in the spinal cord and primary motor cortex (M1) was assessed by Fluoro-Jade C (FJC) and Cresyl violet (Nissl) staining for motor neuron quantification. Statistical analysis was performed using two-way ANOVA followed by Tukey's post hoc test.

Compared with WT, SOD1-G93A mice exhibited significant impairments in motor function and muscle strength, as well as reduced body weight and survival rate. IN-DAN, but not IN-VEH, produced robust improvements in motor function in SOD1-G93A mice. Neurological scores improved by 90%, balance beam crossing time decreased by 78%, foot slips were reduced by 84%, and grip strength increased by 213% (all $p < 0.0001$). Thirty-day survival increased from 67% to 89%, and body weight loss was completely prevented. Plasma NFL increased by 564% in ALS mice compared with WT mice and decreased by 50% with IN-DAN treatment ($p < 0.0001$). FJC-positive degenerating neurons increased by 128% in the spinal cord and 488% in area M1 of SOD1-G93A mice compared to WT (both $p < 0.0001$). IN-DAN reduced neurodegeneration by 62% in the spinal cord and 72% in M1 (both $p < 0.0001$). Nissl staining revealed a 66% loss of spinal cord motor neurons in ALS mice, which was improved by IN-DAN by 153% ($p = 0.0068$).

These findings demonstrate that IN-DAN provides robust neuroprotection and significantly improves functional outcomes in SOD1-G93A ALS mice.

KEYWORDS: *Developmental/Systems Biology; Dissemination & Open Science/Education; Molecular/Cellular Neuroscience; Integrated Approaches*

Distributed encoding of behavioral variables in auditory cortex shows structured laminar and subregional organization

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Sensory cortices comprise multiple subareas and layers, yet how areas jointly encode both sensory and behavior-related information and their laminar distinctions is unclear. Here, we used two-photon calcium imaging to record the activity of ~200,000 neurons from >300 behavioral sessions across layers (2-5) and subregions of the auditory cortex (ACtx) in mice performing a two-alternative forced-choice auditory task. We examined excitatory neurons labeled by Thy1 (Thy1-GCaMP6s; B6.CAST-Cdh23Ahl+/Kjn) or Cux2 drivers (Cux2tm3.1(cre/ERT2)Mull; B6.CAST-Cdh23Ahl+/Kjn; Ai162(TIT2L-GC6s-ICL-tTA2)-D), as well as projection-defined corticostriatal neurons. We found that neurons encoding sensory, motor, or outcome variables were broadly distributed and that their mixed-encoding properties reflected the learned task rules. The timing of sensory, motor, and outcome information varied across information types, subregions, and layers, suggesting a distinction in the laminar processing hierarchy for different behavioral variables within primary or higher-order ACtx subregions. Further analysis of the population activity suggests a more parallel, antagonistic, or homogenous circuitry involved in sensory, motor, or outcome encoding, respectively. The response properties of Cux2+ neurons resembled those in the Thy1+ population, suggesting a relatively conserved circuitry across these excitatory neuron populations. TS-projecting neurons were more mixed-selective and showed faster sensory and motor encoding, suggesting their specialized roles in sensorimotor integration. Together, these findings support a distributed yet structured organization of behavioral encoding in ACtx, shaped by laminar-, subregional-, and cell-type-specific circuitry that reflects and adapts to learned behavioral tasks.

KEYWORDS: *Behavioral Sciences/Psychology; Neural Networks (topology, etc.); Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Inferring distributed computational mechanisms from multi-area neural recordings

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Understanding how computation is distributed across interacting brain areas requires separating the dynamics of each area from signals communicated between them. Existing methods have limitations that make them difficult to interpret: single-area dynamics models often suffer from hallucinations and/or leave external inputs underdetermined, while communication-only models lack explicit dynamics. We introduce DynISys (Dynamically-Interacting-Systems), a multi-area latent dynamics model that infers per-area dynamics, inter-area communication, and external inputs directly from simultaneously recorded spiking activity. DynISys combines neural-ODE dynamics, injective normalizing-flow readouts, and low-dimensional inter-area communication channels, resulting in expressive, trustworthy, and interpretable models. We applied DynISys to simultaneous PMd and M1 Neuropixels recordings from a monkey performing a two-target sequential reaching task, helping disambiguate neural activity patterns associated with planning from those involved with execution. DynISys reconstructed single-neuron responses and single-trial state-space trajectories with high fidelity and unlike a comparable RNN-based model was resistant to feature hallucination. DynISys also captured the flow of information between areas, inferring a unidirectional transfer of the motor plan from PMd to M1 that recapitulated the order in which target information emerged across areas. Finally, DynISys also allowed us to interrogate the inferred dynamics for computational mechanism. We found that during the preparatory phase of individual trials, inferred M1 dynamics contained a single fixed point whose location encoded the upcoming reach for that trial. The location of this fixed point was determined largely by the inferred inputs to M1 from PMd. We found that in silico perturbations of these inputs led to predictable effects on the location of M1's fixed points, putting forward an experimentally testable hypothesis of the mechanism of PMd/M1 interactions during motor planning. By separating each area's intrinsic dynamics from the signals exchanged between them, DynISys allows researchers to distill multi-area recordings into interpretable accounts of distributed computation.

KEYWORDS: *Computational Biology/Modelling; Theory & Data Analysis Tools*

Parallel and flexible hippocampal coding of space and reward

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Our strongest memories are often anchored to rewarding experiences, enabling us to learn what spatial locations predict reward and to navigate toward them in the future. In humans, reward memory can become dysfunctional in disorders such as dementia and drug addiction, highlighting the need to understand how the brain amplifies information associated with rewards. Hippocampal place cells are known to overrepresent reward locations, potentially providing a substrate for strong reward memories. Yet whether this overrepresentation extends to sequences of events across the full spatial environment—encoding experience relative to reward at a distance—remains unknown. To address this, we used 2-photon calcium imaging in hippocampal area CA1 to track the same neuronal population across days as head-fixed mice navigated virtual environments with hidden, relocating reward zones, dissociating reward from sensory cues. We found that when reward moved, a subpopulation of neurons updated their preferred firing to maintain the same relative position with respect to reward, including neurons active far from the reward zone itself. This reward-relative code expanded as more neurons were recruited over learning, while a parallel subpopulation preserved a stable map of the spatial environment. These coding identities were dynamic, as individual neurons shifted between codes across days, and coding properties were expressed independently within individual place fields. We further found that reward-relative activity exhibited mixed selectivity for multiple features of experience, that the spatial organization of reward-relative fields predicted behavioral precision, and that shifts in reward-relative coding often preceded changes in behavior. Together, these findings reveal that the hippocampus flexibly amplifies information linked to rewarding experiences while simultaneously maintaining a stable spatial memory. This parallel, population-level coding scheme could serve to selectively strengthen memories with high motivational significance without disrupting the underlying representation of the external world.

KEYWORDS: *Integrated Approaches; Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics; Theory & Data Analysis Tools*

Layer 5B dendrites multiplex value, action, and prediction during active sensory learning

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Sensory discrimination requires cortical circuits to transform sensory inputs into reliable perceptual decisions, yet how distinct output pathways contribute to this transformation remains unknown. Layer 5B (L5B) thick-tufted pyramidal neurons are uniquely positioned to integrate bottom-up sensory drive onto basal dendrites with top-down predictions onto apical tufts, making them candidate substrates for predictive computation. However, whether different L5B projection classes, defined by their long-range targets, implement functionally distinct computations during perceptual learning remains unexamined. Here, using two-photon calcium imaging of apical tuft and trunk compartments in projection-class-identified L5B neurons across learning of a two-whisker active touch discrimination task, we reveal a dissociation among three major output streams. Posterior medial thalamus (POM)-projecting L5B neurons show increasing tuft-trunk coupling from naive to intermediate performance, followed by a reduction at expert-level proficiency, consistent with an actor-critic architecture in which early learning amplifies reward prediction-error signals that are suppressed once behavior is optimized. Superior colliculus (SC)-projecting neurons exhibit monotonically increasing coupling alongside the progressive emergence of trial-locked spatiotemporal population structure, as revealed by Slice Tensor Component Analysis (Slice TCA), implicating this pathway in the continuous updating of an action policy for the task. Pontine (PONS)-projecting neurons, by contrast, show neither coupling changes nor trial-locked dynamics, but display strong time-locked activity consistent with a circuit mechanism that conveys sensory prediction error to PONS for cerebellar learning. Interpreted and recapitulated within an Active Predictive Coding (APC) framework, these results suggest that L5B functions not as a uniform output layer but as a multiplexed predictive engine, parcellating actor-critic valuation, motor update signaling, and forward model computation across anatomically distinct projection classes. These findings establish a circuit-level substrate for hierarchical predictive coding during active sensory perception.

KEYWORDS: *Cell Type/Interactions; Neural Recording & Modulation*

Volatile structure modulates olfactory-guided avoidance in *Drosophila suzukii*: A neuroethological framework for sustainable pest management

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Insects make rapid, adaptive decisions by transforming volatile chemical cues into neural activity that guides attraction, avoidance, oviposition, and feeding. The spotted wing drosophila (SWD), *Drosophila suzukii*, offers a tractable neuroethological system for studying how chemical structure is encoded by the olfactory system and converted into ecologically meaningful behavior. Unlike most *Drosophila* species, SWD uses a serrated ovipositor to lay eggs in ripening soft fruits, making chemosensory-driven host selection a key contributor to its invasive success and a major threat to berry production. Although synthetic repellents such as DEET can reduce infestation, their limitations highlight the need for mechanistically informed, sustainable alternatives. Here, we used SWD avoidance as a behavioral readout of olfactory processing to compare methyl benzoate, a naturally occurring volatile organic compound, with structurally related analogs. Female flies were tested in repellency assays with 24 flies per treatment group across multiple concentrations and timepoints. Dose-response models were used to estimate RD50 values, allowing quantitative comparison of behavioral potency across compounds and chemical classes. Several anthranilate and ether-substituted benzyl ester analogs produced strong repellency, suggesting that specific structural features can shift odor-guided behavior from permissive host-seeking toward avoidance.

These findings support a brain-relevant framework in which pest-management compounds are not only evaluated by field efficacy, but also by their ability to modulate sensory-guided decision-making. By linking volatile chemistry, peripheral olfactory detection, and whole-animal behavioral output, this work creates a foundation for future studies combining receptor-level assays, neural activity mapping, and circuit-based analyses of odor-evoked avoidance. More broadly, SWD provides an accessible comparative model for investigating how nervous systems encode complex chemical environments and translate sensory information into adaptive action. Integrating chemical ecology with systems neuroscience may reveal conserved principles of olfactory coding while also informing environmentally sustainable strategies to protect food systems.

KEYWORDS: *Behavioral Sciences/Psychology; Chemistry; Developmental/Systems Biology; Integrated Approaches; Neural Recording & Modulation; Human Neuroscience, Clinical Science, or Public Health*

GluN2A subunit binding drives NMDAR autoantibody-mediated neurotoxicity and anxiety impairment in a neuropsychiatric lupus (NPSLE) mouse model

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Systemic lupus erythematosus (SLE) is associated with neuropsychiatric manifestations driven in part by anti-double-stranded DNA autoantibodies (DNRAbs) that cross-react with NMDA receptors (NMDARs). Following blood-brain barrier disruption, these autoantibodies enter the brain and induce excitotoxic neuronal death. While DNRAb-mediated injury has been linked to behavioral dysfunction, the receptor mechanisms underlying regional vulnerability remain unclear. Evidence suggests that GluN2A and GluN2B NMDAR subunits differ in susceptibility to antibody-mediated neurotoxicity. We hypothesized that GluN2A-containing NMDARs mediate DNRAb-induced neuronal loss and anxiety-like behavioral dysfunction in the amygdala.

Female GluN2A knockout mice were immunized with DWEYS on a polylysine backbone (DNRAb+) or polylysine backbone alone (DNRAb-). Epinephrine was administered to transiently increase blood-brain barrier permeability. Pre- and post-immunization dsDNA ELISAs were performed to confirm DNRAb generation. Eight weeks later, anxiety-like behavior was assessed using the elevated plus maze (EPM; n=10/group) and elevated zero maze (EZM; n=10/group). Neuronal survival was quantified by NeuN stereology in the lateral amygdala (LAD) and basolateral amygdala (BLA) (n=5/group). Statistical significance was determined using t-tests ($\alpha < 0.05$).

In prior wild-type cohorts, DNRAb exposure produced significant anxiety-like behavioral changes (EPM: $p = 0.0178$; EZM: $p = 0.0048$) and neuronal loss in both the LAD ($p = 0.0054$) and BLA ($p < 0.0001$). In contrast, GluN2A knockout mice showed no differences between DNRAb+ and DNRAb- groups in behavior (EPM: $p = 0.7599$; EZM: $p = 0.8853$) or neuronal counts (LAD: $p = 0.1780$; BLA: $p = 0.6908$), indicating that loss of GluN2A abolishes DNRAb-mediated behavioral and neuronal effects.

These findings demonstrate that GluN2A-containing NMDARs are necessary for DNRAb-mediated neuronal loss and anxiety-like behavioral dysfunction in the amygdala. Our results identify a receptor subunit-specific mechanism linking neuroimmune signaling to circuit-level vulnerability and behavior, suggesting that NMDAR subunit composition may determine susceptibility to antibody-mediated brain injury. These findings further support GluN2A-dependent signaling as a potential therapeutic target for mitigating neuroimmune-mediated circuit dysfunction in neuropsychiatric lupus.

KEYWORDS: *Behavioral Sciences/Psychology; Cell Type/Interactions; Developmental/Systems Biology; Integrated Approaches; Molecular/Cellular Neuroscience; Synaptic Plasticity*

Dissociable effects of selective attention and global arousal on neuronal populations in sensory cortex

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Selective attention enables preferential processing of behaviorally relevant stimuli. In contrast to this selective amplification, global arousal is a state of increased alertness driving broad, nonselective changes in cortical state. Although both processes modulate cortical gain and often occur together during behavior, the degree to which they rely on shared versus separate neural mechanisms remains poorly understood. This distinction has implications for developing more precise, targeted therapies for attention disorders, given growing evidence that current treatments such as stimulant medications may have broad, nonspecific effects.

In mice performing a sensory detection task, we recently showed that past rewards steer attention to specific whiskers, locally boosting activity in the corresponding columns of primary somatosensory cortex (S1) in a layer-specific manner. Here, we investigated how arousal and attention interact across cortical layers and cell types. Using two-photon calcium imaging and Neuropixels recordings, we computed single-cell indices of attentional modulation (responses when attending toward versus away from the stimulated whisker) and arousal modulation (tracked via pupil size, whisker motion, and body motion with DeepLabCut).

Selective attention strongly boosted stimulus-evoked responses of layer 2/3 pyramidal (PYR) neurons in specific whisker columns, while arousal boosted them broadly across columns. However, PYR neurons modulated by attention or arousal formed largely distinct, intermingled populations: cells most strongly boosted by arousal were weakly boosted by attention, and vice versa. Layer 2/3 vasoactive intestinal peptide (VIP) interneurons showed a different profile, with broad, nonselective recruitment by arousal and only a small subset (approximately 15%) selectively boosted by attention. Arousal, like attention, primarily boosted activity in L2/3 and L5 but not L4. However, attention effects in L2/3 and L5 were present at both high and low arousal during task performance, indicating that attention is preserved across arousal fluctuations.

Together, these findings suggest that despite both enhancing cortical gain and engaging similar cortical layers, selective attention and global arousal act through dissociable, spatially intermixed neuronal populations, potentially reflecting distinct circuit mechanisms for local versus global modulation of cortical state.

KEYWORDS: *Behavioral Sciences/Psychology; Cell Type/Interactions; Electrophysiology; Integrated Approaches; Monitor Neural Activity; Neural Recording & Modulation*

Distributed neural computation and the evolution of the first brains

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The origin of brains was a landmark in animal evolution, enabling new behavior and natural histories. We do not know how the first brains were organized or how they functioned. Acoel worms, the likely sister lineage to all other animals with brains, offer a unique window into the possible functional organization of early brains. Here, I will present recent work in which we develop the acoel *Hofstenia miamia*, a marine predator that hunts planktonic invertebrates, as a new model for neuroscience. Developing methods to quantify the structure of its brain and behavior, we discovered that *H. miamia* has an unusual “diffuse brain,” a subepidermal network of dense neuropil exhibiting little regionalization or stereotypy in gross anatomy or distribution of neural cell types. Remarkably, behavior in *H. miamia* is robust to large, arbitrary amputations of brain regions, suggesting that most regions can perform most computations. More brain tissue improves performance, especially on challenging tasks like the hunting of actively escaping prey, but no specific brain region is required. These results lead us to propose that *H. miamia*’s brain is composed of computationally pluripotent “tiles” that interact to generate coherent behavior. This architecture suggests a trajectory for nervous system evolution in which early brains may have arisen through the condensation of diffuse nerve nets into unregionalized brains, with regionalization evolving secondarily. Moreover, our work enables the use of *H. miamia* as a model to study distributed computation, the robustness of neural circuits to injury, how circuits and behavior regenerate after injury, and how brains and complex behavior first evolved.

KEYWORDS: *Behavioral Sciences/Psychology; Integrated Approaches; Molecular/Cellular Neuroscience; Theory & Data Analysis Tools; Developmental/Systems Biology*

Escape response reveals computations of network robustness

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Understanding the balance of information flow through degenerate routes on a trial by trial basis for the whole-brain has been limited by methodological constraints. We address this question for the evolutionarily conserved escape response in *C. elegans*. They have 302 neurons that are all at most 3 synaptic hops away from each other. We performed whole-brain Bessel illuminated calcium imaging at 68-100 Hz along with optogenetic stimulation of ASH, a polymodal sensory neuron that initiates avoidance from dangerous stimuli. A functional map of participating neurons is generated for the robust escape response induced via repeated stimuli in longer intervals of baseline and stimulus periods. We detect movement state-dependent responses and observe that more neurons are generally engaged during reversals and turns, two ways in which directions can be changed. Considering onset times and slopes, we observe that there are equivalent numbers of interneurons and motor neurons that respond in the first 15 milliseconds even though motor neurons are not directly connected to sensory neurons being stimulated. Reverse-conditional first onsets are more distributed than forward-conditional first onsets that occur in fewer neurons. Upon closer comparison of the trials where the VNC motor neuron DA2 responds first vs the trials where central pattern generator AVA responds first, it is clear that more functional categories of neurons are co-active with DA2 first responses and that the signal spreads to equally higher functional categories in 500 ms after AVA first responses. AVA is directly connected to ASH, but DA2 is 3 hops away. VNC motor neurons have high excitability while inputs coming to DA2 likely exhibit short-termed depression, resulting in observed division in routes of information transfer. Together, these mechanisms explain network robustness for the escape response and provide a few ways in which biology organizes information routing for robust task completion. These principles are extendable to artificial networks and will help us create more efficient systems and understand biological implications in greater depths. Thus, our approach revealed principles of network dynamics as a conceptual advancement in neuroscience with implications for improving artificial systems.

KEYWORDS: *Computational Biology/Modelling; Monitor Neural Activity; Neural Networks (topology, etc.); Physics or Microscopy/Optics; Theory & Data Analysis Tools; Circuit Diagrams*

What writes the rhythm? Gene networks underlying memory relevant oscillations in ex vivo human cortex

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Episodic memory is a defining feature of human cognition, requiring precise temporal integration of neuronal activity across cortical networks. The temporal cortex is a critical hub, with intrinsic oscillatory dynamics implicated in memory processes. While neural oscillations are conserved across species, oscillations found in the human temporal lobe are thought to exhibit distinct, functional properties related to human behavior and cognition. Notably, human theta range oscillations occur at comparatively lower frequencies, and evidence suggests functional heterogeneity within human theta range. Slower theta oscillations are specifically implicated in episodic memory encoding and depend on cholinergic modulation via muscarinic receptor signaling. These oscillations act as a window into collective and precisely coordinated network activity, however, the cell-type-specific gene networks that enable cells to participate in coordinated oscillatory dynamics remain unknown.

To address this, we utilize live, cultured human temporal cortex. Here, we use carbachol, a cholinergic agonist, to recapitulate memory relevant network dynamics. Microelectrode array recordings are paired with spatial transcriptomics and multiomics following carbachol application. This design allows direct comparison of oscillatory dynamics and gene expression following enhanced cholinergic activity. We find that cholinergic induction of slow oscillations in ex vivo cortical tissue engages memory relevant gene networks, implicating distinct transcriptional programs underlying this oscillatory activity. Our results highlight a novel framework for identifying gene level contributors to memory-relevant neural dynamics in the human cortex. This platform has the potential to uncover therapeutic targets for memory disorders and guide strategies for precision interventions such as gene therapy and neuromodulation.

KEYWORDS: *Electrophysiology; Genetics/Genomics; Molecular/Cellular Neuroscience; Human Neuroscience, Clinical Science, or Public Health*

SqueakPose Studio: An end-to-end platform for pose estimation and real-time edge-AI deployment

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National Institute on Alcohol Abuse and Alcoholism

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Accurate pose estimation underpins quantitative analysis of behavior, yet many deep learning-based tracking tools remain optimized for offline workflows that rely on fragmented software pipelines, workstation-grade GPUs, or external middleware to enable real-time deployment. Here we present an integrated software-hardware ecosystem for pose estimation that spans dataset creation, model training, offline analysis, and real-time deployment on embedded edge-computing devices. SqueakPose Studio provides a software suite for whole-frame, deep learning-based pose estimation that unifies dataset creation, manual and model-assisted labeling, model training, validation, and large-scale offline inference. The system leverages modern object-detection architectures to enable efficient end-to-end training and inference without patch-based sampling or multi-stage postprocessing, and supports execution on CPUs, GPUs, and Apple Silicon. For experimental settings requiring continuous recording and synchronized data acquisition, SqueakView enables real-time model deployment, video capture, and sensor logging on embedded edge-computing hardware, while MouseHouse provides a compact, modular enclosure designed for home cage-based experiments that integrates embedded GPU compute, microcontroller-based timing, and peripheral I/O. A shared data format and deterministic timing architecture ensure consistency across offline analysis and real-time deployment. Together, SqueakPose Studio, SqueakView, and MouseHouse provide a unified platform for pose estimation that supports both conventional offline analysis and embedded, real-time experimentation, without reliance on workstation-grade hardware or external middleware.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Dissemination & Open Science/Education; Integrated Approaches; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering*

Neuroeducation across adulthood: a proof-of-concept study on cerebrovascular health

PRESENTER: **A. Schmied**

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The human brain retains significant plasticity throughout adulthood and later life, remaining responsive to learning, experience, and lifestyle factors. Adults actively shape their cognitive health and well-being, yet many are unaware of how their everyday behaviors influence brain function. Neuroeducation aims to educate non-specialists about neuroscience. While existing research has focused primarily on teacher training, little is known about the benefits for adults in later life. This proof-of-concept study addresses this gap with a documentary-style neuroeducation program for adult learners. Grounded in andragogy principles, the 13-episode series employs straightforward analogies to foster intuitive understanding. Each 30-minute episode introduces core concepts—such as the central nervous system, cerebrovascular disease, stroke recognition, emotional impacts, neuroplasticity, and the Cognitive Reserve Model—using character-driven dialogue and relatable scenarios, complemented by low-stakes interactive quizzes. The program is delivered through a digital learning platform designed for accessibility, with clear typography, strong color contrast, and an empathetic visual design. Currently under development, it will be evaluated through a pilot study involving 20 participants. User surveys, formative assessments, and interviews will determine feasibility and acceptability, leading to a randomized controlled trial comparing this program with two alternative interventions. Cognitive, emotional, and neurobiological measures will assess mechanisms and outcomes, positioning neuroeducation as both a standalone intervention and part of a comprehensive approach to support brain health practices.

KEYWORDS: *Behavioral Sciences/Psychology; Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health*

Training courses for new users of Neuropixels probes

PRESENTER: **A. Graves**

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Over the past decade, the development of new electrophysiology tools has significantly increased the capacity of neural recording. In particular, Neuropixels probes offer tremendous opportunities to record from hundreds to thousands of neurons across the brain. However, many barriers exist to broader adoption of this potentially transformative technology, mainly related to training new users how to make Neuropixels recordings and analyze large ephys datasets. Supported by a Brain Initiative U24 grant, our team is now running a series of training courses across the US focused on teaching new users all the fundamental skills necessary to set up a Neuropixels recording system, how to surgically implant probes, make recordings, and process data. We provide four tuition-free courses each year, alternating every 3 months among Baltimore (Johns Hopkins, October 12-14 2026), Los Angeles (UCLA; Jan 2027), Denver (April 2027), and Boston (Harvard/Beth Israel Deaconess; July 2027). The course covers all aspects of Neuropixels software, hardware, and analysis, including lab sessions for students to handle, mount, and insert probes and record from head-fixed mice. Participants will also receive direct mentoring and hands-on experience with data processing and spike sorting of large-scale recordings.

KEYWORDS: *Dissemination & Open Science/Education; Electrophysiology; Monitor Neural Activity; Neural Recording & Modulation; Software (analysis, etc.) and Engineering*

First-in-human validation of a novel directional depth-microelectrode configuration in human hippocampus

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DISC (Directional and Scalable) is a new depth-electrode configuration—64 radially distributed microcontacts (100 x 150 microns, 150 to 300 micron vertical pitch) within a standard sEEG form factor. Conventional sEEG averages signal around a single macro-contact, blurring mesial-temporal epileptiform structure. We report first-in-human recordings of this configuration, obtained intraoperatively under general anesthesia to test whether radial, depth-resolved sampling resolves interictal heterogeneity not captured in conventional contacts.

In 5 adults with drug-resistant mesial-temporal lobe epilepsy, DISC was inserted intraoperatively into the hippocampus, within tissue planned for resection. An ECoG strip recorded simultaneously for validation (approximately 8 to 10 min interictal recording, 30 kHz). Spikes were detected (>5 SD), manually validated and clustered by morphology (K-means then hierarchical), then analyzed for current-source density, radial polarity, and ripple-band content.

Despite the anesthetized intraoperative setting, DISC recorded physiologically faithful signals—hippocampal theta (4 to 8 Hz, 4/5 subjects) and anesthesia-induced burst suppression—confirming valid recording. Against simultaneous ECoG, spike detection diverged sharply: 30% of spikes co-occurred (± 50 ms), 51% were DISC-only, and 19% ECoG-only - DISC activity often preceding ECoG. Radial sampling exposed structure macro-contacts cannot: current-source-density dipoles approximately 100 ms before spike peak, opposing polarities on opposite sides of the cylinder, and superimposed ripples. Morphologically, DISC resolved 16 distinct spike groups versus only 3 on ECoG. Spike recovery was heterogeneous (T90 42 to 168 ms, median 82 ms) and predicted by pre-spike dynamics (Spearman $\rho = 0.68$, $p < 0.0001$).

In its first-in-human deployment, this novel electrode configuration recorded valid hippocampal physiology under anesthesia and revealed a far richer taxonomy of epileptiform activity than conventional sEEG/ECoG—16 versus 3 spike subtypes—with directional and laminar detail. Radial micro-sampling recovers structure that sEEG electrodes average away.

KEYWORDS: *Implantable Devices (probes, etc.); Neural Recording & Modulation; Electrophysiology; Monitor Neural Activity; Human Neuroscience, Clinical Science, or Public Health; Software (analysis, etc.) and Engineering*

PRIME (PReserving Memory in Epilepsy): within-patient evaluation of low-frequency stimulation across four limbic targets in the first enrolled subject

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Objective. To test whether low-frequency stimulation (LFS; intended to induce long-term depression) of limbic targets reduces seizure burden while preserving memory, and whether the optimal target can be identified within a single patient. PRIME (NCT05608408) is a planned 8-subject trial in drug-resistant epilepsy; we report PR001, the first to complete all four arms.

Methods. PR001 (34-year-old woman, mesial-temporal lobe epilepsy) received two sensing-enabled Percept PC devices, four leads across four limbic sites, and was followed approximately 2.5 years. LFS was delivered continuously at 0.4 Hz. These were piriform cortex (PiC), entorhinal cortex (ERC), anterior nucleus of the thalamus (ANT), and fornix, evaluated sequentially, each an approximately 4-month LFS block separated by approximately 3-month standard-of-care (SOC; high-frequency ANT) washouts, with a follow-up visit after each period. Per arm, we tracked the seizure diary and a chronic-BrainSense outlier rate (per-day high-amplitude events), plus serial memory and quality-of-life testing.

Results. Pre-trial seizures were approximately 2 to 4 per month. Overall, LFS reduced seizure rate relative to SOC washouts (pooled all-LFS vs all-SOC = -25%), with the largest diary reductions at ERC (0.71 seizures/month, -51% vs the SOC washout mean) and fornix (-36%). The chronic-BrainSense outlier rate, a continuous seizure proxy, reproduced this ranking, falling most under ERC (-82 to -88% vs baseline) and fornix (-90%). Under LFS, power consumption was approximately 10 times lower than high-frequency ANT, projecting approximately 10 times longer battery life. Memory was preserved: RAVLT delayed recall trended upward across phases (Spearman rho = 0.89, p = 0.04) and was unchanged from baseline at ERC; at ERC, mood and quality of life remained stable.

Conclusion. In this first patient completing all four arms, ERC low-frequency stimulation produced the greatest seizure suppression while preserving memory and quality of life, at approximately 10 times lower power consumption than high-frequency ANT. Chronic BrainSense supplied an objective seizure-burden proxy concordant with the diary, supporting device-guided best-site selection.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices; Neural Recording & Modulation; Interventional Tools; Electrophysiology; Monitor Neural Activity*

Effect of YTHDF1 inhibition on learning and memory in a Fragile X syndrome model

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Fragile X syndrome is a genetic disorder caused by a mutation in the FMR1 gene, leading to profound cognitive impairments. Affected individuals often struggle with learning, memory, attention, executive function, and social interaction. Recently, epitranscriptomic modifications, specifically N-6-methyladenosine (m6A) RNA methylation, have emerged as critical regulators of brain development, synaptic plasticity, and neurological disease. YTHDF1 inhibitor, derived from a natural plant source, targets a primary m6A “reader” protein and has gained attention for its neuroprotective properties. By modulating m6A-dependent translation, this inhibitor has the potential to regulate synaptic function, reduce neuroinflammation, and enhance neurogenesis, which could improve cognitive and social behaviors in neurological conditions. Our experiment hypothesized that YTHDF1 inhibition might reduce cognitive deficits in Fragile X syndrome by addressing the hyperactive synaptic state in Fragile X mice. The cognitive impairments in Fragile X syndrome are linked to an imbalance between excitatory and inhibitory neurotransmission, leading to hyperactive neural circuits. We proposed that targeting m6A-mediated translation could help restore this balance, improving cognitive behavior. Our results demonstrated significant cognitive enhancements in treated groups, as evidenced by the Barnes Maze behavioral assessment. These improvements indicate better spatial learning and memory retention compared to control subjects. Furthermore, electrophysiological assessments using a multi-electrode array (MEA) demonstrated a promising alleviating effect on neural network hyperactivity, further supporting our hypothesis that modulating synaptic dynamics via epitranscriptomic pathways can counteract Fragile X syndrome deficits. These findings align with research emphasizing the importance of m6A RNA methylation and neurotransmitter signaling in cognitive function. YTHDF1 inhibitor may serve as a promising therapeutic agent for Fragile X syndrome, highlighting the therapeutic potential of targeting the m6A epitranscriptome, though further research is needed to fully understand their precise mechanisms of action.

KEYWORDS: *Behavioral Sciences/Psychology; Developmental/Systems Biology; Electrophysiology; Molecular/Cellular Neuroscience; Synaptic Plasticity; Implantable Devices (probes, etc.)*

A data-driven effective-connectivity resource linking hippocampal neuron types, excitability, and synaptic physiology

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Understanding how cellular diversity supports circuit-level computation requires open-access resources to connect curated neuron-type knowledge with quantitative experimental measurements. We developed a database-aligned effective-connectivity model of the rodent hippocampal formation that integrates neuron type-specific excitability, cell census, circuit stoichiometry, and synaptic physiology into inspectable matrices for secondary analysis and cross-scale modeling. The framework leverages the Hippocampome.org neuron classification framework and computes a directed synaptic population matrix from five data-driven edge-level terms: presynaptic neuron counts, connection probability, synaptic conductance, driving force, and decay time constant. To link structural connectivity with activity dynamics, each postsynaptic neuron type is assigned a gain term derived from neuron type-specific firing-rate/current (f-I) curves generated with constrained Izhikevich models, yielding a separate effective-connectivity matrix while preserving the original synaptic matrix for future computational simulations. Applied to an 85-type registry spanning dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex, the model represents $>10^6$ neurons or 90% of the whole mouse hippocampal formation. A data-driven effective-connectivity resource linking hippocampal neuron types, excitability, and synaptic physiology to neuronal count, and produces 1,641 directed neuron-type edges among 7,744 possible pairs. The outputs include exportable heatmaps and CSV matrices that link all individual parameters—cell census, synaptic biophysics, connection probability, and postsynaptic excitability—to published experimental data. These matrices provide a transparent bridge from curated structural knowledge to functional circuit representations, supporting future measurement refinements, graph-theoretic analyses, multiscale simulations, and validation against detailed spiking models. Thus, this work advances a neuron type-level functional connectomics modeling resource aligned with BRAIN priorities in connectivity across scales, secondary analysis, and brain tools and technologies.

KEYWORDS: *Cell Type/Interactions; Computational Biology/Modelling; Connectome; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Theory & Data Analysis Tools*

Engineering genetically encoded fluorescent opioid sensors for characterizing fentanyl and exogenous opioid pharmacology in vivo

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Opioid-based analgesics are the most widely used treatments for pain. However, opioid use and misuse have resulted in an overdose crisis fueled by untreated opioid use disorder (OUD), exacerbated by fentanyl's introduction into the drug supply. Fentanyl is a potent synthetic opioid and binds to the μ -opioid receptor (μ OR). However, the pharmacological and spatiotemporal profile of fentanyl distribution in the brain is poorly understood. Traditional tools to monitor opioid accumulation in the brain often fall short in terms of sensitivity, specificity, and real-time kinetics. To address this need, the Berndt Lab developed μ MASS, a genetically encoded μ OR-based sensor that couples real-time opioid detection to an increased fluorescence response. However, μ MASS detects all opioids, making it difficult to discern specific ligands. We hypothesized this was due to μ MASS recapitulating the native μ OR's promiscuous ligand binding. As a solution, we tested whether structural analysis of μ MASS-fentanyl binding may elucidate residues within the binding pocket governing specificity. We generated AlphaFold2 μ MASS models and docked fentanyl using AutoDock4, and observed fentanyl did not maintain a conserved salt bridge in the opioid binding pocket. Introducing mutations in this region rendered μ MASS specific for fentanyl while greatly reducing affinity for endogenous opioids, and we dubbed this sensor FentSense1.0. To enhance FentSense1.0 signal, we introduced μ OR receptors from alternative species. This resulted in FentSense1.7, which demonstrated increased dynamic range while maintaining fentanyl specificity. Preliminary in vivo experiments in the OFC of WT female mice revealed FentSense1.7 displays a dose dependent response to IP fentanyl injections. Additionally, in the CeA of WT male mice, FentSense1.7 rapidly detects IV infused fentanyl, and does not respond to morphine or naloxone infusions. Future in vivo experiments can determine fentanyl pharmacokinetics in the brain during various stages of fentanyl use to link real-time pharmacology measurements to behavioral phenotypes in freely behaving animals.

KEYWORDS: *Integrated Approaches; Molecular/Cellular Neuroscience; Monitor Neural Activity; Computational Biology/Modelling*

Characterizing the specificity and regulatory activity of layer-specific enhancers in mouse brain

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Deciphering complex brain functions requires a precise understanding of neural circuits at the cell-type level. However, discovering cell-type-specific enhancers remains challenging. In this study, we evaluated Adeno-associated virus (AAV) vectors engineered with machine learning-designed enhancers, originally identified via ATAC-seq from non-human primate tissue, to characterize their expression patterns in mice. Here, we packaged a layer 5-specific pyramidal neuron enhancer into AAV.PHP.eB capsids to generate a versatile delivery library. We subsequently performed systemic injections of this enhancer-driven AAV and a control AAV, which contained the pan-neuron hSyn promoter, into separate cohorts of wild-type mice. Histological analysis demonstrated targeted neuronal labeling within the cortex and some off-target expression in other structures. Despite the off-target expression, we sought to quantify the performance in layer 5, relative to the control. This quantification revealed that the control AAV labeled 13% of layer 5 neurons, whereas the layer 5-specific enhancer L5E1 significantly enriched targeting, driving GFP expression in 29% of layer 5 neurons in the primary motor area and 50% in the primary somatosensory area. These results demonstrated that the machine learning-guided enhancer successfully enriched transgene expression within cortical layer 5. Future work will use spatial transcriptomics to identify gene expression profiles in off-target cells and use this information to refine future enhancer constructs to improve layer-specific targeting. Our goal is to validate a suite of enhancers capable at directing optogenetic construct expression to various cortical cell types and furthering cell-type- and circuit-specific neuroscience studies.

KEYWORDS: *Cell Type/Interactions; Molecular/Cellular Neuroscience*

Species-divergent pharmacological responses in matched human and rodent 3D TBI models identify mitochondrial calcium dysregulation as a conserved therapeutic target

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Over thirty neuroprotective agents have shown efficacy in rodent traumatic brain injury (TBI) models, yet none has translated into an approved human therapy. This failure is widely attributed to species differences that have never been directly tested under matched injury conditions. We report the first parallel pharmacological comparison of human (hiNSC-derived) and rodent (E16.5 mouse) 3D cortical tissue subjected to identical controlled cortical impact (CCI) injury on a silk fibroin/collagen scaffold supporting long-term culture, standardized injury delivery, and repeated biochemical sampling. Twelve neuroprotective candidates spanning excitotoxic, ion-channel, and mitochondrial target classes were applied as single acute doses immediately post-injury, and neuronal network integrity, mitochondrial signaling, necroptotic pathway activation, and cell-death markers were assessed at species-optimized timepoints and longitudinally to two weeks. Five drugs reversed direction across species. GABA, NBQX, TTX, riluzole, and kaempferol were neuroprotective in rodent tissue but caused significant network degradation in human tissue; kaempferol reduced human network density roughly 6.75-fold while remaining protective in rodent constructs. This reversal reflects in part chloride cotransporter immaturity and the vulnerability of established human networks to broad activity suppression. By contrast, the NMDA receptor antagonists AP5 and MK-801 preserved network integrity in both species, and the mitochondrial calcium-targeting agents KB-R7943 and UK-5099 produced convergent protection across species. This protection was supported by significant injury-induced upregulation of the mitochondrial calcium uniporter (MCU) in human tissue that was normalized by treatment. Longitudinal studies confirmed partial network recovery with both mitochondrial agents, though repeated UK-5099 dosing revealed a metabolic constraint defining a finite therapeutic window rather than sustained coverage. Together, these findings demonstrate that critical species differences in neuroprotective drug response are directional rather than graded, a signal invisible to rodent-only preclinical pipelines. They establish mitochondrial calcium dysregulation as the most translationally conserved pharmacological target in acute TBI, with direct implications for human-relevant drug prioritization under emerging new approach methodology (NAM) frameworks.

KEYWORDS: *Cell Engineering; Cell Type/Interactions; Integrated Approaches; Molecular/Cellular Neuroscience; Neural Networks (topology, etc.); Developmental/Systems Biology*

BioLuminescent OptoGenetics—Molecular control with biological light

PRESENTER: **U. Hochgeschwender**
Central Michigan University

AUTHORS: U. Hochgeschwender

BioLuminescent Optogenetics (BL-OG) drives optogenetic elements with internal, locally generated, bioluminescent light created by a nearby luciferase in the presence of its luciferin. The use of biolight to control light-sensing domains expands standard optogenetics based on physical light sources to a BL-OG tool platform that enables unique applications of controlling and integrating biological processes within and across cells. Having both light emitter and light sensor genetically encoded allows versatility in how the two moieties are expressed. In luminescent opsins, luminopsins (LMOs), the luciferase is tethered to an opsin, enabling bimodal—opto- and chemogenetic—control of the cell's membrane potential. In Interluminescence (Int), the two moieties are expressed in different cells for applications in cell-to-cell communication. Expressing a luciferase in a presynaptic neuron and an opsin in a postsynaptic neuron enables synaptic communication through photons. Presynaptic light emission can be made dependent on neural activity, thus creating a real time optical synapse. In Bioluminescent Activity Dependence (BLADe), the engineered split luciferase accommodates sensor moieties that make light emission dependent on the presence of various intracellular agents. The luciferase sensor reports a cell's state, resulting in the integration of intracellular states with outcomes effected by a co-expressed optogenetic actuator. Combining such conditional light emitting systems with light sensing ion channels, transcription factors, and other photoreceptors opens many opportunities for self-regulation of cellular states. BL-OG tools have been employed in contexts of disease therapies and to address basic biological questions. BL-OG was successfully used in preclinical, translational studies in animal models of epilepsy, peripheral nerve and spinal cord injury, stroke, neurodegenerative diseases, sleep disorders, diabetes and various forms of cancer. Basic science studies were conducted in areas including neurodevelopment, memory and learning, and the dissection of motor circuitry. All applications benefited from the advantages of BL-OG over standard optogenetic and chemogenetic approaches, particularly its non-invasiveness, spatial access, fast kinetics and absence of cross-reactivity of luciferins. BL-OG tools offer alternatives to chemo- and optogenetics approaches and provide unique features for sensing, controlling, and integrating neural activity.

KEYWORDS: *Cell Engineering; Cell Type/Interactions; Electrophysiology; Integrated Approaches; Interventional Tools; Molecular/Cellular Neuroscience*

High-throughput engineering of genetically encoded μ -opioid sensors with enhanced sensitivity and neuronal expression for detecting opioids in vivo

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The mu-opioid receptor (MOR) regulates diverse physiological processes including analgesia, reward, stress responses, and affective signaling through endogenous opioid peptides. However, directly monitoring MOR activation in living systems remains challenging. Genetically Encoded Fluorescent Indicators (GEFIs) provide a powerful strategy for real-time visualization of receptor activity, but optimizing sensor performance requires balancing fluorescence dynamic range, ligand sensitivity, and pharmacological properties. Using iterative sensor engineering approaches, we developed successive generations of MOR-based fluorescent sensors with progressively improved performance. Previously developed μ MASS1.5 and μ MASS1.7 were designed to enhance fluorescence output and exhibited substantially increased dynamic range relative to μ MASS1.0. Across multiple opioid ligands, these sensors produced approximately 1.5- to 3-fold greater maximal fluorescence responses, with μ MASS1.7 showing particularly strong signal enhancement toward ligands including met-enkephalin, leu-enkephalin, dynorphin, and fentanyl in mammalian cells. Building upon these advances, we developed μ MASS2.0, a next-generation sensor optimized for improved pharmacological performance, with particular emphasis on endogenous ligand sensitivity and receptor response characteristics. Functional characterization revealed refined EC50 profiles across multiple opioid peptides. μ MASS2.0 demonstrated improved sensitivity toward met-enkephalin and leu-enkephalin, exhibiting EC50 values of approximately 72 nM and 230 nM, respectively. Robust responses were also maintained toward additional endogenous ligands including beta-endorphin and dynorphin, supporting improved pharmacological tuning for endogenous opioid sensing. Together, these studies establish a progressive engineering framework in which distinct μ MASS generations independently optimize fluorescence performance and receptor pharmacology. To further accelerate biosensor discovery and optimization, we developed Opto-MASS, a high-throughput screening platform enabling functional evaluation and selection of genetically encoded sensor libraries. By integrating iterative engineering with scalable screening approaches, this platform provides a versatile toolkit for investigating endogenous opioid signaling and advancing next-generation genetically encoded biosensor development in cellular, neuronal, and in vivo systems.

KEYWORDS: *Chemistry; Computational Biology/Modelling; Integrated Approaches; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation*

Machine learning-driven optimization of red genetically encoded calcium indicators for in vivo imaging

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Red fluorescent genetically encoded calcium indicators (GECIs) are important tools for monitoring calcium dynamics in living cells, especially in experiments requiring spectral separation from green reporters or compatibility with blue-light activated opsins. However, most current red GECIs are limited by low baseline fluorescence, slow kinetics, and poor photostability, which reduce their utility in deep brain regions. Additionally, the engineering process remains a time- and resource-intensive challenge due to the vast sequence space of possible protein variants. To address these challenges, we adapted ProteiML, an ensemble machine learning framework developed in the Berndt Lab, to predict mutation-dependent changes in red GECI performance and prioritize candidate variants for experimental testing. By introducing gain-of-function mutations into jRGECO1a and systematically evaluating in HEK293 cells, iPSC-derived cardiomyocytes, and primary cultured neurons, we identified multiple variants with improved performance. These variants reliably detected single action potentials in neurons and spontaneous calcium transients in cardiomyocytes. Among these, we observed distinct functional improvements: one variant exhibited a 1.75-fold increase in dynamic range while maintaining baseline fluorescence comparable to the parental construct, another showed enhanced calcium sensitivity with an EC50 of 134 nM in purified protein assays, and the third one displayed faster kinetics across multiple experimental contexts. These improvements were further validated by in vivo imaging. Additionally, by transferring ProteiML-predicted mutations to related red GECI scaffolds generally improved indicator kinetics and dynamic range, demonstrating the broader utility of this optimization strategy. Together, our results demonstrate that machine learning-guided protein engineering can accelerate the optimization of red GECIs by efficiently prioritizing functional variants for validation. This approach reduces the experimental burden of navigating large protein sequence spaces and provides a scalable strategy for developing improved fluorescent biosensors for neuroscience, genetics, and bioengineering applications.

KEYWORDS: *Computational Biology/Modelling; Integrated Approaches; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neural Recording & Modulation*

Neuromorphic computing for energy-efficient AI

PRESENTER: **P. Date**

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The unprecedented scale of modern artificial intelligence—driven by large language models, transformers, and agentic AI systems comprising hundreds of millions of neurons and billions of synapses—has produced an unsustainable energy bottleneck that threatens the continued growth of the field. This poster presents Oak Ridge National Laboratory's multi-year research program on neuromorphic computing as a pathway to dramatically more energy-efficient AI. Spiking neural networks (SNNs), built on leaky integrate-and-fire (LIF) neurons that communicate via discrete events rather than continuous activations, consume 1,000x to 10,000x less power than conventional artificial neural networks while preserving computational expressiveness. We summarize foundational contributions from 2019 through the present, including theoretical results establishing the Turing completeness and computational complexity of neuromorphic algorithms, the SuperNeuro simulator, the NeuroCoreX FPGA emulation platform with on-chip learning, and applications spanning learning, graph algorithms, and broader scientific computing. Building on this foundation, we introduce HyperNeuro, a high-performance PyTorch-based LIF simulator engineered to exploit leadership-class systems such as Frontier, Lux, Discovery, and Alps. HyperNeuro enables Spiking Graph Neural Networks (SGNNs) to scale to hundreds of millions of neurons and billions of synapses, and we validate this capability on two demanding workloads: node classification across massive citation networks organized by research area, and regression for predicting precise materials properties. Together, these demonstrations confirm that spiking architectures can match the scale and accuracy of conventional deep learning at a fraction of the energy cost, laying the groundwork for spiking transformers, spiking LLMs, and ultimately spiking agentic AI.

KEYWORDS: *Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering; Synaptic Plasticity; Theory & Data Analysis Tools; Computational Biology/Modelling*

Scalable cell type-specific barcoded connectomics reveals the projectional architecture of the mouse midbrain dopaminergic system

PRESENTER: **H. Kim**

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The structure of single-neuron projection patterns provides critical insights into how information flows between brain regions. It defines projectional cell types as the cellular units of signal transduction, and sheds light on their specific functions. As a pioneering barcoded connectomics method, MAPseq has enabled the high-throughput mapping of single-neuron projections by translating neuroanatomy into a format solvable by DNA sequencing. However, the original MAPseq protocol has relatively low sensitivity and is expensive per sample. As MAPseq relies on the use of RNA virus Sindbis for barcoding, it also does not directly support cell type specific mapping of neuronal populations of interest, such as those defined by gene expression, input, or activity. As a result, elucidating the comprehensive projectional architecture of the specific neural systems involved in behavior, disease, development, and aging remains challenging.

Here, we introduce two new methods that address these bottlenecks and together enable scalable, readily accessible, and cell-type-specific mapping of single-neuron projections.

MAPseq2 addresses sensitivity and cost issues. It is a streamlined and cost-effective protocol that achieves up a 10-fold higher sensitivity while decreasing costs by 10-fold over the original MAPseq protocol. As MAPseq workflows are shared across a range of barcoded connectomics methods, including BARseq, BRICseq, and ConnectID, all improvements in MAPseq2 directly transfer to these technologies.

POINTseq enables cell type-specific barcoded connectomics by combining pseudotyped barcoded Sindbis virus with the cell type specific expression of the cellular receptor of the pseudotyped virus. It thus restricts barcoding to the cell population of interest. We validated POINTseq in genetically and projectionally defined neuronal populations in the mouse motor cortex. We then applied POINTseq to midbrain dopamine (DA) neurons and reconstructed the brain-wide single-cell projections of approximately 6,000 DA neurons in ventral tegmental area (VTA) and substantia nigra pars compacta (SNc). We define over 25 connectomic cell types, vastly exceeding the known diversity of DA cell types. Further, we identify stereotyped co-innervation patterns and projection motifs that may mediate parallel DA signaling implicated in specific DA functions. This data constitutes the anatomical substrate on which the diverse functions of DA in the brain are built.

KEYWORDS: *Cell Type/Interactions; Circuit Diagrams; Connectome; Neural Networks (topology, etc.)*

Chemogenetic switches for temporal and cell-type-specific control of PKA activity

PRESENTER: **Y. Zhuo**

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Neuromodulation exerts powerful control over brain function. At the cellular level, cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) acts as a central downstream integrator of multiple neuromodulatory pathways and plays a key role in regulating synaptic plasticity, neuronal excitability, and other cellular functions. While recent advances in genetically encoded sensors have enabled visualization of PKA activity during behavior, tools for regulating PKA signaling with comparable spatiotemporal precision remain limited, hindering causal interrogation of its functions. To address this gap, we engineered a suite of chemogenetic actuators that employ complementary strategies for selective and reversible manipulation of PKA activity across distinct temporal domains. These inhibitors enable ligand-dependent, precise, and efficient inhibition of PKA activity in cultured cells, brain slices, and living animals. Together, these switches provide a powerful toolkit for dissecting the functional roles of PKA in defined cell populations and neural circuits.

KEYWORDS: *Integrated Approaches; Molecular/Cellular Neuroscience; Neural Recording & Modulation; Neural Networks (topology, etc.)*

Universal viral barcoding reveals convergent evolution of human-like cortical projection logic in the avian vocal system

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Comparative connectomics can reveal fundamental principles of brain organization and computation. However, in vertebrates, such comparisons are hindered by model-specific or low-resolution tracing methods. To address this bottleneck, we here develop the barcoded connectomics method, MAPseq, for use across all vertebrates. MAPseq enables rapid single-neuron projection mapping by uniquely labeling neurons with barcoded viruses and reading projections via sequencing. It is currently largely limited to mice due to viral tropism and barcode trafficking. We developed a flexible pseudotyping system to enable robust barcoding in macaque, marmoset, zebra finch, mouse, and xenopus brains and identified a species-general carrier protein that enables efficient barcode transport across mammals and birds. Using this universal method, we contrasted the single cell projectional architecture of the avian vocal system in closed and open song learners, songbirds and parrots. We focused on the functionally homologous premotor song nuclei RA and AAc in zebra finches and budgerigars, respectively, and compared our results to existing data from mice (non-learners) and the laryngeal motor cortex of humans, who are open learners like parrots. While zebra finch RA comprises only ipsilaterally descending projection neurons, budgerigar AAc contains both descending and ascending projection neurons with highly symmetric innervation of ipsi and contralateral hemispheres. On the ipsilateral side, budgerigar descending neurons are structured nearly identically to zebra finch RA neurons, and neurons from both species overall mirror corticothalamic (CT) and extratelencephalic (ET) projection neurons of the mammalian neocortex. Intriguingly, the budgerigar-specific ascending projections were structured highly similarly to mammalian intratelencephalic (IT) neurons, indicating that parrot AAc consolidated a near-complete repertoire of cortical projection-neuron classes within a non-laminar nucleus. Moreover, the budgerigar neurons targeting the brainstem song nucleus nXIIts bifurcated bilaterally, paralleling structures found in the human laryngeal motor cortex and its bilateral innervation of the nucleus ambiguus. Taken together, our results demonstrate a stepwise increase in projectional complexity from closed to open song learners and a remarkable convergence of projection logic at single-cell resolution between parrots and humans.

KEYWORDS: *Connectome*

Multimodal synaptomics reveals coordinated synaptic activity, protein synthesis, and reorganization in NMDAR regulation

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Complex neuronal circuit functions emerge from local, actively regulated synaptic protein levels that interplay with synaptic neurotransmission across heterogeneous synapse populations. Understanding the mechanisms by which chemical and disease-associated genetic perturbations impact neuronal circuit functions requires simultaneous measurement of these factors with single-synapse resolution at population scale. Here, we combine in situ multimodal imaging of local mRNA translation, synaptic multiprotein composition, and synapse activity measured via calcium or glutamate fluxes, within the same spatially resolved synapses. We apply this approach of multimodal synapse profiling to study ketamine plasticity. Results map a causal network of NR2A-depletion-induced changes to synaptic scaffolding and receptor proteins, driven by synaptic activity and local mRNA translation, which translates to Grin2a models of schizophrenia in vitro and in vivo. Thus, multimodal synaptomics can reveal mechanistic neurobiology that underlies chemical and genetic perturbations within the context of scalable neuronal cultures, which can serve as models for human disease and therapeutic development.

KEYWORDS: *Integrated Approaches; Molecular/Cellular Neuroscience; Monitor Neural Activity; Physics or Microscopy/Optics; Synaptic Plasticity; Genetics/Genomics*

Enhanced distal signaling in human hippocampal neurons despite lower intrinsic excitability

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The hippocampus is critical for memory and spatial navigation, and is central to the pathophysiology of temporal lobe epilepsy—the most common drug-resistant epilepsy. Yet our understanding of the cortico-hippocampal circuit, and neuronal function relies on rodent studies, which may not fully model human features. Here, we combined patch-clamp electrophysiology, histology, and microscopy to functionally and morphologically characterize human hippocampal neuron types at high-resolution from freshly resected tissue from epilepsy patients. We found striking region-, species, and pathology-specific differences in neuronal excitability, synaptic dynamics, and dendritic branch patterns. Dentate gyrus granule cells are the most excitable human hippocampal principal neurons. Human neurons are intrinsically less excitable than mouse neurons—requiring more current to fire—but paradoxically show higher action potential firing rates. Human pyramidal neurons from non-sclerotic CA1 show reduced sag compared to their sclerotic tissue, and its mouse counterpart. Human neurons more effectively preserve distal dendritic signal propagation to the soma. Neurons in each hippocampal sub-region display distinct activity-dependent synaptic plasticity dynamics. Morphologically, human neurons are larger with more elaborate and diverse dendritic branching patterns. Taken together, our results suggest that human hippocampal principal neurons have evolved in form and function to enhance synaptic input integration and signaling.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Molecular/Cellular Neuroscience; Synaptic Plasticity; Cell Type/Interactions*

Temporal coding expands the bandwidth of GPCR-mediated neuromodulation

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The advent of modern transcriptomic approaches has revealed a breadth of neuromodulatory G protein-coupled receptor (GPCR) co-expression far exceeding what was previously thought. This raises a fundamental question about neuromodulatory system architecture, because there is a much smaller number of available G protein transducers. Does this impose an information bottleneck, or can a single transducer pathway distinguish the effects of different neuromodulators? We addressed this question by focusing on four GPCRs that are natively co-expressed in essentially all hippocampal pyramidal neurons and that signal through the canonical Gs-coupled cyclic AMP (cAMP) cascade. We show that each GPCR produces a similar cAMP elevation upon acute activation but the effects observed at downstream steps diverge, to the point that the GPCRs differ dramatically in their ability to drive a transcriptional response. We also show that they differ in their ability to maintain functional responsiveness, with neuropeptide receptors remaining responsive for hours but monoamine receptors rapidly losing responsiveness. We conclude that the effective chemical bandwidth of cellular neuromodulation by GPCRs is not limited by the number of available transducers, and that there exists additional temporal coding which enables individual neurons to distinguish a richer neuromodulatory input.

KEYWORDS: *Cell Type/Interactions; Molecular/Cellular Neuroscience; Monitor Neural Activity*

Applying Universal Cell Embedding foundation model to integrate and map brain single-cell transcriptomics data

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The rapid expansion of single-cell transcriptomic data in neuroscience has outpaced existing integration tools, which remain semi-automated and limited to a few million cells. We present a framework for building comprehensive brain single-cell transcriptome references by applying the Universal Cell Embedding (UCE) foundation model, a 650-million-parameter transformer trained on 36 million cells across 300+ datasets and 8 species, to integrate data from major neuroscience consortia including BICAN and SEA-AD. Our reference encompasses 20 million human nervous system cells from 92 studies, spanning diverse brain regions, developmental stages, and disease states. We demonstrate that UCE inference enables robust mapping of new datasets onto the reference, achieving high ontology-aware prediction accuracy across varied cell types and preprocessing pipelines. It outperforms existing tools such as SCimilarity and is on par with MapMyCells in cross-ontology benchmarks.

To support broad community use of these references, we are developing the UCSC Brain Explorer, a web portal that enables researchers to map their own single-cell data to the references and explore the results interactively. It leverages pyramid data tiling to visualize tens of millions of cells in under 0.5 seconds with interactive panning and zooming. The website currently supports three references: adult human brain, developing human brain, and human brain organoid. Researchers upload their h5ad file, which is then embedded using UCE, projected into a reference, and assigned cell labels based on the 30 nearest reference neighbors. Users can interactively explore the mapping overlaid on top of the reference UMAPs, download the cell labeling results, and explore additional analyses, such as differential gene expression, using our chatbot. The UCSC Brain Explorer is currently in beta and open for public use and feedback.

KEYWORDS: *Computational Biology/Modelling; Genetics/Genomics; Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Databases for neural morphology and hippocampal cell types

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The tree-like morphology of neurons and glia is a key cellular determinant of circuit connectivity and metabolic function in the nervous system of essentially all animals. To elucidate the contribution of specific cell types to both physiological and pathological brain states, it is important to maximize accessibility to detailed and well documented neuroscience data. Here we discuss two mature neuroinformatics projects aimed at facilitating computational modeling and quantitative analysis of neural morphological and network dynamics. NeuroMorpho.Org is the largest online collection of freely available digital neural reconstructions, with hundreds of thousands of reconstructed morphologies and related metadata, and is continuously updated with new datasets. Our semi-automated pipeline enables the release of new data as soon as they are ready, maximizing the collective benefit of research and forging a positive culture of open data. On the other hand, Hippocampome.org uses axonal and dendritic morphology as a foundational approach to classify neurons in the rodent hippocampal formation. This curated knowledge base defines over 180 neuron types across dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex. Hippocampome.org then organizes known characteristics of neuron types by linking neuronal morphology to transcriptomics, electrophysiology, cell counts, synaptic signaling, connection probabilities, and more. All properties are directly supported by peer-reviewed experimental evidence and best-fitted with computational models. Thus, Hippocampome.org enables building real-scale, biologically detailed, data-driven spiking neural network simulations. Both NeuroMorpho.org and Hippocampome.org are fully open source, extensively documented, and programmatically accessible, enhancing the usability of existing data for rigorous analysis and realistic models from single cell to neural circuits and beyond.

KEYWORDS: *Cell Type/Interactions; Computational Biology/Modelling; Theory & Data Analysis Tools; Electrophysiology*

Neuro-MINE: A pipeline for neural response data analysis

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Modern neuroscience methods generate vast quantities of data by recording from many neurons simultaneously as animals perform behavioral tasks. A common initial question is how the activity of neurons relates to stimuli the animal experiences or behaviors the animal performs. A classical approach to this problem is to use linear regression: a powerful and interpretable method to relate predictors (such as stimuli and behaviors) to neural activity and determine which predictors drive a given neural response. By providing time-shifted versions of predictors, linear regression can furthermore capture neurons that integrate or differentiate their inputs. However, by construction, linear regression is limited to capturing linear relationships between predictors and neural activity. Here, using our research group's imaging data, we present a neural response analysis technique: Neuro-MINE. Neuro-MINE is a machine-learning based Python package with two modules: training and prediction. The training module links predictors to neural activity and provides key information on their relationship, which can be accessed via a GUI or the command line. Training uses a convolutional neural network allowing for linear and non-linear relationships between predictors and activity, which are characterized using Taylor decomposition. The second module—prediction—allows users to compute the most likely neural response to novel inputs. In the prediction module, users can provide predictors so that Neuro-MINE can compute the most likely neural response.

In summary, Neuro-MINE presents a flexible, user-friendly, and mathematically robust pipeline for generating insights from neural responses generated by stimuli or behaviors.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Dissemination & Open Science/Education; Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

NiChart: Neuro-imaging chart of AI-based biomarkers

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Recent advancements in machine learning (ML) and artificial intelligence (AI) for MRI-based phenotyping offer great promise for developing imaging-centric diagnostic and prognostic biomarkers. Concurrently, translating these methods into clinical and research workflows requires a large annotated dataset, seamless integration to research and clinical workflows, and intuitive user interfaces. To address these needs, we introduce Neuro-imaging Chart of AI-based Biomarkers (NiChart): a novel, scalable neuroimaging platform equipped with advanced ML/AI methods to compute dimensional brain charts from multi-modal MRI data where users could perform an end-to-end analysis from raw DICOM files to research outcomes and clinically relevant insights. NiChart leverages a massive reference dataset of 106,902 MRI scans from 78,450 participants across 50 studies, successfully capturing multivariate imaging signatures of brain anatomy and functional signals while leveraging robustness to inter-scanner variability, both with and without statistical harmonization. We demonstrated NiChart's utility across independent diverse cohorts, including patients with neurodegenerative, cardiovascular, and metabolic diseases. Specifically, we found that these clinical conditions are associated with increased brain age gap, higher white matter lesion (WML) burdens, and elevated atrophy subtypes. To foster community-driven growth and accessibility, NiChart is freely available as both a cloud-based platform and a locally installable package. We envision NiChart to continue to grow with the scale of incoming data and machine learning pipelines from collaborators.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Informatics, Statistics, or Applied Mathematics*

From local geometry to network organization: Insights from connectomes

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One of the major challenges in neuroscience is bridging the gap across scales: understanding how local geometric features of dendrites and axons give rise to specific patterns of synaptic connectivity and, ultimately, to large-scale network organization. Recent mouse and human connectomes, including MICrONS, V1DD, and H01, provide a unique opportunity to test whether shared geometric principles link fine-scale neuronal interactions to network organization across species.

Here, we show that neurons with higher dendritic spine density receive inputs from a larger and more diverse set of presynaptic partners. This structural feature increases their propensity to share inputs with other neurons, driving their participation in neuronal ensembles. We further demonstrate that excitatory neurons with longer axons exhibit a stronger overall preference for targeting dendritic spines. Moreover, along individual axons, the probability of forming synapses onto dendritic spines increases with distance from the soma. Together, these results suggest that local geometry plays a major role in shaping network architecture.

Yet the rules governing synapse selection at the level of individual axon-dendrite contacts remain poorly understood. In cortical neurons, only ~10% of physically proximal axon-dendrite appositions (within 2 μm) actually form synapses. To determine which of these proximal pairs connect, we first evaluate whether local geometric features alone can predict connectivity patterns. We then integrate structural (EM) and functional (calcium imaging) data from the MICrONS dataset to test whether synapse formation depends not only on geometric opportunity but also on activity-dependent factors.

These findings suggest that the logic of cortical wiring may arise from simple local geometric rules together with activity-dependent mechanisms. Ultimately, understanding these rules may help link cellular geometry, connectivity, and network function across scales.

KEYWORDS: *Computational Biology/Modelling; Connectome; Neural Networks (topology, etc.); Theory & Data Analysis Tools; Circuit Diagrams*

STAMPED principles for reproducible research objects

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Neuroscience increasingly depends on the interplay of code, data, and computational environments, yet the record of how they were used together is often incomplete, scattered across repositories, wikis, and notebooks, or lost entirely. This fragmentation undermines rigor, reproducibility, reusability, and efficiency in BRAIN Initiative pipelines that routinely span multiple institutions, archives, and compute platforms. Existing frameworks such as FAIR and FAIR4RS govern discovery and interoperability of digital objects but do not specify how research objects should be structured and managed so they can be re-executed, extended, and audited. The community lacks a shared vocabulary for this operational layer.

Building on data management traditions from neuroimaging, and on patterns that have independently converged across geophysics, genomics, statistics, and neuroimaging over three decades, we formalize seven principles a research object should satisfy: Self-containment, Tracking, Actionability, Modularity, Portability, Ephemerality, and Distributability, collectively STAMPED. Each spans a spectrum from practical minimum to aspirational ideal, so adoption is non-prescriptive and incremental. Formal LinkML schemas, an interactive compliance checklist, and the curated collection of examples are provided as enabling tools to this end.

Here we demonstrate STAMPED through two products within BRAIN-funded projects. OpenNeuroDerivatives reorganized derivative neuroimaging datasets so they exist as independent Ephemeral units that reference raw inputs as subdatasets rather than nesting under them, removing an upward dependency that previously violated Self-containment, Modularity, and Portability. DANDI Compute, utilizing the Allen Institute for Neural Dynamics electrophysiology pipeline, packages spike-sorting outputs into nested BIDS-derivative units in which each leaf contains the exact code, runtime logs, outputs, and provenance metadata needed to re-execute the analysis, satisfying STAMPED end-to-end. These adoptions show that STAMPED provides a tool-agnostic, incrementally adoptable vocabulary that lets researchers, reviewers, collaborators, and emerging AI agents evaluate and improve the operational maturity of computational neuroscience. By making research objects re-executable and inspectable by construction, STAMPED converts reproducibility from an aspiration into a measurable property of everyday neuroscience practice.

KEYWORDS: *Informatics, Statistics, or Applied Mathematics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

AI-driven neuroinformatics workflows for scalable neuroscience data analysis and visualization

PRESENTER: **A. Alhan**

Independent Researcher

AUTHORS: A. Alhan

Advances in neuroscience research are generating increasingly large and complex datasets that require scalable computational tools for efficient analysis, visualization, and interpretation. This project presents an AI-driven neuroinformatics framework designed to automate neuroscience data workflows using Python-based analytics, machine learning techniques, and interactive dashboard systems.

The framework integrates automated data preprocessing, statistical analysis, visualization, and reporting pipelines to support scalable neuroscience research operations. Using structured analytics workflows, the system enables rapid processing of multidimensional datasets while improving reproducibility and reducing manual analysis time. Interactive dashboards were developed to monitor trends, identify anomalies, and visualize longitudinal neural and behavioral data in real time.

Machine learning and predictive analytics approaches were incorporated to explore pattern recognition and data interpretation capabilities within neuroscience datasets. The workflow also emphasizes modular software engineering principles to improve flexibility, scalability, and integration with future neuroscience research environments.

This project demonstrates how computational automation and neuroinformatics methodologies can improve efficiency, accessibility, and analytical depth in neuroscience research. By combining data science techniques with scalable visualization systems, the framework supports more adaptive and data-driven approaches to understanding complex brain-related datasets.

Future directions include integration with real-time neural recording systems, advanced deep learning models, and cloud-based collaborative neuroscience platforms to support next-generation neuroscience research and discovery.

KEYWORDS: *Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Integrated Approaches*

Sliding-window channel capacity: An information-theoretic measure of time-resolved effective connectivity and neural noise

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Understanding how coordinated neural activity across diverse brain regions underlies brain function requires methods that identify directed interactions while capturing their temporal evolution. However, existing measures of effective connectivity (EC) often rely on strong modeling assumptions and lack temporal resolution. To overcome these limitations, we introduce sliding-window channel capacity (SWCC), a novel EC measure that integrates information theory with a sliding-window approach.

Within this framework, the directed interaction from one region of interest (ROI) to another is conceptualized as a communication channel. Within each sliding window, the channel is modeled as a finite impulse response (FIR) filter with additive white noise. Filter coefficients are estimated from functional neural recordings via linear regression, while the regression residuals represent samples of the underlying noise process. Channel capacity, defined as the maximum rate at which information can be transmitted through the channel, is then computed to reflect the noise characterization directly inferred from the data, unlike conventional approaches that assume a simple Gaussian distribution.

The proposed measure was validated using multi-modal neural recordings. First, in bilateral local field potential (LFP) and fMRI recordings, the directional asymmetry observed in SWCC was significantly smaller than the scan-to-scan variability of SWCC, demonstrating high specificity against spurious connectivity. Second, using task fMRI data from the Human Connectome Project (HCP), SWCC demonstrated high sensitivity to task-evoked changes, outperforming the conventional benchmark Granger causality. Finally, SWCC was computed with and without the Gaussian noise assumption using EEG and LFP recordings and showed measurable differences, underscoring the importance of data-driven noise characterization.

In conclusion, SWCC provides a principled, highly sensitive, and modality-agnostic framework for tracking dynamic, directed brain connectivity. By capturing causal directionality and temporal variability without relying on rigid noise assumptions, this framework offers a powerful tool for investigating the complex, time-varying communication networks of the brain.

KEYWORDS: *Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Theory & Data Analysis Tools; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Spatial statistics and point pattern analysis reveal lifespan trajectories of microglial density and clustering in the primate hippocampus

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The hippocampus undergoes substantial structural remodeling across the lifespan, yet how its resident immune cells, microglia, reorganize during development and aging remains poorly understood in primates. We quantified microglial density and spatial organization across hippocampal subfields in 15 female rhesus macaques spanning late gestation (gestational day 140) to advanced age (32.4 years) using tissue from the MacBrain Resource Center. Animals were grouped as perinatal (GD140-7 days postnatal), postnatal (2.5-6 months), juvenile/adult (11.4 months-9.8 years), and aged (18.7-32.4 years). Microglial density exhibited a U-shaped trajectory, declining during early postnatal life before increasing through adulthood and aging, with the dentate gyrus showing the greatest age-related change. Nearest-neighbor distance followed an inverse pattern, indicating maximal microglial dispersion during the postnatal period. Ripley's H-function analysis revealed age-dependent alterations in microglial territorial organization, including an expanded exclusion radius in aged animals. Tile-based spatial analyses further identified increased microglial clustering within CA1 in the aged group. In the oldest animal, regions of microglial clustering corresponded with amyloid- β and phosphorylated tau immunoreactivity. Together, these findings demonstrate dynamic lifespan-dependent remodeling of microglial spatial organization and establish a quantitative framework for studying neuroimmune architecture in the aging primate hippocampus.

KEYWORDS: *Cell Type/Interactions; Developmental/Systems Biology; Informatics, Statistics, or Applied Mathematics; Molecular/Cellular Neuroscience; Software (analysis, etc.) and Engineering*

Physiological biometrics for adaptive neuroprosthetic control: A bibliometric perspective on brain-computer interfaces

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ThinkNeuro, LLC

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Brain-computer interfaces (BCIs) enable the restoration of motor and communication functions for individuals with stroke or spinal cord injury, yet conventional systems remain constrained by stochastic neural noise and high cognitive load. This study utilizes a systematic bibliometric analysis to identify research trends and innovation gaps, guiding the design of adaptive, personalized neuroprosthetics intended to improve long-term usability. Through a systematic inquiry of the Web of Science Core Collection (2003-2025), 203 preliminary articles related to adaptive control and multimodal signals were identified. The 100 most-cited papers were ranked by citation weight, with data extraction and mapping conducted in R and Excel to characterize disciplinary influence, keyword co-occurrence, and technical performance variables. Results reveal a research landscape heavily concentrated in the subject areas of "Engineering" and "Neurosciences & Neurology," indicating a mature transition from technical theory toward clinical motor restoration. A significant innovation gap was identified: While electroencephalography is ubiquitous, autonomic biometrics such as heart rate variability appear in fewer than 5% of studies. Nevertheless, technical analysis confirms multimodal sensor fusion is the primary mechanism for mitigating cognitive load. Gating neural intent with residual muscle activity or eye-gaze tracking also stabilizes control by reducing false-positive rates below 10%, while fusing prefrontal oxygenation with cardiovascular biometrics improves mental stress classification accuracy to 85%. Discussion of longitudinal data identifies closed-loop decoder adaptation (CLDA) as the indispensable engine for long-term usability, facilitating exponential learning curves through human-machine co-adaptation. Clinical validation of the motorized ankle-foot orthosis (BCI-MAFO) reveals significant increases in motor-evoked potential size, providing empirical evidence of induced cortical neuroplasticity even in chronic stroke survivors. Ultimately, the evidence accentuates a mandatory shift toward hybrid architectures and subject-independent decoders (75.3% accuracy) to eliminate lengthy patient-specific calibration; prioritizing bidirectional interfaces with real-time haptic feedback (72% accuracy) ensures that adaptive neuroprosthetic systems move toward intuitive, scalable clinical solutions that comprehensively restore embodied movement and communication.

KEYWORDS: *Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Neural Recording & Modulation; Software (analysis, etc.) and Engineering; Synaptic Plasticity; Theory & Data Analysis Tools*

Principled inference of neural population dynamics across multiple timescales

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Modern neuroscience experiments produce large-scale recordings of neural population activity across multiple brain regions during complex behaviors. Extracting computational mechanisms from such data requires more interpretable, data-driven AI methods that go beyond time-series prediction and identify structured dynamical principles underlying neural computation. A central challenge is that neural activity contains multiple interacting timescales, ranging from fast intrinsic responses to slower contextual or cognitive processes. But existing approaches often struggle to disentangle these temporal structures in high-dimensional, variable, and task-dependent neural recordings.

To address this challenge, we develop a novel data-driven dynamical systems framework for inferring neural population dynamics across multiple regions and timescales. Our approach is based on a structured generative state-space model in which latent neural dynamics are explicitly organized into multiple temporal components. The model is trained using variational inference, together with targeted regularization that promotes interpretable temporal organization and separates fast and slow dynamical modes from high-dimensional neural activity.

We apply this framework to neural population recordings from monkeys performing reaching movements. The model infers distinct latent timescales that are entangled within the observed neural activity. We further find that these timescales vary systematically across behavioral contexts and neural populations. In particular, in the somatosensory area Area 2, the inferred neural dynamics are faster during external perturbation conditions than during standard center-out reaches. This suggests that latent timescale structure can reveal how neural populations adapt their dynamics across behavioral demands.

By combining structured state-space modeling and biologically meaningful regularization, our approach provides a principled tool for studying how temporal organization in neural circuits supports flexible behavior. More broadly, this work is part of our ongoing effort to develop interpretable and reliable data-driven AI for neural data analysis, where dynamical system models are used not only to predict neural activity but also to reveal dynamical and functional principles of neural computation.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Theory & Data Analysis Tools; Electrophysiology*

SLAy-ing oversplitting errors in high-density electrophysiology spike sorting

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The growing channel count of silicon probes has substantially increased the number of neurons recorded in electrophysiology (ephys) experiments, rendering traditional manual spike sorting impractical. Instead, modern ephys recordings are processed with automated methods that use waveform template matching to isolate putative single neurons. While scalable, automated methods rely on assumptions that often fail to account for biophysical changes in action potential waveforms, leading to systematic oversplitting of individual neurons into multiple putative units. Consequently, manual curation of these errors, which is both time-consuming and lacking in reproducibility, remains necessary. To improve efficiency and reproducibility in the spike-sorting pipeline, we introduce the Spike-sorting Lapse Amelioration System (SLAy), an algorithm that automatically merges oversplit spike units. SLAy employs two novel metrics: (1) a waveform similarity metric that uses a neural network to obtain spatially informed, nonlinear waveform representations, and (2) a cross-correlogram significance metric based on the earth mover's distance between the observed and null cross-correlograms. To improve reproducibility and remove the need for manual tuning, we also develop an automatic parameter setting procedure for SLAy that accounts for dataset-specific characteristics. On simulated oversplitting across a diverse set of animal models, brain regions, and probe geometries, SLAy substantially outperforms an existing merging algorithm, achieving high recall without merging extraneous units. On the original datasets without simulated oversplitting, SLAy recovers ~95% of merges found by human curators and human curators agree with ~90% of merges suggested by SLAy. SLAy leverages multithreading for computational efficiency, running in less than 10 minutes for all recordings we tested. SLAy is also compatible with SpikeInterface, making it a practical and flexible solution for large-scale ephys data analysis across acquisition systems and spike sorters.

KEYWORDS: *Electrophysiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

MIMIC-MJX: Neuromechanical emulation of animal behavior

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To reduce the complexity inherent in how the brain controls behavior, we often parse underlying neural circuits into modules studied in isolation. Yet such reductionist approaches have failed to provide a view of complex sensorimotor control that can explain the diverse set of phenomena involved in behavior, like the co-adaptation of perception and behavior, motor learning dynamics through environmental interaction, and the influence of internal states on motor control and exploration. Artificial Neural Networks (ANNs) trained to control biomechanically realistic animal models in physics-constrained environments provide a promising alternative, enabling the study of embodied neural control in transparent and configurable systems. However, the computational cost and engineering effort of training such controllers has limited adoption. To address this, we developed MIMIC-MJX, an open-source Python pipeline for fast, GPU-accelerated training of neural controllers that imitate real animal behavior. It uses deep reinforcement learning (DRL) to link 3D markerless motion capture with controllers modeling the control strategies driving movement. On a single prosumer GPU, MIMIC-MJX trains a controller in 3 hours—a 7x speedup over CPU-based pipelines.

We train controllers across body models spanning *C. elegans*, fruit flies, stick insects, and rats, showing the framework scales readily to new species and datasets. Analyzing a trained controller's internal representations, we find it learns a low-dimensional encoding of behavioral features—PCA of the latent intention space recovers a one-dimensional speed axis (PC1) and an orthogonal gait limit-cycle in the PC2/PC3 plane whose frequency and amplitude scale with locomotor speed—yielding an interpretable description of the underlying control strategy. Finally, we use the trained network as a low-level controller in ethologically relevant tasks, producing naturalistic solutions not found with standard task-trained policies.

In short, MIMIC-MJX empowers scientists to move beyond isolated neural models and tackle the challenge of embodied intelligence—linking neural control, physical constraints, and behavior in a single framework.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Addgene: Powering scientific sharing in support of the BRAIN Initiative

PRESENTER: **M. Rego**
Addgene

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Addgene is a 501(c)(3) nonprofit with a mission to accelerate scientific progress through open sharing of research materials. With a catalog of over 170,000 plasmids, 1,000 viral vectors, and 250 recombinant antibodies, Addgene serves as a trusted global repository connecting researchers with the tools they need to advance discovery.

Addgene has a longstanding partnership with the NIH BRAIN Initiative and is proud to serve as a designated reagent resource for the Armamentarium for Precision Brain Cell Access. The Armamentarium aims to develop and disseminate a collection of molecular genetic reagents, including viral vectors, for cell type-specific access across species, from rodents to non-human primates. Addgene distributes these tools broadly to support neuroscientists studying the circuit basis of behavior and brain function.

On the antibody front, Addgene is engaged in two complementary NIH-funded efforts, both focused on expanding access to antibodies validated for advanced tissue clearing and imaging techniques. In collaboration with UC Davis and Weill Cornell, we are working to identify and validate existing antibodies compatible with these methods, and to develop new antibodies purpose-built for them. Through our partnership with the UM1 Center for Multi-scale Multi-Omic Human and Non-human Primate Brain Cell Atlases, Addgene will distribute antibodies validated for advanced staining across human, mouse, and non-human primate brain tissue. Together, these projects are building a foundation of rigorously characterized reagents for next-generation neuroanatomy and connectomics.

Addgene is also co-leading the BICAN Antibody Task Force, a community-driven initiative to catalog open-access antibodies alongside validation data and distribution sources, with a particular emphasis on tools suitable for tissue clearing and broader neuroscience applications. Collectively, these efforts reflect Addgene's commitment to ensuring that high-quality, well-characterized reagents are reproducible, openly shared, and widely available across the neuroscience community.

KEYWORDS: *Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health; Molecular/Cellular Neuroscience; Neural Networks (topology, etc.); Connectome*

Reducing event jitter inherent in wireless (Wi-Fi) signaling using hardware-level IR event triggers in the Open Ephys and Intan RHD compatible wireless recording system from DSPW

PRESENTER: **R. Paugh**
DSP Wireless, Inc. - DSPW

AUTHORS: R. Paugh

Untethered electrophysiology is essential for studying natural behavior; however, high-bandwidth wireless (Wi-Fi) protocols introduce variable packet-delivery delays. This unpredictable network jitter corrupts the precise sub-millisecond temporal alignment required between behavioral events and neural activity.

To significantly reduce synchronization jitter, the DSPW team developed an end-to-end hardware architecture that routes timing signals independently of the wireless network layers. The system features a custom infrared (IR) transmitter that accepts standard hardware TTL inputs or generates event sequences directly via UART-over-USB software commands. A headstage-mounted IR receiver detects these optical triggers, and a passive resistor divider scales the output voltage for an Intan RHD2132 amplifier/ADC. Depending on user preference, the signal can be routed either to an auxiliary input or, using higher attenuation, to a standard electrode channel to bypass the 1/4 sub-sampling rate limitation of the auxiliary input.

By sampling the IR event trigger and neural data simultaneously using the same hardware clock, the temporal marker is embedded into the data stream before wireless transmission for real-time visualization and recording using the DSPW RCB Wi-Fi Plugin for the BRAIN Initiative-funded Open Ephys GUI. This approach decouples event timing from unpredictable network latencies, limiting the jitter to the output pulse width tolerance of the optical receiver (approx. $\pm 100 \mu\text{s}$) plus the chosen hardware sampling resolution. This provides a complete, high-accuracy system for wireless neurophysiology event marking.

KEYWORDS: *Behavioral Sciences/Psychology; Dissemination & Open Science/Education; Electrophysiology; Software (analysis, etc.) and Engineering; Monitor Neural Activity*

Advancing cross-species single-neuron circuit mapping with next-generation MAPseq and BARseq

PRESENTER: **H. Zhan**

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The MAPseq/BARseq Core Facility at Cold Spring Harbor Laboratory provides cutting-edge, high-throughput technologies for mapping neuronal connectivity at single-neuron resolution across diverse experimental systems. MAPseq (Multiplexed Analysis of Projections by Sequencing) transforms neuroanatomical tracing into a massively parallel sequencing-based approach, enabling quantitative measurement of long-range axonal projections from thousands of individual neurons within a single brain. BARseq (Barcoded Anatomy Resolved by Sequencing) extends this strategy by sequencing neuronal barcodes in situ within intact tissue, thereby preserving spatial information and enabling the joint analysis of neuronal connectivity, spatial organization, and molecular identity.

Traditional neuroanatomical methods for resolving circuit architecture at single-cell resolution are often labor-intensive, costly, and limited in throughput. MAPseq and BARseq address these limitations by combining high-diversity RNA barcoding with next-generation or in situ sequencing, substantially increasing scalability while reducing experimental complexity. These technologies have been successfully applied across multiple species, including laboratory mice and rats, singing mice, macaques, and marmosets, demonstrating their robustness and adaptability across different brain sizes and experimental contexts.

The Core Facility continues to expand the accessibility and capabilities of these technologies. It is disseminating PointSeq, a cell-type-specific viral strategy for MAPseq that enables projection mapping of genetically or molecularly defined neuronal populations. The Core is also implementing MAPseq2, an improved MAPseq workflow designed to increase neuronal barcode recovery while improving experimental efficiency and cost-effectiveness. In addition, the Core provides BARseq services on 60 μm sections prepared from fixed tissue. BARseq performed on thick fixed sections achieves higher throughput while lowering technical barriers for user and enabling spatially resolved barcode identification to be integrated with brain-wide projection measurements.

The MAPseq/BARseq Core Facility provides end-to-end support to the neuroscience community, including viral library preparation and distribution, experimental design consultation, sample processing, sequencing, and data processing.

KEYWORDS: *Circuit Diagrams; Connectome; Dissemination & Open Science/Education; Molecular/Cellular Neuroscience; Neural Networks (topology, etc.); Integrated Approaches*

Behavioral correlates for a cartesian coordinate system for the human forebrain

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American University of Sovereign Nations

AUTHORS: J. LaMuth

The first Cartesian Coordinate System for the Human Forebrain enjoys similar advantages to the dramatic influence that the Periodic Table of the Elements has enjoyed with respect to Chemistry and Physics. The radical expansion of the neocortex is observed to occur in a discrete pattern suggestively termed cortical growth rings. The general pattern of cortical evolution specifies that older structures are periodically modified to create newer functional areas: the precursor circuitry also preserved, all persisting side by side. The neocortex represents the most logical initiation point for such an interpretation, celebrated as the crowning culmination of human forebrain evolution. In terms of the human neocortex, the two fundamental variables defining forebrain evolution are the parameters of phylogenetic age and input specificity. The precise number of age and input parameter levels has accurately been determined for both basic forebrain parameters. Sanides (1972) proposed that the human neocortex evolved as a sequence of five concentric growth rings comprising a medio-lateral hemisphere gradient. Furthermore, the interoceptive, exteroceptive and proprioceptive input categories each project to their own four-part complex of cortical bands defining an antero-posterior hemisphere gradient. When the para-coronal variable of phylogenetic age is plotted as the ordinate and the para-sagittal parameter of input specificity charted as the abscissa in a Cartesian coordinate system, the resulting dual parameter grid is spatially oriented in a pattern analogous to the standard cortical representation (depicted below as folded flat). Here each of the cortical areas described by Brodmann and von Economo, as well as the affiliated thalamic (relay) nuclei correspond to schematically unique age/input parameter coordinates. Through the aid of the Cartesian Coordinate system for the Human Forebrain employing the exteroceptive, interoceptive, and proprioceptive input categories, an intimately detailed pattern of correspondence can be established in terms of the instinctual principles underlying behavioral psychology.

KEYWORDS: *Behavioral Sciences/Psychology; Circuit Diagrams; Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Theory & Data Analysis Tools*

Therapeutic evaluation of eugenol on learning and memory impairments in a Wistar rat model of vincristine-induced peripheral neuropathy

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Vincristine is a frontline chemotherapeutic whose clinical value is strictly limited by neurotoxicity, manifesting as both peripheral sensorimotor neuropathy and cognitive impairment, colloquially termed “chemobrain.” This study evaluated the therapeutic efficacy of eugenol, a blood-brain barrier-permeable phytochemical, against spatial learning and recognition memory deficits in a Wistar rat model of vincristine-induced neuropathy.

Twenty-five adult male Wistar rats (150-200 g) were randomized into five groups (n=5 per group): Group I (normal control); Group II (Vincristine control, 100 µg/kg i.p. daily for 14 days); and Groups III, IV, and V (vincristine co-administered with oral eugenol at 2.5 mg/kg, 5 mg/kg, and 10 mg/kg daily, respectively). Cognitive function was thoroughly evaluated on Days 0, 7, and 14 utilizing the Elevated Plus Maze (EPM) and the Novel Object Recognition Test (NORT) models.

In the EPM, chronic vincristine exposure induced marked spatial memory deficits, characterised by increased transfer latency on retention trials. Co-administration of eugenol (particularly at 2.5 mg/kg and 10 mg/kg) significantly ($p < 0.05$) decreased transfer latency over the weeks, successfully restoring spatial memory retrieval. In contrast, NORT results showed that chronic vincristine administration severely impaired visual-spatial recognition, causing a profound drop in novel object preference. Eugenol co-treatment yielded no statistically significant differences in preference scores across the groups compared to the control group throughout the study ($p > 0.05$).

In conclusion, oral eugenol exerts a significant therapeutic effect on hippocampal-dependent spatial memory retrieval in Wistar rats with vincristine-induced neuropathy. However, it offers minute to no protective effect on long-term cortical-dependent working memory at these doses. This selective neuroprotective profile suggests that eugenol may target hippocampal-dependent spatial networks rather than wider cortical recognition pathways under chemotherapy-induced stress.

KEYWORDS: *Behavioral Sciences/Psychology; Human Neuroscience, Clinical Science, or Public Health; Interventional Tools*

Seasonal and gestational stage variations associated differences in aflatoxin exposure in pregnant women in Yaoundé, Cameroon

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University of Yaounde

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Aflatoxins are naturally occurring mycotoxins produced by *Aspergillus* species that commonly contaminate agricultural commodities, and is a public health concern in Cameroon, where existing studies focused healthy relatively less vulnerable adult populations, than the most susceptible groups such as pregnant women.

This study evaluated the seasonal and gestational differences in aflatoxin exposure among pregnant women and the associated risk factors.

A survey amongst pregnant women in Yaounde was carried out using structured questionnaires. Blood and urine samples were collected, and analyzed for presence of AFB1 and AFM1, respectively, using ELISA kits.

Most participants were aged 20-29 years (66%), single (51%) with university-level education (67%). Dietary habits included frequent consumption of leafy vegetables and cereal- or nut-based foods, with 54% noticing mold on their food. Most women were in their second trimester (60%) and reported common pregnancy issues like preterm birth (27%), and low birth weight (8%). Despite 95% attending antenatal visits and 96% lacked knowledge of food safety practices to prevent mold contamination. The mean serum AFB1 level was 75.26 µg/kg (range 6.98-327.58), with trimester-specific means of 68.70 µg/kg in the first, 78.16 µg/kg in the second, and 61.27 µg/kg in the third trimester. Urinary AFM1 averaged 0.82 µg/kg (range 0.32-1.81), increasing slightly through pregnancy stages: 0.83 µg/kg (first), 0.80 µg/kg (second), and 0.86 µg/kg (third trimester).

For the first time in Cameroon, aflatoxin exposure patterns and differences across gestational stages and seasonal changes amongst pregnant women in Yaoundé is revealed. All studied pregnant women were exposed to aflatoxins in their blood and urine. The mean AFB1 level in blood samples from the studied pregnant women were found to fluctuate according to gestational stages and the mean AFM1 level in urine samples was increasing across the gestational stages.

KEYWORDS: *Behavioral Sciences/Psychology; Human Neuroscience, Clinical Science, or Public Health; Molecular/Cellular Neuroscience; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Genetics/Genomics*

Machine learning-based evaluation of tremor severity and treatment response using wearables following focused ultrasound surgery

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Focused ultrasound (FUS) is a promising tool for the surgical treatment of essential tremor (ET) and Parkinson's disease (PD). Currently, assessing and diagnosing tremor disorders rely on qualitative assessments, limiting reliability and accessibility. Advances in wearable Inertial Monitoring Units (IMUs) and machine learning models present a means to address this gap. Here we demonstrate a validated machine learning based analysis designed for utilizing wearable IMU data to evaluate tremor severity and treatment efficacy in patients with tremor disorders following FUS.

Seventeen patients (15 ET, 2 PD) received MRI guided FUS thalamotomies. Bilateral upper extremities were assessed at baseline and at 2- and 6-month follow-up visits utilizing wrist-worn IMUs (APDM Wearable Technologies, Tigard, OR). Patient reported tremor severity was assessed using the 7-point Clinical Global Impressions rating scale. Tremor severity was quantified through power spectral analysis using Fourier transformation and principal component analysis, then analyzed using a probabilistic machine learning framework, Bayesian hierarchical regression, with leave-one-out cross-validation.

Fifteen patients were male (88%). Mean age was 76.2 years (± 6.3). FUS treatment resulted in significant reductions in tremor power at both 2 months ($\beta = -2.19$; 94% HDI [-2.73, -1.58]) and 6 months ($\beta = -2.15$; 94% HDI [-2.67, -1.61]), corresponding to an average of an 88% decrease in power on the treated side (94% HDI [81%, 94%]) relative to baseline at both follow up points. Secondary ordinal regression analysis revealed that greater tremor power was associated with more severe patient reported tremor (OR = 3.06; 94% HDI [1.63, 6.3]).

FUS treatment produced durable, objectively quantifiable reductions in tremor power persisting through 6-month follow-up. Wearable-derived metrics converge with patient-reported severity, validating their utility as objective complements to clinical assessment. Future studies could implement a similar framework for remote monitoring or estimating treatment response in-clinic.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Theory & Data Analysis Tools; Interventional Tools*

Spectral decompositions of neural voltage recordings are susceptible to model misspecifications that cause meaningful estimation error

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The power spectra of neural voltage recordings vary systematically across brain states and contain both narrowband rhythmic and broadband components. A large class of algorithms seeks to parametrize these spectra by separating rhythms from broadband structure, enabling many robust empirical findings. Here we show that two common assumptions underlying popular spectral decomposition methods are incompatible with standard physical and statistical properties of neural recordings. First, field potentials arise from additive linear superposition of biophysical processes, yet several methods implicitly impose multiplicative structure. Second, power estimates are Gamma distributed, with variance proportional to squared power, yet many methods assume Gaussian, homoscedastic errors across frequencies. Using simulations with known ground truth, we demonstrate how these misspecifications bias estimates of rhythm amplitude and broadband height and slope, even under well-behaved conditions. We introduce a corrected decomposition framework, released as the open-source package *SL_specdecomp*. Relative to the most widely used method, *specparam*, our approach recovers rhythms and broadband parameters accurately, while *specparam* decompositions are biased and can confound rhythmic peaks with broadband slope. We then apply these methods to monkey electrocorticography during propofol anesthesia. *SL_specdecomp* estimates a substantially steeper, more negative, 40 to 60 Hz broadband slope during anesthesia than during wakefulness, whereas *specparam* shows a smaller state difference. We show using simulation that the differences in the two decompositions can arise directly from *specparam* model misspecification. We also introduce a formal method based on cross-validated log likelihood to compare candidate power spectral decompositions and show that it favors *SL_specdecomp*. These results suggest that misspecified decompositions can attenuate or distort broadband slope changes in the presence of strong rhythms, and motivate the use of *SL_specdecomp* as a more reliable decomposition tool.

KEYWORDS: *Behavioral Sciences/Psychology; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Monitor Neural Activity; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Bibliometric analysis on the top 100 most cited literature on SMA and associated long-term treatment outcomes: Treatments for improving motor-function in spinal muscular atrophy patients

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Spinal muscular atrophy (SMA) is an inherited neurodegenerative disease that affects motor neurons, leading to muscle weakness and paralysis. It is caused by mutations in the SMN1 gene, which is crucial for motor neuron function. Prevalence of SMA has been reported to be 1 per 10,000 live births, and severity of the condition varies. The FDA has approved Spinraza, Zolgensma, and Evrysdi as SMA treatments, but research gaps still exist. The research requires early biomarkers for better diagnosis timing and standardized long-term outcome measures for treated patients and more data about therapy effectiveness across SMA types. The effects of gene therapy on patients' long-term health remain unknown.

To explore the long-term effects of various treatments aimed at improving motor function in Spinal Muscular Atrophy patients. Long-term is defined as sustained improvements in motor abilities observed over a period of 12 months or more following intervention.

Weekly meetings were held to divide tasks among team members, ensuring a structured approach to data collection and analysis. Through our analysis of spinal muscular atrophy (SMA), we have deepened our understanding of its long-term effects on patients and identified key treatments that show promise in improving motor function. By utilizing bibliometric analysis and reviewing highly cited literature, we highlighted the most effective therapies, influential research institutions, and critical gaps in current studies. While advancements in treatment, such as gene therapy and targeted drug interventions, have improved patient outcomes, further research is needed to address accessibility, long-term efficacy, and individualized treatment approaches.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Neural Networks (topology, etc.); Theory & Data Analysis Tools; Informatics, Statistics, or Applied Mathematics*

Cortical microstructural variation of the default mode network during the transition into a caregiver role

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Caregiving in late adulthood is a significant life stressor, and the resulting burden may negatively impact brain health and cognition. Prior work has linked caregiver burden to brain macrostructural changes, most notably reductions in gray matter volume (GMV). However, stress-related alterations may also manifest in cortical microstructure, such as intracortical myelination (ICM), which supports efficient neural processing and may reveal neural signatures of stress not captured by volumetric measures. Whether and how caregiver stress and known protective factors, such as social support, shape ICM remains unknown. Here, we examined associations between ICM and psychosocial experiences following the transition to a caregiver role and whether ICM carries a stress-related neural signature distinct from GMV. Participants were drawn from the Human Connectome Project Aging Adult Brain Connectome study. We identified individuals who reported transitioning into a caregiver role in the past year ($N = 144$). Given evidence of stress-related deterioration within the default mode network (DMN) across diverse populations, we extracted ICM values from the T1w/T2w ratio within four DMN cortical subdivisions: medial prefrontal (mPFC), posterior cingulate (PCC), inferior parietal lobule (IPL), and medial temporal lobe (MTL). We used hierarchical linear regression models to evaluate associations between ICM and levels of social support, social satisfaction, affective appraisal, and perceived stress experienced by caregivers. Models sequentially adjusted for demographic and lifestyle covariates (e.g., body mass index, sleep quality). Lastly, analyses were repeated for DMN GMV to assess whether ICM carried distinct stress-related signals. Lower social satisfaction was significantly associated with higher ICM in the IPL ($\beta = -0.21$, $p = 0.04$), with a comparable association in the PCC approaching significance ($\beta = -0.19$, $p = 0.06$). No other psychosocial measures were consistently associated with DMN ICM. GMV results showed limited overlap, with perceived stress alone showing an association with MTL GMV ($\beta = -0.25$, $p < 0.01$). Overall, social satisfaction, but not other psychosocial factors, was associated with regional variation in DMN cortical microstructure. Our findings suggest that, within caregivers, cortical microstructure may capture neural variation linked to subjective social experience not readily reflected in traditional structural brain indices, such as GMV.

KEYWORDS: *Behavioral Sciences/Psychology*

Accelerating clinical translation of next-generation neurotechnologies through NeuroNEXT

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The Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) provides a nationally coordinated clinical research infrastructure to accelerate the translation of innovative interventions from discovery to clinical application and to support the validation of biomarkers. Funded by the National Institute of Neurological Disorders and Stroke (NINDS), NeuroNEXT was established to improve the efficiency of neuroscience clinical trials, expand the capacity to evaluate promising neurotherapeutics, and rapidly respond to emerging opportunities in neurological research across both adult and pediatric populations.

A key strength of NeuroNEXT is its integrated national framework, which includes a network of clinical trial sites, a Clinical Coordinating Center, and a Data Coordinating Center. This infrastructure enables rapid and rigorous protocol development, centralized data management, and efficient participant recruitment across geographically distributed populations. Through standardized operational procedures and experienced trial leadership, NeuroNEXT supports the execution of highly efficient, high-quality, multicenter clinical trials.

NeuroNEXT utilizes a two-stage application process under Other Transaction Authority (OTA), offering greater flexibility than traditional grant mechanisms. The OTA framework supports rolling submissions, milestone-driven project management, iterative feedback during the submission process, and streamlined review. These features facilitate collaboration among academic investigators, industry partners, startups, and nontraditional research participants while accelerating the evaluation of innovative interventions. With extensive experience conducting complex multicenter studies, NeuroNEXT provides an ideal environment for the clinical validation of emerging neurotechnologies. By leveraging its established infrastructure and collaborative network, NeuroNEXT helps advance promising technologies toward clinical implementation, enabling more efficient generation of evidence related to safety, feasibility, and effectiveness, and ultimately accelerating access to innovative solutions for patients with neurological disorders.

KEYWORDS: *Dissemination & Open Science/Education; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Interventional Tools; Neural Recording & Modulation*

Spatial transcriptomic architecture of the human melanocortin system: Population-scale mapping of neuro-metabolic core circuits and trophic boundaries

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While preclinical models document the architecture of the melanocortin feeding circuit in the hypothalamus, there are gaps in human-specific spatial data mapping these critical neural populations. Using spatial transcriptomics data, we aimed to define the exact molecular borders of five essential neuro-metabolic biomarkers associated with the feeding circuit and to segregate metabolic surveillance hubs from adjacent structural networks.

High-resolution in silico transcriptomic analyses were conducted using the Allen Human Brain Atlas. For normalized microarray expression profiles of N=6 neurotypical adult human donors, genomic probe IDs were mapped to isolate critical neuro-metabolic regulators: leptin receptor (LEPR), brain-derived neurotrophic factor (BDNF), pro-opiomelanocortin (POMC), agouti-related peptide (AGRP), and neuropeptide Y (NPY). We selected for core hypothalamic microstructures—the arcuate, ventromedial, and paraventricular nuclei. Expression values were aggregated to compute population-scale mean expression levels with R.

Data across the cohort revealed consistent and reproducible anatomical borders among metabolic signaling networks. The arcuate nucleus (ARC) of the hypothalamus emerged as the central sensory hub with a dense concentration of primary neuropeptides (mean expression level range, NPY: 12.2-13.5, AGRP: 8.12-8.94, and POMC: 8.33-8.35, across both hemispheres). LEPR expression was dense and localized within these same ARC coordinates (5.84-5.43). The inverse was seen for BDNF, which exhibited localized expression peaks within the adjacent ventromedial hypothalamic nucleus (VMH; left mean: 5.60) and paraventricular nucleus (PVN; left mean: 4.30) while dropping off significantly within the LEPR-dense sensory core.

The human hypothalamus is organized around distinct transcriptomic boundaries that compartmentalize metabolic sensing. By establishing the precise co-localization profiles of AGRP, POMC, NPY, and LEPR within the arcuate core, this study identifies the spatial coordinates of the primary human homeostatic feeding circuit. Furthermore, the sharp anatomical segregation of BDNF within adjacent nuclei maps a neurotrophic boundary that delineates sensory hubs from downstream effector networks. Precision mapping of this healthy baseline provides a structural paradigm useful for evaluating circuit vulnerability and signaling failure in central metabolic pathology.

KEYWORDS: *Computational Biology/Modelling; Genetics/Genomics; Human Neuroscience, Clinical Science, or Public Health; Molecular/Cellular Neuroscience; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering*

The influence of REM behavior disorder on motor, cognitive, and vascular-autonomic outcomes in people with Parkinson's disease engaged in chronic aerobic exercise?

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PwPD with RBD (PD-RBD) have a distinct neuropathological burden, faster disease progression, and worse autonomic function and cognition than PD without RBD. We theorize that these features of PD-RBD have implications for disease management/treatment of this subgroup. AE is a powerful therapy for PD that can slow disease progression and improve motor and cognitive function. Given the impairment of cardiovascular control and autonomic centers in PD-RBD, our aims are 1) determine whether PD-pRBD experience less improvement in motor signs, endurance, and cognition than PD-no-pRBD after chronic AE and 2) determine whether PD-pRBD has higher arterial stiffness than no-pRBD.

We leverage a cohort (pwPD = 51) engaging in 83 hours of AE (partnered dance or walking) over 12-16 months. Participants are stratified via RBD questionnaires. Participants complete 4 visits over the trial period to assess motor symptoms/function, arterial stiffness (pulse wave velocity (PWV)), endurance, cognition, and autonomic questionnaires.

1) Due to greater autonomic dysfunction and neuropathological burden in pRBD, exercise recovery will be impaired, resulting in attenuated AE-induced motor and cognitive gains compared to PD-no-pRBD. 2) Given that higher PWV is associated with autonomic failure in PD, we hypothesize that the chronic autonomic dysfunction associated with PD-pRBD will correlate with higher PWV.

Findings will inform whether different exercise rehabilitation strategies (e.g., changes in dosage and recovery time) may be warranted for PD-pRBD.

2) Given that higher PWV is associated with autonomic failure in PD, we hypothesize that the chronic autonomic dysfunction associated with PD-pRBD will correlate with higher PWV.

Findings will inform whether different exercise rehabilitation strategies (e.g., changes in dosage and recovery time) may be warranted for PD-pRBD.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health*

Mapping feature-specific cortical response topographies across controlled and real-world environments using whole-head HD-fNIRS

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Recent advances in wearable high-density functional near-infrared spectroscopy (HD-fNIRS) have enabled the investigation of cortical activity outside traditional laboratory environments. In this study, we investigated whether cortical response patterns associated with sensory features observed in controlled laboratory settings generalize to real-world environments by comparing feature-specific cortical responses during indoor movie viewing and outdoor walking using whole-head HD-fNIRS.

Eighteen healthy adults watched a 34-minute feature film (indoor condition), and 20 participants completed a walking task in a complex real-world environment (outdoor condition). Whole-head HD-fNIRS data were collected in both conditions, and mobile eye-tracking was additionally performed during outdoor walking. fNIRS measurements were acquired using a high-density system consisting of 56 sources, 144 detectors, and 561 measurement channels. For the indoor condition, audiovisual features were extracted directly from the movie. For the outdoor condition, participants' fields of view were captured using a Pupil Labs Neon eye tracker, and the scene-camera video was used for feature extraction from each participant's visual experience during real-world walking. Time-varying features, including sound intensity, luminance, and face intensity, were extracted from both indoor and outdoor recordings and incorporated as regressors in a general linear model (GLM). Analyses were performed in image space using the Python-based Cedalion toolbox. Group-level statistical t-maps were generated for each feature and condition to characterize feature-specific cortical response topographies.

Preliminary findings revealed distinct cortical response patterns across features. Luminance responses were primarily localized to occipital visual regions. Sound intensity elicited broader activation across temporal and parietal cortices. The face feature produced predominantly posterior cortical responses. To assess cross-condition consistency, spatial correlations between indoor and outdoor group-level t-maps were computed for each feature and evaluated using permutation testing. Feature-specific cortical responses showed significant spatial correspondence across indoor and outdoor conditions, with the strongest correspondence observed for the auditory feature, suggesting that certain feature-specific cortical response patterns may be preserved across laboratory-based and real-world naturalistic paradigms.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Neuroimaging (invasive, non-invasive imaging)/Radiology; Monitor Neural Activity*

Subthalamic nucleus stimulation elicits phase-locked pallidal neuronal firing aligned to evoked resonant neural activity

PRESENTER: **E. Dunbar**

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Deep brain stimulation (DBS), a valuable therapy for Parkinson's disease, elicits an oscillatory field potential termed evoked resonant neural activity (ERNA) during local stimulation in either the subthalamic nucleus (STN) or the globus pallidus interna (GPi). These two regions are the primary drivers of the indirect pathway, where the STN sends excitatory glutamatergic projections to the GPi to modulate movement. While local ERNA in the STN and GPi is well known, it is unclear if stimulation of STN would elicit ERNA in the pallidum. The mechanistic basis of this oscillatory field potential is unknown as well.

Six patients with PD underwent awake DBS surgery with unilateral implants in both the STN and pallidum. We delivered single and paired electrical stimulus pulses from the subthalamic nucleus macroelectrode and recorded spikes and microscopic local field potentials in the ipsilateral pallidum. Pulses were biphasic with 3 mA amplitude, 80-40-80 μ s phases, interstimulus intervals ranging from 0.45 to 7.7 ms, and ≥ 50 ms between conditions. We parsed spikes into clusters for manual unit consolidation and generated stimulus-locked spike patterns and histograms for overlay onto the ERNA waveform from the subthalamic pallidal field potentials.

STN stimulation yields ERNA in both the internal and external segment of the pallidum. Spikes align with ERNA oscillations in both pallidal segments, and discharge probability changes based on paired pulse interval.

Single and paired pulses delivered to the subthalamic nucleus elicited time-locked action potentials and ERNA in the ipsilateral pallidum. These findings indicate that ERNA is a circuit-level phenomenon within the indirect pathway and suggest that its mechanistic basis at least partially arises from neuronal spike timing. Collectively, our results suggest that therapeutic deep brain stimulation synchronizes neural activity within basal ganglia circuits.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation*

Evoked potential magnitude scales with deep-brain stimulation amplitude in the subthalamic nucleus in Parkinson's disease

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Deep brain stimulation (DBS) is an established treatment for the motor symptoms of Parkinson's disease (PD). Subthalamic nucleus (STN) elicits multiple local neural responses, including a tapering sinusoidal oscillation called evoked resonant neural activity (ERNA). STN DBS contacts that display larger ERNA magnitude are associated with effective therapy, suggesting it could serve as a clinically relevant biomarker for circuit engagement. Here, we sought to better characterize how STN DBS amplitude alters ERNA across the therapeutic window—a clinically defined amplitude range that defines sub-therapeutic, therapeutic, and adverse DBS parameters for a given stimulation site.

Five patients with PD underwent awake unilateral STN DBS surgery with an 8-contact directional lead. During lead implant, we delivered monopolar stimuli below, within, and above the therapeutic window (60 μ sec pulse width, 80 stimuli per condition). The therapeutic window was established intraoperatively. We recorded responses from the unused adjacent contacts, binned the signals into 27 ms windows from -2 to +25 ms after stimulus onset, and constructed bipolar montages between horizontal adjacent directional contacts. We then compared ERNA magnitude as a function of DBS amplitude relative to the therapeutic window.

ERNA magnitude increased non-linearly near the therapeutic window floor and began to plateau around the therapeutic window ceiling. After testing different models, quadratic or logarithmic models best fit the magnitude of the response to stimulation amplitude in all participants.

In five patients with PD, ERNA magnitude scaled non-linearly with DBS amplitude, with the largest increases at the therapeutic window floor and an asymptote near the therapeutic window ceiling. These findings have potential implications for the relationship between ERNA magnitude and clinical outcomes and suggest that ERNA could inform tailored neuromodulation strategies for both open- and closed-loop DBS for PD and other movement disorders.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation*

Deep brain stimulation local evoked neural potentials differ among globus pallidus interna, globus pallidus externa, and subthalamic nucleus

PRESENTER: **S. Brinkerhoff**

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AUTHORS: S. Brinkerhoff, A. Nakhmani, A. Mysore, H. Cowart, M. Holland, N. Bentley, J. Thum, H. Walker

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) is an established treatment for Parkinson disease (PD). DBS of these structures evokes local neural responses, including ERNA a stimulus-locked oscillatory field potential that exhibits short-term facilitation. Although the globus pallidus externa (GPe) is not a canonical stimulation target, whether GPe DBS elicits ERNA is unknown.

Eight patients with PD underwent awake unilateral dual-target DBS surgery, receiving an 8-contact directional lead in the STN followed by another lead in the GPi. During implantation, the surgeon advanced the leads at 2-mm intervals en route to each target, during which we delivered monopolar stimulation from the ventral directional contacts. Along the pallidal trajectory, this anatomic span included stimulation and recording within the GPe. Biphasic stimuli were delivered at 3 mA and 60 μ sec pulse width across single and paired pulses with interstimulus ranging from 0.8 to 15.3 ms. Recordings were rereferenced to a bipolar montage, detrended, filtered using Savitzky-Golay filters, and analyzed using the Coastline Burst Index (CBI)—accumulated voltage—from 3 to 20 ms after the test pulse. We contrasted the short-term facilitation of response latency and magnitude (CBI) across the three regions (STN, GPi, GPe) by paired pulse interval.

Stimulation within the STN and GPi elicited ERNA with characteristic short-term facilitation. In contrast, GPe stimulation evoked a morphologically distinct field potential response in all 8 patients that instead displayed paired-pulse depression.

In 8 patients with PD, paired pulse stimulation in the GPe elicited a local field potential response distinct from STN and GPi ERNA that displayed short-term depression rather than facilitation. These findings expand the map of stimulus-evoked physiology across the human basal ganglia and may help identify functionally distinct subregions during DBS targeting.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation*

Neural mechanisms of cognitive control in patients with Parkinson's disease and essential tremor

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Cognitive control involves processing sensory information from the environment and identifying relevant cues to govern actions. Motor control occurs in an anticipatory (proactive) or late-corrective (reactive) manner. Patients with Parkinson's disease (PD) often exhibit impaired cognitive control and altered scalp potentials compared to healthy controls. However, the spatiotemporal dynamics of these EEG signals remain debated. Here, we investigated the neural basis of cognitive control in patients with movement disorders using subdural cortical recordings during deep brain stimulation (DBS) surgery.

Twelve patients (five with PD and seven with essential tremor, ET) performed an AX-version of the continuous performance task (AX-CPT) during DBS surgery. The task evaluates cognitive control by presenting a conditioning cue followed by a probe event requiring context-dependent responses. In the proactive context, the patient must anticipate a response based on the conditioning cue. The reactive context requires the patient to override the cue conditioning and wait for the probe to execute a response. To observe neural interactions between brain areas associated with cognitive control, two six-contact electrocorticography (ECoG) strips were temporarily placed along the cortex during DBS surgery: one anteriorly over dorsolateral prefrontal cortex (DLPFC) and one posteriorly over primary motor cortex, ipsilateral to the DBS implant.

Four PD and two ET patients had higher error rates in the proactive context. Additionally, ECoG contacts in the left rostral DLPFC displayed sustained gamma amplitude (60-200 Hz) during proactive control (200 ms after cue onset until response) but transient peak activity during reactive control (for 250 ms before response). Moreover, the ET patients displayed stronger sustained low-frequency activity (2-8 Hz) in the proactive context in bilateral rostral DLPFC during the anticipatory response interval (100 ms after cue onset until response) compared to PD patients.

Rostral DLPFC shows differential activation in low frequencies and high-frequency broadband in proactive versus reactive control based on different movement disorders. Ongoing analyses are evaluating the spatiotemporal dynamics of these responses by recording site, brain hemisphere, and disease. Better understanding these dynamics could expand fundamental knowledge on cognitive control and guide future neuromodulation therapies.

KEYWORDS: *Behavioral Sciences/Psychology; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Monitor Neural Activity*

Functional network signatures identify cortical sites critical for speech and language

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Speech and language are complex processes involving multiple brain networks. Direct electrocortical stimulation (ECS) identifies cortical sites "critical" for these functions to guide resection and reduce post-operative deficits. Yet the network properties that distinguish cortical sites critical for speech and language from non-critical ones remain elusive. Our recent work using electrocorticography (ECoG) suggests that critical sites occupy distinct roles within functional networks. However, ECoG arrays capture only regional cortical coverage unlike functional magnetic resonance imaging (fMRI), which enables network analysis across the entire brain. We therefore hypothesized that critical sites exhibit distinct fMRI-derived functional network signatures. Eighteen participants with epilepsy or brain tumors performed five distinct language tasks. Network nodes comprised electrode sites within each participant's ECoG grid and parcels from the 1000-node Schaefer atlas; edges were correlations of fMRI activity between node pairs. Critical electrode sites were defined as language error (LE) or speech arrest (SA) sites. We compared six network metrics between critical and non-critical sites: local efficiency (Eloc), clustering coefficient (CC), strength, eigenvector centrality (EC), participation coefficient (PC) and gateway coefficient (GC). Next, we examined the metrics' anatomical distribution averaged across participants. Finally, we used all six metrics to train support vector machines and balanced random forests to predict criticality. Critical sites exhibited significantly lower local (CC, Eloc) and global connectivity (EC, strength) than non-critical sites. LE sites also had significantly higher inter-subnetwork connectivity (PC, GC) than SA and non-critical sites. Further, connector sites (high PC) were concentrated primarily in temporal cortices. Finally, these metrics predicted critical sites significantly above chance. Rather than serving as local or global hubs, critical sites are less connected overall than non-critical sites. Sites critical to higher language function also act as connectors across functional subnetworks. The concentration of connector sites in temporal regions highlights the temporal lobe's role in linking speech and language subnetworks. By characterizing network signatures of ECS criticality, we provide a framework for predicting speech and language-critical cortex and understanding the effects of ECS on language networks.

KEYWORDS: *Computational Biology/Modelling; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Informatics, Statistics, or Applied Mathematics*

Reduced neuronal m6A RNA modification enhances amyloidogenic metabolism of amyloid precursor protein by modulating secretases activities

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Aberrant N6-methyladenosine (m6A) RNA epitranscriptome is implicated in the pathogenesis of multiple neurodegenerative diseases, including Alzheimer's disease (AD). Our prior studies demonstrated reduced m6A modifications in AD neurons contributes to brain degenerative changes. In this study, we investigated whether reduced neuronal m6A modifications affect the metabolism of amyloid-beta (A β) in neuronal cell cultures. We found that methyltransferase-like proteins 3 (METTL3), the major m6A writer, inhibits endogenous beta-site APP cleaving enzyme 1 (BACE1) protein production and A β release in primary neuronal cultures. On the contrary, METTL3 knockdown (KD) mediated by shRNA-Mettl3 delivery resulted in dramatically increased A β peptide production in the supernatant of human APP-overexpressed primary neuronal cultures. In addition, METTL3 deficiency differentially regulates APP secretase expressions in neuronal cultures. We observed that METTL3 KD significantly increased gene expressions of Bace1 and Presenilin 1 (Psen1, the catalytic core of γ -secretase) which could lead to increased amyloidogenic processing of APP. Interestingly, METTL3 KD reduced gene expression of the α -secretase Adam17 (A Disintegrin and Metalloproteinase 17) that mediates APP non-amyloidogenic processing. Secretase activity measurements revealed that METTL3 deficiency led to increased BACE1 β -cleavage activity and impaired Adam17 α -cleavage activity in primary neurons. However, App gene expression, other measured APP secretases and the major A β degradation enzymes were not apparently affected by METTL3 deficiency in neuron cultures. Our methylated RNA immunoprecipitation m6A-seq and PCR analyses revealed that these targeted secretase transcripts were extensively modified by m6A methylation in mouse brains and human cells. Importantly, inhibition of m6A modification by universal m6A inhibitor induces Bace1 gene expression in primary neurons, and elevated m6A modification by the demethylase inhibitor has an opposite effect. The m6A reader IP PCR analysis revealed that Bace1 mRNA could be bound by YTHDF2 reader that mediates m6A-dependent mRNA degradation. Mechanistically, we observed that METTL3 KD caused Bace1 m6A hypomethylation and impaired its mRNA degradation, resulting in excessive mRNA accumulation. In summary, our data suggest a novel METTL3-m6A regulatory mechanism underlying enhanced amyloidogenic metabolism and amyloid accumulation in AD.

KEYWORDS: *Behavioral Sciences/Psychology; Human Neuroscience, Clinical Science, or Public Health; Molecular/Cellular Neuroscience; Synaptic Plasticity*

Effects of confined migration and physiological oxygen tension on nuclear mechanics in human neural stem cells using microfluidic devices

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Neural stem cells (NSCs) migrate and proliferate within mechanically constrained brain microenvironments where extracellular restriction and oxygen availability can influence nuclear architecture. Most in-vitro migration models are performed under atmospheric oxygen, which may not reflect physiological brain oxygen tension. We asked whether defined microfluidic confinement and brain-level oxygen tension interact to regulate NSC nuclear integrity, mechanics, and post-migratory cell state.

Human NSCs were studied in PDMS microfluidic devices containing defined micron-scale constrictions under Normoxia (21% O₂) or Brainoxia (5% O₂). Live-cell imaging tracked nuclear deformation and nuclear envelope rupture (NER) using NLS-GFP leakage, 53BP1-mCherry recruitment, cGAS puncta, and morphologic analysis of nuclear blebs and micronuclei. Recovered cells were assessed using neurosphere clonogenic assay and, where applicable, transcriptomic profiling. Nuclear mechanics were quantified by Brillouin microscopy, and Lamin A/C and H3K9me3 were evaluated by Western blot and confocal/STED imaging.

Increasing microfluidic confinement produced a Nuclear Mechano Impact phenotype marked by severe nuclear deformation, transient NER, DNA damage signaling, cGAS-positive cytosolic DNA, nuclear blebs, and micronuclei. High-confinement migration decreased total clonogenic recovery but enriched for surviving NSCs that generated larger neurospheres. p53-deficient NSCs showed enhanced post-confinement survival, indicating that impaired checkpoint control permits persistence of confinement-induced nuclear damage. BrainOxia lowered Brillouin shifts, consistent with reduced nuclear stiffness, and potentiated confinement-associated nuclear softening. This mechanical state coincided with reduced Lamin A/C nuclear envelope localization and attenuated H3K9me3 signal.

Defined microfluidic confinement is sufficient to couple nuclear mechanical stress with DNA damage and selection of clonogenic NSC states. Physiological oxygen tension further remodels nuclear mechanics and chromatin-associated architecture, indicating that oxygen level is a critical design variable for in vitro models of NSC mechanobiology.

KEYWORDS: *Developmental/Systems Biology; Molecular/Cellular Neuroscience*

Effect of alcohol consumption in acetylation-dependent tauopathy in mice

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Alzheimer's disease (AD), increasingly prevalent in aging populations, is exacerbated by alcohol consumption, which impairs brain metabolism and promotes AD risk. Alcohol may influence tau pathology via disruptions in protein acetylation, alterations in histone and tau acetylation are hallmark features of AD. While alcohol induces neurodegeneration in rodents, its role in tau-driven dementia remains unclear.

Using 9-month-old wild-type and humanized htau mice (an A β -independent tauopathy model), we combined metabolic tracing and molecular analyses to assess alcohol's impact on tau acetylation, phosphorylation, and aggregation. Acute alcohol (3 mg/kg body weight IP injection) induced time-dependent phosphorylation of tau at threonine 205 (pTauT205) and serine 396 (pTauS396, PHF-1)—key sites associated with neurofibrillary tangles formation—in the hippocampus of wild-type mice. These changes were associated with increased total tau (Tau5) accumulation. In htau mice, the same dose elevated cortical tau acetylation (acTauK174) and phosphorylation (pTauSer202/T205) and increased total tau within 4 hours. Dose-escalation studies (0-5 mg/kg) revealed that higher alcohol doses (≥ 3 mg/kg promoted high molecular weight tau phosphorylation and aggregation, correlating with elevated CBP expression, the enzyme responsible for tau acetylation. Mass spectrometry analysis of htau mice administered deuterated ethanol (EtOH-d6) showed significant [2H3]acetyl enrichment in cortical histones, but no detectable [2H3]acetyl incorporation into tau after short-term exposure. These results indicate that alcohol-induced epigenetic changes likely influence tau accumulation indirectly, rather than direct tau acetylation.

Acute alcohol exposure disrupts tau acetylation and phosphorylation, fostering tau aggregation and potential formation of neurofibrillary tangles involved in neurodegeneration. These findings implicate epigenetic and post-translational modifications as mechanisms by which alcohol accelerates tauopathy progression, highlighting potential targets for therapeutic intervention.

KEYWORDS: *Behavioral Sciences/Psychology; Chemistry; Molecular/Cellular Neuroscience*

Load-dependent reorganization of neural dynamics in human working memory

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Working memory (WM), a cornerstone of complex cognition, is disproportionately impaired in neuropsychiatric conditions. Although human intracranial recordings have begun to reveal the circuit computations underlying WM, the mechanisms by which these computations adapt to increased cognitive demand remain poorly understood. Here, we combine human single-unit and local field potential (LFP) recordings with biophysically constrained recurrent neural networks (RNNs), using the models to generate hypotheses for subsequent tests against biological data. We consider three candidate mechanisms of load adaptation: additive recruitment of load-specific neuron pools, nonlinear rearrangements in population geometry (e.g., through mixed selectivity), or load-dependent modulation of oscillatory dynamics. Each predicts distinct signatures in single-neuron activity and LFPs.

We analyzed the Daume et al. (2024) dataset, in which epilepsy patients with depth electrodes performed a Sternberg WM task requiring maintenance of 1 or 3 images before a recognition probe. From 1,426 single neurons recorded from the medial temporal lobe (MTL) and prefrontal cortex (PFC), alongside macroelectrode LFP, we identified maintenance-active neurons selective for load ($n=45$ for load-1; $n=49$ for load-3) and neurons tuned to stimulus category ($n=48$), in both regions. We also found elevated MTL theta (4-7 Hz) power during the maintenance period of high-load trials, a signature predicted by the oscillatory-modulation hypothesis.

We then trained biophysically-constrained RNNs obeying Dale's principle with sparse connectivity on both load-1 and load-3 Sternberg tasks. The networks reproduced principal features of the recordings, including load-selective maintenance activity, stimulus category tuning, and heterogeneous response profiles consistent with mixed selectivity. This establishes a model in which candidate mechanisms can be dissociated. The additive-recruitment hypothesis makes a specific prediction that neurons encoding stimulus information at load-1 should remain selective at load-3 while additional selective neurons are recruited. We will test this prediction in both the recordings and the model, where it distinguishes additive recruitment from geometric reorganization. By linking human intracranial recordings to biophysically-constrained models, this work establishes a framework for dissecting the circuit basis of human WM and, ultimately, its disruption in neuropsychiatric conditions.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Theory & Data Analysis Tools; Neural Networks (topology, etc.)*

pH-Responsive release of model ogremorphin drug from double-network hydrogels for localized GBM therapy

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Spring Valley High School

AUTHORS: G. Atim

Glioblastoma (GBM) remained one of the most aggressive challenges in neuro-oncology due to the blood-brain barrier and severe systemic neurotoxicity of current therapies. This study presented a novel, localized “smart” biomaterial technology designed to exploit the acidic tumor microenvironment (TME) for controlled therapeutic delivery. A polyacrylamide/alginate/calcium double-network hydrogel (DNH) was synthesized, and its swelling behavior, loading efficiency, and pH-dependent release dynamics were evaluated over a longitudinal 228-hour period using fluorescein as a structural mimic for the emerging small-molecule therapeutic, Ogremorphin.

The engineered DNH exhibited a structural swelling degree of 135.8% and an exceptionally high drug-loading efficiency of 87.4%. Spectroscopic analysis demonstrated that payload release kinetics were strongly modulated by environmental pH. Crucially, the hydrogel demonstrated acid-induced payload retention at pH 4 and 5, driven by protonation and a more compact polymer network. Conversely, alkaline conditions (pH 8) triggered network swelling and ionic crosslink disruption, which accelerated release. A one-way ANOVA confirmed that these pH-dependent variations in diffusion kinetics were highly statistically significant.

By minimizing the dangerous “burst release” phenomenon under TME-mimicking acidic conditions (pH 5-6), this DNH technology offered a promising model for safeguarding healthy brain tissue while sustaining localized, long-term therapeutic levels at the tumor site. This work established a foundation for bio-programmable implants capable of treating aggressive brain pathologies from the inside out, avoiding systemic toxicity and improving patient outcomes.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Chemistry*

Effects of confined migration on nuclear integrity and DNA damage in neural stem cells in vivo and ex vivo organotypic brain slices

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Neural stem cells (NSCs) migrate through dense brain microenvironments where narrow interstitial spaces impose mechanical strain on the nucleus. Although engineered platforms establish that spatial confinement can alter migrating cells, the extent to which the cyto-architecture of native brain tissue produces similar nuclear stress during NSC migration remains unclear.

NSCs expressing nuclear and cytoplasmic reporters were studied in cranial-window preparations and organotypic mouse brain slices. Intravital microscopy was used to visualize NSC movement within native brain tissue. In ex vivo living brain slices, labeled NSCs were injected and exposed to a growth factor gradient to promote directed migration through the brain slice. Longitudinal imaging tracked migration paths, nuclear shape changes, and reporter redistribution consistent with nuclear envelope rupture. Immuno-labeling evaluated nuclear morphology, DNA damage markers, and cytoskeletal organization in relation to restrictive tissue spaces.

In in vivo and ex vivo brain environments, migrating NSCs adopted elongated and compressed nuclear configurations while moving through interstitial paths. Cranial-window imaging captured dynamic nuclear deformation during migration in intact tissue, whereas brain slices enabled controlled induction and recording of directional migration. Nuclear deformation in tissue was accompanied by transient loss of nuclear compartmentalization and increased DNA damage marker burden in cells occupying restrictive spaces. Two-photon imaging of NLS-GFP-labeled nuclei captured dynamic nuclear deformation during migration. Complementary brain slice model with NLS-GFP-labeled nuclei revealed DNA damage-associated and micronuclei formation and in vitro confinement models further confirmed that mechanical restriction is sufficient to induce nuclear rupture and DNA damage.

In vivo and ex vivo brain-tissue models show that physiological interstitial confinement can deform and stress NSC nuclei and compromise nuclear integrity during migration. These platforms establish a tissue-relevant framework for studying how migrating neural cells maintain nuclear integrity while navigating mechanically restrictive brain microenvironments.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Molecular/Cellular Neuroscience; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics*

Correlation-based ECoG features for chronically stable speech iBCIs in an individual with ALS

PRESENTER: **K. Grajski**

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AUTHORS: K. Grajski

Chronically implanted brain-computer interfaces (iBCIs) for speech decoding face a key translational challenge: neural signal drift that requires recalibration. Many recent systems decode from electrocorticographic (ECoG) high-gamma log power (HGLP), which is exposed to amplitude drift from biological, mechanical, and electrical sources. Functional connectivity (FC) in neuroimaging has long shown that relational representations can be informative beyond amplitude. We asked whether the same idea, transposed from slow BOLD to fast electrical signals, could yield a chronically stable iBCI features.

We performed a secondary analysis of an open-source ALS-BCI dataset (single ALS participant, 13 sessions over ~7 months, two 8x8 subdural grids, syllable repetition task). From identical 70-170 Hz high-gamma envelopes we derived three feature streams: HGLP (log power), HG-C (pairwise Fisher-Z correlations), and HG-PC (partial correlations). Identical two-layer LSTMs decoded each stream for neural voice activity detection (NVAD); HG-C and HG-PC were first projected to 64-D via a learned linear network to match HGLP. No session-level normalization or recalibration was applied. Robustness was probed by permutation marginal-effects analysis and simulated random and systematic electrode disconnections.

For NVAD, HG-C degraded only -8% in F1 from test to a session six months later versus -23% for HGLP (robust across 20 independent runs, Wilcoxon, Bonferroni-corrected) and tolerated focal and distributed electrode loss substantially better. Marginal-effects maps showed that HG-C and HG-PC distribute speech-related information across multiple electrode pairs, in contrast to HGLP's small ventral hotspot. HG-PC unexpectedly and consistently elevated dorsal-grid pairings that prior HGLP and HG-C analyses had down-weighted, prompting reconsideration of the dorsal grid's contribution. Initial experiments on syllable (12-way) and keyword (7-way) identification yield comparable F1 across features but reveal systematic confusion-matrix biases in HG-C and HG-PC that HGLP does not show. This suggests a feature/task interaction consistent with correlation features favoring chronically stable binary detection and power features favoring fine-grained multi-class discrimination. These results position HG correlation structure as a candidate feature for low-calibration speech iBCIs and may motivate adapting FC methods for chronic iBCI decoder design.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Informatics, Statistics, or Applied Mathematics; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Monitor Neural Activity*

Geometry-matched curved implantation of ultra-flexible neural probes for region-specific and circuit-level brain recording

PRESENTER: **Y. Sun**

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AUTHORS: Y. Sun, Z. Zhao, Y. Cheng, D. Lin

Understanding brain function requires neural interfaces that access distributed circuits with high spatial precision while maintaining stable long-term recordings. However, functionally important circuits, including the septo-temporal hippocampal axis and cortico-basal ganglia networks, follow curved or multi-depth anatomical trajectories difficult to sample with conventional straight rigid probes. To address this challenge, we developed geometry-matched curved ultra-flexible neural probes for high-spatial-resolution, region-specific implantation and chronic electrophysiological recording across complex brain architectures. A key advantage of this platform is its ultra-flexible mechanical design, which reduces mechanical mismatch with brain tissue and supports stable chronic integration. In mice, this technology enabled reliable single-unit and local field potential recordings for up to one year after implantation, demonstrating long-term monitoring with preserved signal quality. Combined with dense recording-site layouts, this stability allows spatially resolved tracking of neural activity across organized circuits over extended time scales. We applied this platform to two circuit systems. First, curved high-density probes were used to profile hippocampal spatial coding along the septo-temporal axis in head-fixed mice performing virtual-reality navigation. The curved implantation geometry allowed recording sites to follow dorsal-to-ventral hippocampal organization while preserving fine-scale single-unit resolution. This enabled high-resolution place-field mapping across hippocampal subregions and a framework for examining how spatial representations vary with anatomical position during behavior. Second, curved multi-shank probes were designed to target cortico-basal ganglia pathways involved in action selection and learning. By matching probe geometry to the spatial layout of cortical, striatal, pallidal, and nigral structures, the probes supported simultaneous, spatially resolved multi-region recordings in freely moving rats during trial-and-error learning. These recordings captured circuit-level neural dynamics associated with choices, outcomes, and evolving task performance. Together, these studies establish geometry-matched curved ultra-flexible implantation as a scalable strategy for high-spatial-resolution chronic brain recording, enabling region-specific and circuit-level access to neural activity with anatomical precision and long-term stability.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation*

Decoding the chronic pain state: Stable networks and dynamic oscillations in the human insula

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Chronic neuropathic pain fluctuates dynamically despite stable underlying disease pathophysiology, presenting a challenge for developing physiologically grounded biomarkers. The insular cortex is a critical hub for pain processing, but distinguishing enduring baseline neural patterns from daily pain variation remains difficult. We analyzed 34 days of resting-state bilateral intracranial electroencephalography recordings from six individuals with chronic unilateral neuropathic pain. Using linear mixed-effects models controlling for longitudinal temporal drift, we quantified spectral power and intra-insular functional connectivity across anterior and posterior insular subregions.

We identified a stable within-cohort spectral organization characterized by lower posterior fast-band power and a contralateral posterior dominance in spectral power relative to the pain side. Against this stable baseline, dynamic fluctuations in distinct pain dimensions were encoded by frequency-specific local oscillations. Daily pain intensity was strongly associated with increased contralateral posterior alpha power, accounting for approximately 33% of within-subject variance. Pain unpleasantness tracked preferentially with contralateral posterior beta power, accounting for approximately 19% of within-subject variance. Intra-insular functional connectivity, including a consistent posterior gamma bias, remained comparatively stable across varying pain states.

Our results indicate that chronic pain is organized around stable insular networks upon which dissociable alpha and beta oscillations encode dynamic pain states. This dissociation provides a critical physiological framework for utilizing posterior insular spectral power as a sensing biomarker, advancing the potential for targeted adaptive neuromodulation therapies in chronic pain management.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Interventional Tools*

Interactions of two neurotransmitter systems in the main olfactory bulb: Metabotropic glutamate receptors and cannabinoid receptors

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AUTHORS: E. Brown, Z. Wang, T. Heinbockel

Metabotropic glutamate receptors (mGluRs) have been implicated in several neurological diseases such as stroke, epilepsy, schizophrenia, Parkinson's disease, and Huntington's disease. Endogenously released cannabinoids (endocannabinoids) have been shown to regulate neuronal activity. Here, we aim to better understand how these two neurotransmitter systems, mGluRs and cannabinoid receptors, interact. Our previous data showed that exposing the olfactory bulb network to cannabinoid receptor antagonist, AM251, or mGluR antagonist, LY367385 alone, resulted in a decrease of mitral cell firing. Based on this data, our hypothesis was that exposure of mitral cells to both AM251 and LY367385 together would result in mitral cell firing to decrease even further. Patch-clamp electrophysiology was used to record from mitral cells. We found that the combined application of LY367385 and AM251 resulted in increased mitral cell firing. To determine whether this was due to glutamate or GABA, mitral cells were treated with the same protocol, but in addition Gabazine, a GABA-A receptor antagonist, was added. In the next phase, APV and CNQX (ionotropic glutamate receptor blockers) were added. In the presence of AM251, LY367385, and Gabazine, mitral cell firing increased. However, in the presence of AM251, LY367385, APV, and CNQX mitral cell firing decreased. Based on these findings, we concluded that the increased firing of mitral cells in response to a combination of AM251 and LY367385 was a glutamate-induced effect. By better understanding how the metabotropic glutamatergic receptor system and endocannabinoid receptor system interact, we will gain insight into how to enhance neuroprotective measures in combating mGluR-related neurodegenerative diseases.

KEYWORDS: *Cell Type/Interactions; Electrophysiology; Monitor Neural Activity; Neural Recording & Modulation; Synaptic Plasticity; Integrated Approaches*

Cortical sites critical to speech and language function have distinctive static and dynamic network properties

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Electrocortical stimulation (ECS) mapping identifies focal brain areas that are “critical” for speech and/or language prior to clinical resection procedures. ECS has been standard-of-care for decades, yet it is imperfect, and the mechanism of its effects remains in question. The behavioral impacts of ECS could be mediated by either local disruption of cortex or network-based changes in speech and language circuits. We investigated functional cortical networks’ role in a speech task (word reading) by recording electrocorticography (ECoG) in frontal, temporal, and parietal areas of human participants. We extracted high-gamma (70-200 Hz) as a proxy for local synaptic potential activity, and described functional networks by computing pairwise correlations between all electrodes. We employed graph theory methods to quantify the network modulations that accompany speech/language behaviors. In particular, we investigated differing timescales, including static (several minutes) and dynamic (<1 s sliding windows) patterns of network connectivity.

Static network properties, measured during entire speech behavior sessions, enabled accurate differentiation of speech arrest and language error sites on cortex from non-critical sites. Overall connectivity (global and local) was lower in critical sites, and language error sites in particular showed an increased role as connectors between subnetworks.

Dynamic network changes occurred on the timescale of the behavior itself, and often deviated substantially from static network profiles. Transitions from rest to task engagement, or the onset of speech, modulated network connectivity within and between local subnetworks.

These results suggest that the pattern of connectivity between a given location in the language network helps determine its importance to language function. Further, these network patterns change dynamically and asymmetrically during behavior. This highlights the importance of examining brain activity during active behavior, at the resolution of the behavior itself, in addition to resting state analysis.

KEYWORDS: *Connectome; Human Neuroscience, Clinical Science, or Public Health; Theory & Data Analysis Tools; Neural Recording & Modulation*

Charge-based BEM-FMM with residual-driven AMR for high-definition TES modeling

PRESENTER: **D. Drumm**
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AUTHORS: D. Drumm, G. Noetscher, Z. Deng, S. Makaroff

There is a growing interest among clinicians and researchers to use transcranial electrical stimulation (TES) to stimulate deep brain structures, with implications in the non-invasive treatment of tumors, major depressive disorder, and other neuropsychiatric disorders. Accurate TES modeling requires resolving numerical singularities in the charge density near electrode-tissue interfaces. The charge-based boundary element fast multipole method (BEM-FMM) can be used with adaptive mesh refinement (AMR) to resolve these singularities. We derive a new error estimator which considers both local and nonlocal contributions of the single-layer potential operator and construct a corresponding AMR criterion. We compare TES solutions on head models derived from the 7-tissue SimNIBS and 40-tissue Sim4Life segmentations. We find that the SimNIBS segmentation model overestimates electrode currents and average electric field strength in the deep cortical structures by 65% compared to those from the Sim4Life segmentation model.

KEYWORDS: *Computational Biology/Modelling; Neural Recording & Modulation; Software (analysis, etc.) and Engineering*

Low-intensity multi-channel steering TMS array for network-level neuromodulation

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Brain stimulation therapies for treatment-resistant depression are increasingly understood to act on distributed cortical networks rather than a single focal target. However, the currently available technologies remain poorly suited for network-level intervention: conventional transcranial magnetic stimulation (TMS) typically employs a single figure-8 coil to stimulate one target region, while transcranial electrical stimulation (tES) requires direct, often gel-mediated, scalp contact. Motivated by the growing evidence supporting the therapeutic potential of low-intensity magnetic stimulation, we present the design, modeling, and prototype validation of a whole-head, multichannel low-intensity TMS (LI-TMS) system intended for both focal and network-level neuromodulation.

The proposed system comprises a 102-channel coil array, independently controlled drivers capable of arbitrary per-channel current-waveform synthesis, and a boundary-element fast-multipole method (BEM-FMM) beamforming framework that determines the coil-current distribution required to generate a prescribed cortical electric-field pattern. The goal of this study is to demonstrate that, using accessible microprocessor-controlled power electronics and software-defined control, it is feasible to design a wearable whole-head, multichannel, steerable LI-TMS array in the form of a helmet. The proposed array is capable of generating cortical electric fields of up to 1.5 V/m, provides acceptable thermal management, and can operate in either pulsed or continuous-wave (CW) modes. A 12-channel hardware prototype comprising independently controlled H-bridge driver circuits with current feedback control was constructed and validated through electric-field measurements in air and thermal testing. In simulation, the system reproduced the cortical electric and magnetic fields of a clinically validated low-intensity magnetic stimulation device, targeted the dorsolateral prefrontal cortex, enabled network-level targeting of the default mode network, and synthesized spatiotemporally varying electric-field patterns for synchronized stimulation of endogenous brain oscillations. Collectively, these results support the feasibility of a new low-power, whole-cortex, steerable, non-contact neuromodulation device for network-level treatment of depression.

KEYWORDS: *Interventional Tools; Neural Recording & Modulation; Software (analysis, etc.) and Engineering*

A deployable syringe-based auricular injectable device that addresses the interface bottleneck for ICU/ED neural recording

PRESENTER: **Z. Xu**

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AUTHORS: Z. Xu, C. Liu, A. Ascani Orsini, S. Wang, S. Cho, N. Thakor

Acute neurological disorders, including traumatic brain injury, stroke, and seizure, often require rapid assessment of dynamic brain activity in emergency department (ED) and intensive care unit (ICU) settings. Conventional scalp electroencephalography (EEG) remains the clinical gold standard for electrophysiological brain monitoring. However, EEG markers of brain injury are heterogeneous and often evolve over time, meaning that some patients may not exhibit detectable abnormalities during routine recording sessions showing normal EEGs after 15 minutes. Portable and reduced-montage EEG systems reduce this workflow burden, but forehead-based or flexible electrodes still rely on external skin adhesion, which is susceptible hair, sweat, and motion. We therefore developed a syringe-deployable auricular injectable-electronics interface that uses the ear canal as a mechanically protected, low-burden “keyhole” access site near the temporal lobe. By combining a conductive textile electrode cap with an injectable conformal coupling layer, this approach adapts to patient-specific ear-canal anatomy without requiring precise manual electrode fitting, supporting rapid deployment and stable electrode-tissue coupling for future in-ear neural recording.

We developed cNeuroTex, a syringe-deployable auricular injectable device that integrates a single-use AgNW-based electrode cap with an injectable, in-situ-forming polymer interface to create a patient-specific conformal coupling layer in the ear canal. The system used a Luer-lock-anchored syringe adapter and an engineered weak-link release ring for one-handed deployment.

cNeuroTex enabled a rapid syringe-based workflow to deploy a conductive textile electrode with low contact impedance lower than 90 k Ω at 15 Hz into the ear canal within approximately 3 minutes. The conformal interface increased effective electrode-tissue contact area by approximately 70%, while the thermoresponsive hydrogel remained flowable during delivery, shear-thinned under syringe-relevant wall shear rates $> 64 \text{ s}^{-1}$ during delivery and transitioned into a static gel-like state near 37°C for localized ear-canal retention. Finite element analysis under 0.5-mm prescribed displacement showed stress localization at the weak-link region, with a maximum von Mises stress of approximately 375 MPa exceeding the estimated ABS yield strength of ~45 MPa. Together, these results support future stable ieECG/ieEEG electrode-tissue coupling in ED/ICU environments.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Monitor Neural Activity*

Beyond the LFP: A multimodal hierarchical control architecture for next-generation deep brain stimulation

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Abbott

AUTHORS: J. Dubuclet, Y. Pathak

Current closed-loop deep brain stimulation (DBS) relies almost exclusively on fast-acting, central neurophysiological signals (e.g., local field potentials (LFPs)). While effective for immediate symptom suppression, this unimodal approach treats a single signal rather than the whole patient. It ignores “slow” systemic biological states, such as metabolic fluctuations and systemic inflammation, that fundamentally drive neural network dynamics and behavioral states. There is a critical need for neuro-technologies that bridge these distinct biological scales.

To map the landscape of systemic-central integration, we conducted a cross-disciplinary synthesis of over 300 disconnected scientific records across neuroscience, endocrinology, and biomedical engineering. This analysis revealed a critical, unproven gap: the complete absence of studies that synchronously measure systemic biochemical states and central neural signals in humans. The synthesis was organized to evaluate the evidence for three core architectural components: (1) quantifiable “slow” systemic state variables, (2) robust “fast” neurophysiological control signals, and (3) candidate mathematical frameworks for integrating multi-scale biosignals.

Addressing this gap, we propose a novel Hierarchical Control Architecture for future neuromodulation systems. This framework integrates two parallel data streams: “slow” systemic biology captured via minimally invasive wearables and Continuous Glucose Monitors (CGMs) and “fast” central neurophysiology captured via intracranial sensing. By applying advanced data science methodologies to fuse these multimodal inputs, the architecture enables a dynamic, state-aware control model that anticipates neurophysiological shifts based on systemic biochemical precursors.

This framework represents a necessary leap in neuro-technology, moving from reactive signal suppression to proactive, multi-scale network modulation. By connecting systemic biochemistry to central neurophysiology, this model establishes a pathway to map the relationships between systemic metabolic fluctuations, central neurophysiology, and clinical behavioral states. This foundational work sets the stage for future discovery studies and the engineering of truly holistic, personalized neuromodulation platforms.

KEYWORDS: *Implantable Devices (probes, etc.); Integrated Approaches; Software (analysis, etc.) and Engineering*

Sustained neural responses to the visual component of audiovisual speech in human superior temporal cortex

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The superior temporal cortex is a locus of human speech perception. Neural recordings from epilepsy patients implanted with stereotactic EEG electrodes suggest that the superior temporal gyrus (STG) processes auditory (A) speech while the superior temporal sulcus (STS) processes face and mouth movements during visual (V) or audiovisual (AV) speech perception. In Zhang et al., only single words were presented, meaning multisensory effects could be due to transient responses to word onset. To explore this possibility, the current study presented longer narratives divided into 5 second blocks randomly assigned to A, V, or AV formats. The amplitude of z-scored broadband high-frequency activity (BHA, 70-150 Hz) relative to inter-block baseline was measured in an "early" window (0-0.5 s after block onset) and a "late" window (0.5-5 s) to dissociate transient and sustained responses.

Across 15 participants, 81 STS and STG electrodes were identified as "bimodal" (significant response in the early window to both A and V speech). One group of electrodes showed a "visual sustained" response pattern, while another group of electrodes showed a "visual transient" response pattern, with significant responses to visual speech in the early window but not the late window.

The response to AV speech was examined. For "sustained" electrodes, there was a significant difference between AV and A responses, with AV > A in both early and late analysis windows (early response peak amplitude: AV = 0.45; A = 0.32; late response, AV = 0.30; A = 0.25). For "transient" electrodes, there was not a significant difference between AV and A responses in either window.

In STS, 83% of electrodes showed a "visual sustained" response pattern, while in STG, 64% of electrodes showed a "visual sustained" response pattern ($p = 0.04$ from chi-square).

These results are compatible with the idea that STS is especially important for integrating A and V speech: "visual sustained" responses were more prevalent in STS than STG, and electrodes with a "visual sustained" response pattern showed a significantly larger response to AV speech than to A or V speech, a neural signature of multisensory integration.

KEYWORDS: *Electrophysiology; Neural Recording & Modulation; Human Neuroscience, Clinical Science, or Public Health*

Brain wide electrophysiology in freely moving mice: Neuropixels NXT probes allow 6144 simultaneously recording channels

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We report the performance of small footprint Neuropixels NXT (3.0) probe in freely moving mice. These new technology, 1536 channel probes are small enough to permit 4 probes to be chronically implanted in a naturally behaving mouse. Shown will be high quality data from multiple mice, 6000+ units across 15-20 brain regions. Initial analysis of the 50+ TB data sets show Granger causality between these regions and the shift in "connectivity brain state" when mice we simulate an neuroinflammation state.

These probes are deployed in fixtures allowing probe recovery and reuse with high reliability even with long term (8 week) implants. The fixture is lightweight (<4 g) and allows normal behavior: Motion, feeding, and sleeping are within normal limits for unimplanted animals over 60 hours.

KEYWORDS: *Behavioral Sciences/Psychology; Electrophysiology; Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Networks (topology, etc.)*

Biomimetic QSensing® quantum sensor for high-resolution mapping of neuronal energy dysfunction and circuitry failure in neurodegenerative disease

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Alzheimer's disease affects over 7.4 million Americans in 2026, with global dementia cases exceeding 55 million. Early detection remains challenging because existing tools lack the sensitivity to identify subtle neuronal circuitry and energy imbalances before clinical symptoms emerge. ABS's patented biomimetic QSensing® platform introduces a novel electrochemical quantum sensor that enables non-invasive, early-stage detection and dynamic 3D mapping of neurodegenerative dysfunction with exceptional spatiotemporal resolution.

The system identifies early asymptomatic neuronal circuitry failure triggered by minute shifts in brain energy homeostasis. It visualizes dysfunctional hotspots through dynamic energy-sensory optical images and 3D functional maps, distinguishing four progressive stages of Alzheimer's—from presymptomatic energy stress to late-stage circuitry collapse—against healthy controls.

At the core of this breakthrough is a nanostructured biomimetic enzymatic membrane integrated with a flexible thin-film Josephson junction (FTJJ) array. This design leverages quantum sensing principles to directly detect multiple interconnected biomarkers of neuronal energy metabolism and neurodegeneration, including N-acetylcysteine (NAC), acetyl-CoA, ATP, pyruvate, acetylcholine, MMP-2, and beta-amyloid. Each biomarker is identified through its unique Josephson nonlinear anharmonic oscillation fingerprint.

Operating at room temperature and zero applied potential, the sensor measures analyte-induced changes in superconducting current or voltage fluctuations caused by magnetic flux variations within the FTJJ array—no external magnetic field or tracers required. The FTJJ architecture establishes a stable direct electron relay (DER) pathway, enabling real-time monitoring of protein refolding energy imbalances within one minute. This provides reagent-free, interference-free detection with 98-100% recovery rates, NIST-traceable accuracy, and dramatically enhanced sensitivity and selectivity compared to conventional methods.

Key advantages include high spatiotemporal resolution, tracer-free and radiation-free operation, rapid acquisition, simplified workflow, portability, and affordability. By mapping energy-circuitry dysfunction at its earliest molecular origins, this technology offers a transformative tool for precision diagnostics, patient stratification, and therapeutic monitoring in Alzheimer's, traumatic brain injury, and epilepsy.

KEYWORDS: *Circuit Diagrams; Integrated Approaches; Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Synaptic Plasticity*

Substantia nigra pars reticulata deep brain stimulation implicates basal ganglia-thalamocortical mechanisms in auditory verbal hallucinations

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Auditory verbal hallucinations (AVH) are among the most disabling symptoms of schizophrenia and are traditionally linked to dysfunction within distributed language and auditory processing networks. Emerging evidence suggests that basal ganglia-thalamocortical (BGTC) circuits may also contribute to hallucination generation. Deep brain stimulation (DBS) of the substantia nigra pars reticulata (SNr), a basal ganglia output nucleus, has shown therapeutic potential in treatment-resistant schizophrenia (TRS), yet its physiological mechanisms remain poorly understood.

We performed simultaneous intraoperative electrocorticography (ECoG) and SNr DBS testing in a patient with TRS undergoing bilateral SNr DBS implantation. A temporary 63-channel ECoG grid was placed over left language cortex. During double-blinded DBS OFF and DBS ON periods, the patient continuously reported AVH onset and offset using a button press. Cortical activity was characterized by spectral power and theta-gamma phase-amplitude coupling (PAC), a measure of cross-frequency synchronization implicated in information processing.

AVH episodes were associated with reduced gamma-band power within the angular and supramarginal gyri, accompanied by elevations in theta-gamma PAC across language-related cortex. Significant cross-frequency coupling was confirmed using surrogate-based permutation testing. Spatial mapping identified focal PAC hotspots within inferior parietal and postcentral regions, suggesting localized cortical nodes involved in hallucination-related processing. Bayesian analyses further demonstrated robust AVH-associated PAC elevations at physiologically responsive cortical sites. Activation of SNr DBS attenuated these PAC abnormalities, shifting cortical synchronization toward baseline states. Concurrently, hallucination frequency decreased by 64%, and the temporal structure of AVH episodes was altered.

These findings provide real-time human electrophysiological evidence that modulation of a basal ganglia output nucleus can rapidly influence cortical dynamics associated with hallucinations. The results support a role for BGTC circuitry in AVH pathophysiology and identify theta-gamma synchronization as a candidate physiological marker of symptom expression and neuromodulation response. More broadly, this work demonstrates how simultaneous cortical recording and subcortical stimulation can be leveraged to investigate mechanisms underlying psychiatric symptoms.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neural Recording & Modulation; Monitor Neural Activity*

Flexible high-precision photoacoustic retinal prosthesis

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Retinal degenerative diseases are the leading cause of irreversible vision loss. Retina prosthesis are implantable devices designed to stimulate diseased retina of individuals with these significant conditions. New technologies are needed for precise and non-genetic retinal stimulation to restore meaningful vision to patient.

Here we report our work on developing flexible photoacoustic implants for retina stimulation. In a photoacoustic process, a pulsed light is illuminated on an absorber, resulting in transient heating and subsequent generation of acoustic waves at controlled ultrasonic frequencies. Our team has pioneered high-precision PA neuromodulation up to single neuron precision and developed various platform technologies. Specifically, we designed a polydimethylsiloxane and carbon-based flexible film that converts near-infrared laser pulses into a localized acoustic field with 56- μm lateral resolution, aiming at high-precision acoustic retina stimulation. Under pulsed laser condition, the film based photoacoustic stimulation resulted in robust and localized modulation of wild-type and degenerated ex vivo retinæ. When a millimeter-sized photoacoustic film was implanted in the rat subretinal space, pulsed laser stimulation generated neural modulation along the visual pathway to the superior colliculus, as measured by functional ultrasound imaging. The biosafety of the film was confirmed by the absence of short-term adverse effects under optical coherence tomography retinal imaging, while local thermal increases were measured below 1°C.

We further explored new designs including microlens array based flexible implant with improved spatial resolution and injectable photoacoustic film, which mitigates the surgical risks of retina implants. These results show the potential of using photoacoustic signal to drive activity in photoreceptor-damaged retinas. Photoacoustic opens potentials as a biocompatible flexible retina prosthesis with a potential offering the potential for high-acuity visual restoration over a large field of view.

KEYWORDS: *Implantable Devices (probes, etc.); Neural Recording & Modulation; Interventional Tools*

Reshaping cortical motor circuits using an intracortical brain-computer interface

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Intracortical brain-computer interfaces (iBCIs) enable individuals with paralysis to control external devices by decoding movement-related neural activity from the precentral gyrus. Classical models of this region propose a somatotopic organization in which body parts occupy distinct cortical territories suggesting implant location constrains which body parts can be decoded. This introduces a challenge when implanting iBCI electrodes, as neurosurgical access to territories is often limited by specific clinical conditions (stroke), minimal electrode coverage, and expansive neurovasculature. These limitations raise two central questions: How much whole-body movement information is accessible from any precentral gyrus region, and can iBCI use be leveraged to modify local cortical motor representations to better support desired BCI functions? We studied two individuals with a cervical spinal cord injury implanted with microelectrode arrays in the hand region of the precentral gyrus as part of an iBCI clinical trial (NCT1894802). Using a motor mapping task involving directional movements of 12 body parts, we observed significant neural modulation for all tested movements. Results were consistent with a graded somatotopic hierarchy: hand responses strongest, leg and face responses weakest, but significantly detectable. We next tested whether these weak representations could be strengthened through targeted iBCI training. One participant completed 5 sessions controlling a BCI using neural activity generated from attempting to move the weakly represented ankle. Across sessions and tasks, BCI performance improved significantly. Similarly, neural separability of ankle movements increased from 57% to 90% (5-class decoding), while wrist representations remained stable (92-96%), suggesting selective strengthening of the ankle representation. Finally, we initiated a longitudinal study to determine whether routine motor iBCI use similarly alters native cortical representations. One participant underwent monthly motor mapping assessments post-implant. Over 1 year across 53 testing sessions, the participant completed 98 hours of experimental testing including 22 hours of online motor iBCI control. Ongoing analyses are evaluating effects of BCI usage on cortical organization. These findings suggest that latent motor representations are broadly accessible across the precentral gyrus and that targeted iBCI training may provide mechanism for reshaping cortical motor circuits.

KEYWORDS: *Implantable Devices (probes, etc.); Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Synaptic Plasticity; Monitor Neural Activity*

Continuous brain-body interaction monitoring using synchronized multimodal wearable neurophysiology

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Continuous monitoring of brain activity in natural environments remains a major challenge in neuroscience. Current approaches often focus on isolated physiological systems and fail to capture the dynamic interactions between neural, cardiovascular, respiratory, and behavioral processes that collectively shape human health and function.

To address this challenge, we developed a synchronized multimodal wearable neurophysiology platform capable of continuously recording electroencephalography (EEG), cardiac activity, respiration, motion, and associated physiological signals in ambulatory settings. The platform integrates low-power wireless bioelectronics, synchronized time-stamping, edge computing, and cloud-based analytics to enable long-term monitoring outside of traditional laboratory environments.

The system has been deployed across diverse human populations spanning the lifespan, including neonates, healthy adults, older adults, and individuals undergoing sleep assessment. Validation studies demonstrate reliable signal acquisition and temporal synchronization suitable for multimodal physiological analysis. The platform enables simultaneous characterization of neural activity together with cardiovascular, respiratory, and behavioral dynamics, providing a framework for studying brain-body interactions in real-world environments.

Beyond signal acquisition, the platform supports scalable computational pipelines for physiological feature extraction, multimodal data integration, and interpretable machine learning analysis. These capabilities establish a foundation for future investigations of neurodevelopment, aging, sleep, neurological disorders, and personalized health monitoring.

This work highlights the potential of synchronized wearable neurophysiology technologies to expand neuroscience beyond episodic laboratory measurements and toward continuous, real-world characterization of human brain-body function. Such approaches may facilitate future discovery of physiological biomarkers and improve understanding of how neural activity interacts with systemic physiology across diverse populations and clinical conditions.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Monitor Neural Activity; Neural Recording & Modulation; Software (analysis, etc.) and Engineering*

Pixel-wise programmable image sensors for high-speed calcium and voltage imaging

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High-speed wide-field fluorescence microscopy can capture neural processes with exceptional spatiotemporal resolution, but conventional cameras face a fundamental tradeoff between frame rate and signal-to-noise ratio (SNR). At high frame rates, short exposure times reduce photon collection and limit the detection of faint fluorescence events.

Here, we introduce a pixel-wise programmable-exposure CMOS image sensor, PE-CMOS, in which each pixel has individually programmable sampling speed and phase. By arranging neighboring pixels with different exposure phase offsets, the sensor can resolve fast fluorescence dynamics without increasing the sampling rate of each individual pixel. This temporally interleaved acquisition strategy preserves long pixel exposure times, thereby improving SNR while maintaining high effective temporal resolution. In high-speed voltage imaging experiments, PE-CMOS achieved approximately 2- to 3-fold higher SNR than a commercial low-noise sCMOS camera at the same temporal resolution. This improvement enabled detection of weak neuronal action potentials and subthreshold voltage activity that were missed by standard sCMOS imaging.

Our first-generation PE-CMOS sensor was fabricated in a 180 nm CMOS process, with a 10 μm pixel pitch, high conversion gain of 110 $\mu\text{V}/\text{e}^-$, 75% photodiode fill factor, and support for temporal resolution up to 1040 Hz. We have now developed a second-generation PE-CMOS v2.0 sensor with increased pixel count and higher operating speed, further extending the platform toward larger fields of view, faster imaging, and broader biological applications.

Because the architecture achieves high effective temporal resolution without requiring every pixel to operate at high sampling speed, PE-CMOS also offers improved power efficiency. This feature makes it well suited for scalable high-speed microscopy and miniaturized head-mounted systems, enabling kHz voltage and calcium imaging in freely moving animals and direct in vivo measurement of fast neural activity underlying complex behavior.

KEYWORDS: *Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Image-guided deep brain stimulation of the nucleus basalis of Meynert for cognitive impairment in Parkinson's disease: Initial human observations

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Cognitive decline begins in early stages of Parkinson's disease (PD) and remains largely untreated. The Nucleus Basalis of Meynert (NBM), the cortical cholinergic hub, and its lateral fiber bundle degenerate early in PD and are linked to cognitive and cognitive-motor impairment. Pre-clinical evidence indicates intermittent stimulation of the NBM improves cognition. The objective of this study is to establish the safety, tolerability, and feasibility of combined continuous subthalamic nucleus (STN) and intermittent NBM DBS in people with Parkinson's disease for cognitive and cognitive-motor impairment.

Four individuals with PD and cognitive impairment approved for STN DBS were enrolled as part of an ongoing clinical trial for combined STN and NBM DBS. Two participants received a "vertical" trajectory in which 2 leads were placed in the STN, and 2 additional leads were placed in the of the anterior portion of the NBM, both using the same burrhole. The two other participants received a "lateral trajectory" in which the NBM leads were placed along the NBM lateral efferent bundle via a punch hole behind the ear. An automated programming algorithm DBS Illumina 3D (Boston Scientific) was used to program the NBM leads based on volume of tissue activated (VTA) modeling. The investigational software Chronos (Boston Scientific) was used to deliver continuous high frequency DBS to the STN 24 hours/day and intermittent patterned DBS to the NBM for 1 hour/day.

The two leads placed in the NBM ("vertical" target) or its lateral efferent bundle ("lateral" target) were successfully and accurately placed as part of the usual STN DBS procedure. All participants were successfully programmed using the Illumina 3D algorithm without adverse effects. Following 6-months of combined STN and NBM DBS, all participants saw clinically meaningful improvements in cognition as part of a neuropsychological assessment battery.

These cases are presented to demonstrate the feasibility of the proposed combined STN and NBM DBS approach to target cortical cholinergic deficits and subsequent cognitive impairment in PD. The safety, tolerability, and feasibility are being tested as part of a pilot clinical trial with expected enrollment of 10 individuals and outcomes at 12 months.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Implantable Devices (probes, etc.); Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Interventional Tools*

State-dependent beta dynamics in the subthalamic nucleus during voluntary movement and passive sensory stimulation

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The subthalamic nucleus (STN) is a key basal ganglia structure involved in motor control; however, STN also serves neglected roles in sensory integration. Oscillatory activity in the beta frequency range (13-30 Hz) within the STN is associated with motor impairment in Parkinson's disease and is modulated during voluntary movement. Motor cortex local field potentials demonstrate differential beta-band modulation during active and passive movements, motivating examination of whether analogous distinctions are present within the STN. Determining whether STN oscillatory activity differs between volitional movement and passive proprioceptive input may provide insight into how basal ganglia-thalamocortical circuits represent motor versus sensory aspects of behavior.

We examined STN local field potential recordings during three behavioral conditions: rest, active hand movement, and passive limb movement (proprioceptive stimulation). Time-frequency analyses using continuous wavelet transform (CWT) will quantify changes in beta (13-30 Hz) and broadband (30-200 Hz) power and their temporal dynamics across conditions. Condition-dependent differences in oscillatory modulation will be assessed to characterize how STN activity varies with motor output versus sensory-driven input. Preliminary analyses of STN recordings indicate condition-dependent modulation of beta-band activity across active movement, and passive vibratory stimulation of the wrist.

STN oscillatory activity exhibits state-dependent modulation across active and passive movements compared to rest. By distinguishing how oscillatory dynamics differ across these conditions, we hope to clarify how STN contributes to sensorimotor integration within the distributed motor circuit. These findings may improve mechanistic models of basal ganglia function and inform future approaches to adaptive neuromodulation in movement disorders.

KEYWORDS: *Electrophysiology; Neural Recording & Modulation; Human Neuroscience, Clinical Science, or Public Health*

KCC2-dependent inhibitory signaling in the substantia nigra pars reticulata regulates behavioral state transitions following morphine exposure

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AUTHORS: A. Pearson, A. Ostroumov

Opioid use disorder (OUD) is associated with persistent alterations in behavior, including disruptions in how organisms select and regulate actions in response to environmental stimuli. These maladaptive behaviors often persist even when environmental conditions change (for instance: when alternative rewards are available, when drugs are unavailable, or when punishments are introduced). The substantia nigra pars reticulata (SNr), a basal ganglia output nucleus, is well positioned to regulate these behaviors through its inhibitory control over downstream motor and thalamocortical circuits. Understanding how SNr dysfunction contributes to these alterations may reveal mechanisms underlying persistent behavioral changes in OUD. The neuron-specific potassium-chloride cotransporter KCC2 is a critical regulator of inhibitory signaling through regulation of intracellular chloride. Disruption of KCC2 function can shift GABAergic transmission from hyperpolarizing to depolarizing, thereby altering circuit function. Previous work has shown that exposure to addictive drugs reduces KCC2 expression in midbrain GABAergic neurons, contributing to maladaptive behaviors. However, whether KCC2 dysfunction in the SNr contributes to maladaptive behavioral persistence and deficits in the regulation of ongoing actions is unknown. Here, we test whether restoring KCC2 function in the SNr can reduce the persistence of maladaptive behaviors following opioid exposure. Our preliminary data demonstrate that KCC2 downregulation in the SNr is sufficient to disrupt adaptive transitions between behavioral states; KCC2 upregulation in the SNr following morphine self-administration improves social interaction and normalizes threat perception. In parallel, KCC2 downregulation in opioid-naïve animals is sufficient to recapitulate multiple behavioral alterations observed following morphine exposure, including reduced social interaction and heightened threat perception, while also increasing approach behavior during a virtual prey capture task. These findings suggest that disrupted SNr inhibitory signaling alters the ability to appropriately enter, maintain, and exit behavioral states. Together, these findings identify KCC2-dependent inhibitory signaling in the SNr as a novel mechanism regulating behavioral state transitions and the control of ongoing actions, highlighting this circuit as a potential target for correcting maladaptive behavioral states associated with chronic opioid exposure.

KEYWORDS: *Behavioral Sciences/Psychology; Electrophysiology; Molecular/Cellular Neuroscience; Neural Recording & Modulation; Synaptic Plasticity*

Metal organic framework (MOF)-modified carbon fiber microelectrodes for enhanced neurochemical detection

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Neurochemical detection with fast scan cyclic voltammetry (FSCV) and carbon fiber microelectrodes (CFMEs) often lacks sufficient sensitivity and selectivity for measuring low dopamine levels found in the brain. In this study, carbon fiber microelectrodes (CFMEs) were modified with the iron-based metal organic framework (MIL-88B(Fe)) to alter the electrode surface and improve dopamine detection performance. When tested with a triangle waveform (scanning from -0.4 to +1.3 V, 400 V s⁻¹, 10 Hz), MIL-88B(Fe)-modified CFMEs showed a higher oxidative peak current for dopamine, increasing from 57.0 ± 5 nA on bare CFMEs to 100.5 ± 5 nA dopamine (n = 7, p < 0.0001), corresponding to an enhancement of approximately 76%. These modified electrodes exhibited a linear response in the nanomolar dopamine range (10-100 nM), with sensitivity increasing from 30 ± 2 nA nA/μM for bare CFMEs to 49 ± 3 nA/μM for MIL-88B(Fe)-modified CFMEs, and a limit of detection of 53 nM (3.3 σ/S) with a limit of quantification of 162 nM. The electrodes simultaneously detected dopamine, tyrosine, and hydrogen peroxide, with distinct oxidation peaks and a high recovery rate (~97%) in biological fluid. Together, these results indicate improved dopamine sensitivity relative to bare CFMEs and demonstrate the ability to distinguish dopamine from co-detected species with FSCV.

KEYWORDS: *Chemistry; Implantable Devices (probes, etc.); Monitor Neural Activity*

A multimodal framework for real-time adaptive auditory modulation using physiological state inference

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Aster Dynamics

AUTHORS: D.F. Wagner

Current digital wellness and neurotechnology platforms typically deliver static interventions despite the highly dynamic nature of human physiological and cognitive states. Advances in physiological sensing and adaptive signal processing create opportunities for systems capable of continuously responding to changes in user state.

We present a multimodal framework for real-time adaptive auditory modulation that combines physiological monitoring with adaptive digital signal processing (DSP). The system dynamically modifies auditory output in response to user-specific conditions, creating personalized auditory environments designed to support changes in cognitive and physiological state.

Internal observational testing was conducted with approximately 200 participants across multiple environments. Physiological measurements included electroencephalography (EEG), heart rate variability (HRV), and session-level behavioral observations. Representative paired-session protocols compared adaptive auditory stimulation with neutral audio conditions while collecting synchronized physiological data. Participants consistently reported improved focus, increased calm, reduced perceived stress, and greater engagement during sessions.

Preliminary EEG and HRV observations suggest measurable changes in physiological dynamics during adaptive auditory sessions, supporting the feasibility of coupling physiological monitoring with real-time auditory adaptation. These findings demonstrate the potential for integrating adaptive DSP with multimodal physiological sensing in a closed-loop framework.

Future development will expand beyond physiological monitoring to include ocular dynamics, wearable-derived biomarkers, behavioral signals, and environmental context within a unified multimodal state inference architecture. This approach aims to support continuously adaptive, personalized sensory environments capable of responding to changes in human state in real time.

KEYWORDS: *Electrophysiology; Integrated Approaches; Monitor Neural Activity; Neural Recording & Modulation; Software (analysis, etc.) and Engineering; Interventional Tools*

Bayesian-enhanced closed-loop optimization of ultrasound protocols for targeted and precise neuromodulation

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Low-intensity focused ultrasound (LIFU) is an emerging non-invasive neuromodulation technique whose translational potential is currently limited by a poorly understood parameter space and by high intra- and inter-subject response variability. Identifying effective stimulation protocols at the subject level requires closed-loop methods that adapt the choice of parameters to an observed neural response, ideally with a small number of evaluations and an explicit stopping rule. Here we developed and validated in vivo a closed-loop optimization framework, Bayesian-enhanced adaptive control of ultrasound neuromodulation (BEACUN), that combines real-time functional ultrasound imaging (fUSI) feedback with Bayesian optimization.

After each LIFU stimulation, the evoked cerebral blood volume (CBV) signal measured by fUSI at the target was quantified online and used to update a Gaussian-process surrogate of the stimulation-response function. The next stimulation parameters were then selected by the BEACUN acquisition function and updated at runtime in the fUSI-LIFU platform. We evaluated BEACUN in two inhibitory LIFU applications: one targeting the rat superior colliculus (SC; N = 5 rats), and a visual-evoked-response paradigm at the dorsal lateral geniculate nucleus (DLG; N = 5 rats). In both experiments, pressure, pulse-repetition frequency, and duty cycle were treated as continuous parameters and were optimized by the BEACUN engine. To enable fully automated optimization, we equipped BEACUN with a probabilistic regret bound (PRB) stopping criterion that halts the loop once a candidate point is deemed optimal under the GP posterior.

At the SC, BEACUN outperformed a real-world random search ($P < 0.01$; Hedge's $g = -4.24$) and produced a CBV signal reduction of $-7.3\% \pm 1.19\%$ (median $\pm$ IQR). At the DLG, BEACUN consistently suppressed the visual-evoked response ($-5.7\% \pm 1\%$ CBV reduction, $P < 0.001$, Hedge's $g = -12.68$), and the PRB criterion stopped the optimization after 23 ± 3.67 evaluations. These results establish BEACUN as an end-to-end closed-loop framework for data-driven, budget-efficient LIFU parameter optimization in vivo. Our method could pave the way for personalized LIFU protocol development in patients with neuropsychiatric disorders.

KEYWORDS: *Interventional Tools; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering*

Behaviorally driven increased glutamatergic activity from lateral entorhinal cortex to hippocampus supports object and spatial memory recall

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Functional interactions between the entorhinal cortex (EC) and area CA1, the major output area of the hippocampus, are crucial for forming episodic memories. However, their role in memory recall is less well defined.

Canonically, within the EC, the medial entorhinal cortex (MEC) primarily codes for spatial information, particularly global environmental cues, whereas the lateral entorhinal cortex (LEC) processes non-spatial sensory information. Although these functionally distinct inputs from MEC and LEC remain largely anatomically segregated within area CA1, multimodal memory processing requires integrating spatial and contextual information. Recent studies have put these strict functional divisions into question, suggesting greater crosstalk between these systems. Global LEC silencing via lesions, or combined suppression of both glutamatergic and GABAergic LEC neurons, impairs associational learning in goal-oriented navigation and multi-object-cued behaviors. However, we know little about the functional role of LEC glutamatergic projections to CA1 in episodic memory recall during object recognition and spatial navigation. To fill this gap, we first used fiber photometry-based calcium imaging of LEC axons within CA1 in freely moving mice during novel object recognition (NOR) and Barnes maze (BM) tasks. We observed that in both tasks, LEC glutamatergic axonal activity was selectively increased during recall compared to encoding. Moreover, in the spatial BM task, LEC-CA1 input activity progressively increased as animals learned the escape location guided by global cues, peaking at the late stages of training and during recall. Accordingly, local chemogenetic silencing of LEC glutamatergic inputs into CA1 after learning impaired recall performance in both the object recognition and Barnes maze tasks. This unmask the role of direct glutamatergic input from LEC into CA1 as crucial for memory recall beyond learning, supporting spatial navigation to a learned escape location in addition to object recognition.

KEYWORDS: *Behavioral Sciences/Psychology; Neural Recording & Modulation; Synaptic Plasticity; Molecular/Cellular Neuroscience*

Voltage imaging of neurons distributed across entire brains of larval zebrafish

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Neurons interact in networks distributed throughout the brain. While much effort has focused on whole-brain calcium imaging, recent advances in genetically encoded voltage indicators (GEVIs) raise the question of whether it might be possible to image neuronal voltage across entire brains. Achieving this requires a microscope with high volumetric imaging rates and signal-to-noise ratio. Here we present a remote scanning light-sheet microscope capable of imaging GEVI-expressing neurons distributed throughout the entire brains of larval zebrafish at a volumetric rate of 200.8 Hz. We measured voltage traces from approximately one quarter of all brain neurons. We found that neurons firing at different times during a sequence occupied different locations: visually evoked sequences mapped across the optic tectum, while stimulus-independent bursts mapped across the cerebellum and medulla. Imaging voltage of neurons distributed across entire brains may open new frontiers for understanding fundamental neural system operations.

KEYWORDS: *Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics*

Electrophysiology-compatible wearable transcranial focused ultrasound array for modulating reward cue-related neural activity and behavior in freely moving rats

PRESENTER: **M.G. Kim**

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The goal of this project is to develop and validate a novel wearable focused ultrasound neuromodulation array transducer, compatible with intracranial electrophysiological recordings, for precise neuromodulation and simultaneous recording of brain electrical activities in behaving animal models. To achieve this, we developed a lightweight 64-element random-array transducer designed for use in freely behaving animals for transcranial focused ultrasound stimulation (tFUS) and evaluated its ability to modulate reward cue-related behavior and neural activity in the nucleus accumbens (NAc), a key hub linking neural activity to motivated behavior. Transducer characterization demonstrated beam-steering capabilities of ± 7 mm along the x- and y-axes and up to 25 mm along the z-axis, allowing precise targeting of deep brain structures. To account for variability in ultrasound focus arising from differences in the amount and angle of dental cement applied during surgical procedures, we established a targeting procedure that involved adjusting beam steering along the x-, y-, and z-axes and identifying peak amplitude and volume of tFUS-induced electrophysiological artifacts. Long-Evans rats were trained in a discriminative stimulus task, in which animals entered a magazine during presentation of an auditory cue to obtain a sucrose reward. To identify a possible neural mechanism for stimulation effects on behavior, a bilateral tFUS paradigm was implemented in combination with intracranial single-unit recordings. Each session pseudorandomly included approximately 25 tFUS trials, 25 negative control trials (transducer positioned identically without ultrasound delivery), and 25 non-discriminative stimulus trials (magazine entries without programmed consequence). In a group of animals, we found that inhibitory tFUS at a center frequency of 1.2 MHz targeting either the NAc or ventral tegmental area (VTA) attenuated cue-evoked firing response in the NAc and increased behavior latency to reward compared with the negative control condition. In contrast, excitatory tFUS targeting the NAc reduced latency to reward, whereas the same parameters did not induce behavioral changes when applied to the VTA. Together, these findings demonstrate that tFUS can bidirectionally modulate reward cue-seeking neural activity and behavior in freely moving rats, highlighting its translational potential for neuropsychiatric disorders, including substance use disorders and depression.

KEYWORDS: *Behavioral Sciences/Psychology; Electrophysiology; Interventional Tools; Neural Recording & Modulation*

Patient attitudes toward the timing of deep brain stimulation and of information in Parkinson's disease

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Deep brain stimulation (DBS) is an established therapy for Parkinson's disease, but the optimal timing of referral and patient education is debated. Clinicians vary in when they consider DBS referral appropriate, and patients are divided on whether they would have wanted DBS earlier. We examined whether patients (DBS recipients, candidates, and decliners) would have wanted to be offered DBS earlier and to receive earlier information about Parkinson's disease and its treatment.

In a larger qualitative study, we conducted semi-structured interviews with 40 US patients (16 DBS recipients, 10 candidates, 14 decliners). Excerpts were coded at the participant level for two questions: wanting to be offered DBS earlier and wanting earlier information about Parkinson's disease and its treatment. Each was classified as "would consider earlier," "would not consider earlier," "ambivalent," or "unclear" and summarized by patient group, age, gender, education, and disease stage. Denominators differ: 28 patients addressed the DBS question and 34 the information question.

Most would not have wanted to be offered DBS earlier (17 of 28); six would consider it and five were ambivalent. Even among DBS recipients, only 3 of 15 would have wanted DBS sooner, and openness to earlier DBS was higher in early-stage disease (2 of 4) than in mid- or late-stage disease (4 of 24). Most also would not have wanted earlier information (23 of 34). The barrier was rarely access: many felt well informed and that information came as they grew ready, some avoiding advanced-treatment information until later. Those wanting earlier information asked for specific things: a clinician-guided source rather than searching alone, long-term-planning framing, and earlier mention of all options (medications, DBS, focused ultrasound). Not wanting earlier information was most common among patients with some college education or less (12 of 13).

Most patients wanted neither earlier DBS nor earlier information, even though expert consensus emphasizes timely referral and warns that eligible patients are often identified late. Efforts to intervene earlier should therefore attend to readiness, pairing earlier referral with individualized, appropriately paced counseling tailored to each patient's preferences, which differed across educational backgrounds.

KEYWORDS: *Implantable Devices (probes, etc.); Neuroethics, Philosophy, Law*

Responsible Neurotechnology Evaluation Tool (RNET): From principles to practice through organizational maturity assessment

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Neurotechnology is a rapidly advancing field that enhances our understanding of human brain, consciousness, and complex cognitive functions. While it holds great potential for improving daily life of people with disabilities and reshaping concepts of human technology integration, it also introduces urgent challenges related to autonomy, identity, privacy, and safety, with direct implications for individuals and society. Despite increasing global attention and the emergence of ethical principles and policy frameworks, a critical gap remains: organizations developing these technologies lack practical, measurable mechanisms to operationalize responsible innovation across the neurotechnology lifecycle.

This research addresses this gap through the development of the Responsible Neurotechnology Evaluation Tool (RNET), a prototype organizational maturity assessment tool. The core innovation of RNET lies in translating high-level ethical principles into measurable, evidence-based organizational practices, enabling systematic evaluation of how responsibly neurotechnology is designed, developed, deployed, and continuously improved. RNET provides structured assessment criteria, evidence-based proof points, and staged maturity indicators to support continuous organizational maturity.

RNET is grounded in the Responsible Neurotechnology Framework (RNF), developed using an empirical design research methodology integrating policy analysis and semi-structured interviews with experts across neurotechnology, healthcare, accessibility, ethics, and policy. The framework defines four domains: Governance, Data, Technology, and User, which underpin the assessment model. Thematic analysis informed the development of actionable metrics, iteratively refined through stakeholder feedback.

Currently at the prototype stage, RNET includes defined domains, scoring logic, and assessment criteria, with initial validation focused on conceptual rigor and expert review. Future work will involve iterative testing in real-world contexts.

RNET is designed for neurotechnology vendors to embed consistent responsible practices across the product lifecycle while also provide structured evidence to inform regulatory oversight, healthcare procurement, and investment in responsible innovation.

KEYWORDS: *Neuroethics, Philosophy, Law*

Evaluating the ethical implications of EEG neurotechnology in workplace environments

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As neurotechnological innovation rapidly advances, its incorporation into corporate workplace environments raises doubts about mental privacy and employee autonomy. Specifically, EEG (electroencephalogram) neurotechnology has become an active tool in monitoring employee activity within a company, such as fatigue, productivity, and emotional state. An overabundance of neural surveillance can blur the line between collecting employee data and mental privacy intrusion; this raises questions about whether it is ethical for employers to utilize EEG-based neurotechnology to monitor workers' state of mind, and if so what legal safeguards could protect mental privacy.

EEGs decode and interpret brain activity by translating brainwaves into measurable frequencies of attention, fatigue, and emotion. Research shows EEG virtual-reality neurotechnology can classify emotions with up to 85% accuracy, using the Valence-Arousal Scale as a reference. However, the development of such accuracy and precision in monitoring workplace activities raises the likelihood for privacy violations to occur, prompting questions about its ethical foundation. Additionally, this brings attention towards legal and policymaking approaches to resolving the issue, hoping to prevent further mental privacy violations. Most data privacy legislations inadequately protect neural data, threatening employee privacy. Although some effort is made, it is not enough to serve as regulatory provisions for cognitive-emotional information.

Legal frameworks surrounding ethical EEG usage remain inadequate and call for improvement. Existing privacy laws fail to clearly protect employees from neural surveillance exploitation. Without lucid safeguards, employers may risk exposing the thoughts and emotions of their employees. Secure regulations should include informed consent, oversight mechanisms, data ownership, and limited data access to only what's necessary.

Though EEG systems can provide important neural data for companies, employees may feel pressured to consent to company policies regarding neurodata monitoring (5), through potential coerced consent, loss of mental privacy, and neurodiscrimination. The collection of data may risk exposing workers' cognitive-emotional data. Therefore, EEG-based employee monitoring should only occur under a robust and ethical system. This important research explores the neuroethical usage of EEG-neurotechnology in professional settings.

KEYWORDS: *Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Monitor Neural Activity; Neural Recording & Modulation; Neuroethics, Philosophy, Law; Dissemination & Open Science/Education*

Digital antibody screening to identify critical targets and epitopes in brain cell clusters

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Antibodies play an important role in identifying critical targets and epitopes in brain cells. Protein folding AI models such as AlphaFold3 (AF3) allow for quickly screening a diverse set of antibodies against numerous targets to identify binding complexes. On a test set of 3400 antibody-antigen interfaces listed in the Structural Antibody Database, AF3 had 42% recall where predictions with high confidence (calculated using predicted aligned error and interface predicted template modeling score), and the correct epitope were classified as positives. AF3 was observed to prefer X-ray crystallography derived complexes over electron microscopy structures. The observations from this structural benchmark were critical for understanding how to screen antibody-antigen complexes with no known structures. Sources such as NeuroMab and CDI Labs freely provide the sequences of numerous antibodies for various target proteins of interest to the neuroscience community: Roughly 2000 and 500 unique antibodies for 400 and 100 different targets respectively. Using AF3, about 300 antibodies were identified as positive binders for these targets in a cross-species prediction assay. Genes such as PVALB, CALB2, MOG, NOVA1, and p1R1B reported high KL-divergence scores from gene expression data and had several binding antibodies. For PVALB, molecular dynamics and digital alanine scanning were used to identify residues in the paratope crucial for binding. The binding contributions of these residues were confirmed through alanine mutations in immunohistochemistry assays on mouse brain tissue, validating the digital predictions for these antibodies. These results are necessary for the curation of a free database of antibodies with structural validation. Such a database would be of immense value to neuroscientists for studying the differentiation of brain cell clusters.

KEYWORDS: *Computational Biology/Modelling; Physics or Microscopy/Optics; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Neuroimaging (invasive, non-invasive imaging)/Radiology*

Recent advances in the human neocortical neurosolver: An open-source biophysical modeling tool for multiscale interpretation of human EEG/MEG signals

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The Human Neocortical Neurosolver software is an open-source Python package (called HNN-core) built on the NEURON simulator that enables researchers to investigate the multiscale cell and circuit origins of MEG/EEG signals using biophysical neural models. Simulations represent activity in a localized patch of neocortex, exogenously driven by layer specific thalamocortical and/or cortical synaptic input, with output expressed in units directly comparable to source-localized current dipole recordings (nAm). HNN is designed around activation workflows to simulate M/EEG measured event related potentials (ERPs) and low frequency oscillations, with simultaneous calculation of LFP/CSD and cell specific spiking, voltage, and calcium activity. Users can also customize network activation patterns to include event-driven, Poisson, or rhythmic input.

We highlight recent major advances in HNN utility, including the implementation of a new neocortical column in which the neurons and connectivity were tuned to reproduce morpho-electric and synaptic properties of human tissue (<https://celltypes.brain-map.org/>), which we refer to as the Duecker ET model. The network's pyramidal neurons also generate dendritic calcium spikes similar to those experimentally observed in L2/3 and L5 of human and rodent cortex. Additionally, parameter optimization has been expanded with the addition of a new population-based evolutionary strategy solver (CMA-ES) and the option to use custom objective functions. The new optimization workflows are accessible through both the HNN graphical user interface (GUI) and the HNN-core Python interface, with corresponding documentation and API.

Based on user feedback, we have also greatly expanded our documentation and HNN accessibility. A new online HNN Textbook offers extensive information to guide both new and experienced users, including expanded website accessibility and new videos that walk through our major tutorials. Furthermore, we have significantly simplified the HNN installation process. HNN can now be easily installed via an Anaconda package, with corresponding documented instructions.

Together, these advances are aimed at helping researchers apply HNN to develop and test hypotheses on the multiscale generating mechanisms of their M/EEG data.

KEYWORDS: *Circuit Diagrams; Computational Biology/Modelling; Dissemination & Open Science/Education; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Simultaneous multi-site imaging across a mesoscale accessible volume with a distributed multi-site laser scanning microscope (DMSLSM)

PRESENTER: **X. Lai**
NIH

AUTHORS: X. Lai, Z. Wang, C.S. Wang, T. Li, Y. Gao, Y. Liu

Understanding how distributed brain regions coordinate to produce behavior is a critical challenge in neuroscience. There still exists a gap in circuit level studies because magnetic resonance imaging (MRI) can provide circuit level information but lack local circuit information because of its limited spatial resolution while optical microscopes are helpful for studying local circuits but lack circuit information because of their limited reachable volume range, usually at $0.5 \times 0.5 \times 0.2 \text{ mm}^3$. We are trying to bridge the gap between sub-cellular local monitoring and long-range network monitoring. We propose a distributed multi-site laser scanning microscope (DMSLSM), that can simultaneously record signals from up to 8 sites across a $9.5 \times 9.5 \times 22 \text{ mm}^3$ volume with subcellular spatial resolution and uncompromised speed as conventional LSM when the number of sites and size of volume increase. We used this system to record activities simultaneously from multiple deep regions in awake, behaving mice. Coupled with implanted GRIN lenses, DMSLSM enables multi-site interrogation of nociceptive ensembles across stages of inflammatory pain, revealing stage-dependent changes in cross-regional timing and coupling at single-cell resolution. DMSLSM not only bridges the gap between brain-wide functional readouts and high-resolution optical microscopy, but also brings new sights into neuroscience, and provides validation opportunities to analyze inter-region interactions, enabling direct tests of how distributed brain regions coordinate during behavior and disease.

KEYWORDS: *Developmental/Systems Biology; Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics; Theory & Data Analysis Tools*

ComBatFamQC: Interactive batch effect diagnosis and harmonization for multi-site neuroimaging within the NiChart ecosystem

PRESENTER: **S. Wen**

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Integrating multi-site and multi-study neuroimaging datasets can enhance statistical power and sample diversity; however, scanner- and site-related batch effects may obscure biological signals and compromise reproducibility. Although ComBat- and CovBat-based harmonization are commonly used, investigators often lack systematic guidance for diagnosing batch effects, selecting appropriate harmonization algorithms and evaluating harmonized data. We developed ComBatFamQC, an R package with both interactive Shiny and command-line interfaces for batch effect quality control and harmonization in neuroimaging studies. This framework combines qualitative visualization and rigorous statistical tests for batch effect assessment with four ComBat family harmonization methods (ComBat, Longitudinal ComBat, ComBat-GAM, and CovBat) in a single analytic workflow, providing flexibility to model nonlinear effects and multivariate patterns in diverse imaging studies. A key new feature is the extension of both ComBat and CovBat from conventional in-sample harmonization to out-of-sample harmonization, allowing harmonization models learned from a training dataset to be applied to the unseen datasets. ComBatFamQC also provides post-harmonization analyses relevant to age-trend visualization and residual generation for downstream modeling. This package is designed as a standardized and extensible platform for hosting existing and newly developed statistical harmonization algorithms, supporting continued methodological development within a unified framework. Furthermore, ComBatFamQC is integrated with the NiChart (Neuro Imaging Chart of AI-based Imaging Biomarkers; <https://neuroimagingchart.com/>) software ecosystem, expanding access to harmonization tools for the neuroimaging community. By integrating diagnosis, harmonization, and downstream analyses in one tool, ComBatFamQC streamlines multisite neuroimaging analyses and helps investigators assess whether harmonization removes unwanted site effects while preserving biological and disease-related variation.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Informatics, Statistics, or Applied Mathematics; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Dissemination & Open Science/Education*

AlongTractComBat: Tract-specific harmonization for multi-site diffusion MRI tractometry analysis

PRESENTER: **S. Amit**
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AUTHORS: S. Amit, D. Dasanayake, B. Chandio

Large multi-site diffusion MRI (dMRI) studies are essential for identifying robust biomarkers of neurological and psychiatric disorders. By combining data across institutions, researchers can achieve the statistical power needed to detect subtle white matter (WM) alterations. However, differences in scanner hardware and acquisition protocols introduce unwanted variability that obscures biological effects and limits the reliability of pooled analyses. Consequently, data harmonization has become a critical step in modern neuroimaging studies. Most existing harmonization approaches operate at the voxel or region-of-interest (ROI) level. However, these methods are not optimized for tractometry, which maps WM microstructure along anatomically corresponding segments of individual fiber bundles. Because scanner bias can vary along the tract, global voxel- or ROI-based corrections may fail to adequately remove localized site effects and preserve biologically meaningful along-tract patterns. To address this, we developed AlongTractComBat, a tract-specific microstructural harmonization framework that extends the Bundle Analytics (BUAN) tractometry pipeline by harmonizing directly on anatomically corresponding tract segments. Using 100-segment along-tract profiles of Fractional Anisotropy and Mean Diffusivity extracted from major WM bundles, we compared unharmonized data from the San Diego State University Traveling Subjects dMRI Dataset (9 participants: 6F; aged: 22-55 years; scanned with both GE and Siemens using 2shell93dir protocol), conventional voxel-based ComBat harmonization applied to microstructural maps, and our tract-specific approach. Our analyses revealed substantial scanner-dependent variability in raw tract profiles. While voxel-based ComBat reduced some global differences, residual site-related biases remained along multiple tract segments. In contrast, AlongTractComBat substantially reduced scanner effects while preserving biologically meaningful spatial patterns, resulting in closely aligned microstructural profiles across acquisition sites. These findings show that harmonization performed directly within anatomically corresponding tract segments provides more effective correction of site-related variability than traditional voxel-based approaches. By enabling reliable integration of multi-site tractometry datasets, AlongTractComBat improves the sensitivity of WM analyses and facilitates robust biomarker discovery in clinical neuroscience.

KEYWORDS: *Human Neuroscience, Clinical Science, or Public Health; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering*

BundleShape: Quantifying white matter morphology using nonlinear bundle registration

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AUTHORS: D. Dasanayake, S. Amit, B. Chandio

Diffusion MRI (dMRI) tractometry has become a widely used framework for studying white matter (WM) alterations in neurological and psychiatric disorders. Most tractometry methods focus on microstructural measures, such as fractional anisotropy (FA) and mean diffusivity (MD), evaluated along WM pathways. While these metrics provide valuable information about tissue integrity, they do not directly measure tract morphology. WM bundles may undergo localized morphological changes during disease progression while conventional microstructural metrics exhibit only subtle changes, leaving key anatomical alterations undetected.

To address this limitation, we propose BundleShape, a novel framework for bundle shape analysis based on nonlinear streamline-based registration. Our method leverages BundleWarp, a recently developed bundle-specific nonlinear registration technique that aligns WM pathways through a smooth deformation field. We derive a new point-wise shape descriptor from this deformation field using the analytical Jacobian determinant. The Jacobian determinant quantifies local volume change, where values greater than one indicate expansion, values less than one indicate compression, and negative values indicate folding and therefore unreliable deformations. Because BundleWarp is formulated using Gaussian-kernel mappings, we derive the Jacobian analytically, providing exact estimates of local shape change without numerical approximation.

Furthermore, we systematically evaluated the influence of BundleWarp regularization on Jacobian behavior and applied the framework to dMRI data from the Parkinson's Progression Markers Initiative (PPMI), including 32 Parkinson's disease patients and 32 healthy controls, aged 39-61 years, 28F and 36M. Strong regularization yielded stable but uninformative deformations; weak regularization produced excessive folding. An intermediate regime preserved diffeomorphic behavior while capturing meaningful morphological variation. Under this setting, the Jacobian determinant localized tract-specific regions of expansion and compression, revealing shape differences that were not apparent from traditional microstructural measurements alone.

These results demonstrate that nonlinear registration-based shape analysis provides complementary information to conventional tractometry. By quantifying localized morphological alterations along WM pathways, the BundleShape framework offers a new avenue for studying disease-related WM remodeling.

KEYWORDS: *Computational Biology/Modelling; Informatics, Statistics, or Applied Mathematics; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools; Connectome*

A biological light sheet links cellular voltage to mesoscopic brain dynamics

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Membrane voltage is the fundamental currency of neural computation, yet imaging large neuronal populations in vivo remains limited by trade-offs among imaging speed, field of view, and optical sectioning. We overcome this challenge by encoding a biological light sheet in the brain: Selective Plane Expression (SPress) restricts fluorescent indicator expression to a user-defined, 20- μ m-thick plane, suppressing background at its source. Following a one-time two-photon photoactivation step, SPress enables standard widefield microscopes to capture high-contrast kilohertz voltage dynamics from hundreds of densely labeled neurons across millimeter-scale cortical sheets in vivo and, when configured vertically with micropisms, across cortical layers. These recordings reveal behavior-dependent, event-specific subthreshold waves that flexibly reorganize neuronal spike timing across cortical space and depth. By shifting optical sectioning from instrumentation to gene expression, SPress makes cellular-resolution voltage imaging accessible at mesoscopic scale.

KEYWORDS: *Monitor Neural Activity; Neuroimaging (invasive, non-invasive imaging)/Radiology; Genetics/Genomics*

Neuronal activity-related sodium (NARS) fMRI for imaging brain function beyond hemodynamic readouts

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Functional MRI has transformed brain mapping, but conventional fMRI signals rely primarily on hemodynamic responses that are temporally delayed and physiologically indirect. To develop a more direct MRI-based readout of neuronal activity, we established neuronal activity-related sodium functional MRI (NARS-fMRI) using ultrafast sodium-23 MRI at 14 T. This approach combines an implantable sodium RF coil with a reshuffled k-t gradient-echo acquisition to capture rapid sodium signal dynamics at 10 ms temporal resolution. In the forepaw somatosensory cortex (FP-S1) of rodents, NARS-fMRI detected a focal negative sodium signal change of approximately 2-3% that peaked within 10-30 ms after sensory stimulation. This response co-localized with conventional BOLD-fMRI activation but occurred on a timescale much closer to neuronal activity than to vascular hemodynamics. To validate the neuronal origin of the signal, we combined NARS-fMRI with simultaneous glutamate fiber photometry using iGluSnFR. Trial-by-trial analyses showed that larger glutamate transients were associated with larger sodium signal decreases, supporting a direct relationship between synaptic activity and the NARS-fMRI contrast. Our current work extends this framework by incorporating optogenetic stimulation to characterize circuit-specific dynamics of NARS-fMRI responses. We are also examining whether resting-state glutamate oscillations exhibit frequency-specific coupling to spontaneous NARS-fMRI signal fluctuations, which would provide a new strategy for mapping intrinsic neuronal dynamics beyond hemodynamic connectivity. Together, these studies advance NARS-fMRI as an emerging x-nuclei imaging approach for probing activity-related ionic dynamics and lay the foundation for bridging electrophysiology, optical neural recordings, and MRI-based brain mapping.

KEYWORDS: *Integrated Approaches; Monitor Neural Activity; Neural Networks (topology, etc.); Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Implantable Devices (probes, etc.)*

A reproducible neural-BOLD state motif links brain-state dynamics across modalities and species

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Brain activity is increasingly viewed as a sequence of recurring neural and hemodynamic states that evolve over time. Although such states have been identified in different recording modalities, it remains unclear whether recurrent neural and BOLD state organizations exhibit shared spatiotemporal dynamics.

We analyzed two independent simultaneous EEG-fMRI datasets in humans ($n = 28$ and 12 , respectively). To examine the biological basis of neural-BOLD correspondences, we further extended the analysis framework to simultaneous Ca^{2+} -fMRI recordings in mice. Human fMRI data were acquired at 3T ($\text{TR} = 2.0$ and 2.52 s) and preprocessed using fmrip, while EEG data underwent artifact removal in EEGLAB, ICA-based cleaning, and source localization. Mouse calcium-fMRI data included glial and Slc17a7 -positive excitatory-neuronal GCaMP-expressing animals. Calcium and BOLD data were registered to a shared Allen CCFv3 space, allowing comparison of state dynamics across corresponding cortical regions. Hidden Markov Models were independently fitted to each modality and to band-limited neural signals. We quantified temporal correspondence between cross-frequency neural-state co-expression and BOLD states using lagged co-occurrence analyses, circular-shift permutation testing, and cluster-based statistics. We assessed relationships between neural-BOLD states and neuromodulatory receptor systems and investigated analogous state correspondence in cell-type-specific calcium-fMRI recordings.

Neural and BOLD state repertoires exhibited limited spatiotemporal correspondence. However, we identified a reproducible cross-frequency neural-state co-expression that selectively co-occurred with a single BOLD state characterized by prominent negative engagement of the frontoparietal and default mode networks. This BOLD state exhibited increased occurrence probability around co-expression onset and significant temporal coupling. Components of the co-occurring state exhibited significant associations with the neuromodulatory receptor systems. Preliminary calcium-fMRI analyses revealed comparable state correspondence in glial calcium recordings, motivating ongoing investigation of the cellular basis of neural-BOLD state coupling.

Overall, these results identify a biologically distinct neural-BOLD state and suggest that interactions among neural, neuromodulatory, and neurovascular processes may contribute to correspondence between brain-state dynamics across modalities and species.

KEYWORDS: *Computational Biology/Modelling; Electrophysiology; Informatics, Statistics, or Applied Mathematics; Integrated Approaches; Neuroimaging (invasive, non-invasive imaging)/Radiology; Neural Networks (topology, etc.)*

Slice-set network with residual bias correction for brain age prediction

PRESENTER: **S. Ghosh**

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Predicting an individual's brain age from T1-weighted structural MRI has emerged as a clinically meaningful biomarker for neurological health. A persistent obstacle is a systematic age-related prediction bias—regression to the mean—that causes all trained models to overestimate the age of young subjects and underestimate that of old ones, distorting the clinical utility of the Predicted Age Difference (PAD). This paper addresses both the accuracy and the bias problems through a two-phase framework. We propose a 2.5-D Slice-Set Network that treats each MRI volume as an ordered set of 32 axial slices, encodes them in parallel with a shared, partially fine-tuned ResNet-34 backbone, and fuses the slice embeddings via a 4-head temperature-scaled attention aggregator. Evaluated on 113 cognitively normal subjects from OASIS-1, the model achieves $\text{MAE}=5.62$ yr., $R^2 \approx 0.712$, and $r \approx 0.96$, substantially outperforming three 3D-CNN baselines. Attention-weight visualization and Grad-CAM heatmaps confirm that predictions are grounded in established aging biomarkers: the lateral ventricles, hippocampus, cortical sulci, and deep grey-matter nuclei. Further, we introduce the **Age-Adaptive Residual Bias Correction (AARBC)** module, a closed-form post-hoc corrector that models the systematic PAD trend as a Gaussian-envelope-weighted function of the raw prediction, and pair it with a Soft-Target Huber Loss that replaces hard integer labels with Gaussian-smoothed distributions. Together these reduce the test-set MAE to 4.62 yr, improve R^2 to 0.815, and flatten the PAD-vs-age slope by 79.8%. Validation on a large-scale cohort of 5,000 ADNI subjects confirms generalizability, yielding $\text{MAE} \approx 2.15$ yr and $R^2 \approx 0.892$.

KEYWORDS: *Connectome; Informatics, Statistics, or Applied Mathematics; Neuroimaging (invasive, non-invasive imaging)/Radiology; Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

State dependence of stimulus representation and paradoxical choice signals in multisensory cortex

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Self-motion perception relies on dynamic integration of visual and vestibular signals, unfolding in distributed fashion across a network of multisensory cortical areas. We aim to understand how different nodes in this network—here, the medial superior temporal (MST) and visual posterior sylvian (VPS) areas—contribute to the speed, accuracy, and confidence of self-motion decisions. We trained rhesus monkeys to perform a reaction-time (RT) heading discrimination task based on optic flow and/or inertial motion cues delivered with a flight-simulator apparatus. Animals reported their self-motion direction relative to straight ahead using a saccadic eye movement (left or right) as soon as they were ready, followed by a binary confidence rating (post-decision wager) with a second saccade to a high or low target. Neural recordings were obtained from areas MST and VPS using 32-channel linear arrays (N=738 units in monkey 1) or Neuropixels NHP 1.0 probes (N=1,274 units in monkey 2). At the population level, demixed PCA revealed separable stimulus- and choice-selective subspaces in both areas throughout decision formation, although linear decoding failed to achieve high accuracy prior to ~200 ms before the choice saccade. Indeed, within the time frame of individual decisions, single-neuron tuning for heading was surprisingly poor, weaker than during a passive fixation task (controlling for stimulus duration) and ~10-fold higher than psychophysical thresholds. Partial correlation analysis showed that this apparent weakness is at least partly driven by a top-down choice signal that is paradoxically misaligned with stimulus tuning. The results suggest that a speeded decision context (and/or confidence assay) drives multisensory cortices into a distinct regime characterized by a complex mixture of sensory, decision, and possibly learning-related signals, prompting a revision of leading circuit models.

KEYWORDS: *Computational Biology/Modelling; Electrophysiology; Neural Recording & Modulation; Behavioral Sciences/Psychology*

Direct reconstruction of DC and low-frequency cortical conductivity from large-scale electron microscopy data

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Electrical conductivity of cortical gray matter fundamentally determines the magnitude and spatial distribution of electric fields generated by brain stimulation and intrinsic neuronal activity measured with M/EEG and intracortical recordings. Reported macroscopic values span more than a threefold range, a discrepancy that undermines computational model fidelity and has left unanswered a foundational question: does this variability reflect measurement artifact or genuine structural heterogeneity?

We introduce a multiscale computational framework that derives mesoscale conductivity maps at 50- μm resolution directly from petascale segmented electron microscopy data (MICrONS Minnie65 mouse visual cortex). The volume is subdivided into 1,224 cubes, each encompassing ~ 40 million membrane facets, with conductivity tensors estimated via the quasistatic boundary element fast multipole method. This enables, for the first time, spatially resolved conductivity mapping at subcortical-column scale. Based on the assumptions of the present model, the results are expected to be valid at DC and for frequencies below approximately 1 kHz.

Spatially averaged conductivities across the cortex (L2/L3:0.34, L4:0.38, L5:0.42S/m) align closely with established microelectrode-derived measurements from rat somatosensory cortex (0.32, 0.33, 0.35S/m, respectively) and fall within the min-max block range across all sampled layers, validating the framework. Critically, the spatially resolved maps reveal pronounced granularity at 50-100 μm scales with significant radial and tangential anisotropy. These findings provide direct structural evidence that mesoscale conductivity heterogeneity is an intrinsic property of cortical tissue.

KEYWORDS: *Circuit Diagrams; Computational Biology/Modelling; Electrophysiology; Human Neuroscience, Clinical Science, or Public Health; Neural Networks (topology, etc.); Physics or Microscopy/Optics*

Ingestible H₂S monitoring for decoding the gut-microbiome-brain axis

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The next frontier of neuroscience lies beyond the brain itself. Increasing evidence suggests that the gut-microbiome-brain axis plays a central role in neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease (PD), and Huntington's disease. Yet our understanding of these interactions remains limited because the gastrointestinal (GI) tract is largely inaccessible, preventing measurement of the biochemical processes that may initiate or accelerate neurological disease. In particular, intestinal gases represent an unexplored signaling modality that may mediate communication between the gut, immune system, and central nervous system. Technologies that directly measure these gaseous biomarkers in vivo are essential for uncovering new mechanisms of neurodegeneration and inventing future strategies for diagnosis and intervention.

Our research focuses on minimally invasive technologies, specifically autonomous ingestible capsules capable of directly measuring biomarkers within the gut. Among these, hydrogen sulfide (H₂S) has emerged as a compelling target for PD because it exhibits a dual role in neurodegeneration: Reduced H₂S signaling in the brain contributes to neuronal dysfunction, while excess production by the gut microbiome may promote intestinal inflammation and disease progression. H₂S is produced by both intestinal epithelial cells and sulfate-reducing bacteria (SRB) and regulates mucosal signaling, immune responses, vascular tone, and host-microbe communication. Despite its biological importance, the spatial and temporal dynamics of H₂S within the GI tract remain largely unknown because no technology has enabled real-time intraluminal measurements.

To address this challenge, we developed the first ingestible capsule (ø 14 x 34 mm) equipped with a conductive Nafion-coated electrochemical sensor to wirelessly detect trace H₂S concentrations (0.21 to 4.5 ppm) under humid GI conditions. The system exhibits excellent selectivity against interferent gases, including hydrogen, methane, and carbon dioxide. We are developing a next-generation platform capable of quantifying both gaseous H₂S and dissolved sulfide species, while maintaining stable operation in the GI environment. Ultimately, these technologies may one day provide insights into mechanisms of gut-brain communication regarding the origins of PD and enable closed-loop intervention before irreversible neurodegeneration occurs.

KEYWORDS: *Implantable Devices (probes, etc.); Integrated Approaches; Software (analysis, etc.) and Engineering*

Localized oral drug delivery for gut-microbiome-brain axis modulation

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The gut-microbiome-brain axis plays a significant role on the progression of neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases. Modulation of the axis to treat these diseases can be achieved by targeting drugs towards the intestinal barrier, the blood brain barrier, or the meninges. Among these locations, the intestinal barrier is the most accessible. Moreover, neurodegenerative diseases are frequently associated with gut dysbiosis, leading to spatially heterogeneous disruption of the intestinal barrier. As a result, therapeutic strategies aimed at repairing the intestinal barrier have emerged. These strategies include reducing inflammation and promoting the expression of tight junction proteins or cytokines to improve barrier integrity and function.

Localized drug delivery provides a way to selectively target spatially heterogeneous barrier disruptions, potentially reducing systemic drug dosage and side effects. Our team has developed an ingestible device that can deliver drugs on-demand with multiple cantilever actuators. The strained cantilever beams act as springs that can drive the penetration of drug-loaded microneedles into afflicted areas. Multiple cantilevers onboard the device enable codelivery of different drugs without the need of coformulation. Consequently, the ingestible device transforms our capacity to control the type of drug and location at which it is delivered, providing a powerful platform for investigating the effect of therapeutic interventions on gut-microbiome-brain axis modulation.

KEYWORDS: *Interventional Tools*

Decoding state transitions in bipolar disorder: A machine-learning approach to mapping behavioral architecture

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Quantifying the fluctuating states of bipolar disorder (BD)—from manic reward-seeking to depressive avolition—remains a central challenge. Traditional metrics, such as simple locomotor activity, lack the granularity to capture the complex cognitive and strategic shifts characteristic of mood-state transitions. To bridge this gap, we developed a self-supervised Bidirectional Long Short-Term Memory (Bi-LSTM) framework. This machine-learning (ML) integrates high-resolution pose-derived features from mice with task-relevant behavioral timestamps, allowing it to decode hidden behavioral states invisible to human observers.

We validated this framework by modulating the endocannabinoid system, a signaling pathway heavily implicated in BD. The Bi-LSTM identified two primary domains: goal-directed reward-seeking (manic phenotype) and self-directed grooming (depressive/stress phenotype) in mice subjected to structured reinforcement tasks. We found that a dose of AM6527, a neutral cannabinoid receptor antagonist, triggered a significant reduction in reward-seeking alongside a sharp increase in grooming behavior. This transition mirrors manic-to-depressive transitions or “mixed featured episodes,” where purposed energy is replaced by repetitive, non-productive actions.

Our results demonstrate that our Bi-LSTM model can identify sub-second “digital biomarkers” for psychiatric symptoms. This ML-assisted high-resolution behavioral mapping offers a translational path toward understanding the temporal architecture of BD behaviors and guiding the development of precise pharmacological interventions.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Software (analysis, etc.) and Engineering*

Characterizing visual neuron function using computational barcodes

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The visual system processes stimuli across large neuronal populations distributed across cortical areas, making it challenging to discern the role of individual neurons in what amounts to global computation. The role of visual neurons is classically viewed as feature detectors: with neural activity signaling the presence of a preferred feature, whether concrete (an oriented bar) or more abstract (motion energy). Here, we explore an alternative perspective of visual neuron function based on computation itself using computational barcodes. Computational barcodes are weight vectors derived from a deep neural network (DNN) trained to predict neuron responses across large-scale recordings. The DNN's "computational core" provides a basis of hierarchical computation, shared by the neuron population, where individual barcodes indicate the computations each neuron requires to explain its stimulus-to-response transformation. By looking across the population of barcodes, we are able to define a "barcode space" with a geometry that places similar and related computations closer together and distinct pathways further apart. Here, we first demonstrate the validity of this approach using a large "ground truth" dataset generated by a large-scale spiking neural network model of primary visual cortex (V1) with biologically realistic connectivity and cell types. Because the computations of all neurons are known in this simulation, we can directly validate the extent to which barcodes find ground truth computational distinction with DNNs trained on this data. We then hone this approach by manipulating the architecture of the DNN using biological constraints. These include a "bottleneck" in the first layer of the network, spatial- and orientation-convolutional units across layers, and explicit temporal delays distributed across the network at higher temporal resolution. We find that these changes not only improve the predictive power of the model but also sharpen the computational distinctions within the V1 population using barcodes. Together, these results establish DNN-derived computational barcodes as a promising framework for understanding the role of individual V1 neurons, offering a holistic view of neural function grounded in computation.

KEYWORDS: *Neural Recording & Modulation; Computational Biology/Modelling*

White matter integrity and nodal plasticity following unilateral sensory denervation

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Limb amputation and peripheral nerve injuries present long-term challenges affecting millions worldwide, including a significant proportion of military service members. These injuries frequently result in persistent sensory dysfunction, which impairs functional recovery. Non-invasive neuroimaging studies in individuals with limb loss consistently report increased bilateral sensory/motor cortex activity (S1/M1) together with reduced white matter (WM) integrity in the corpus callosum (CC). However, the cellular and circuit-level mechanisms linking sensory denervation to circuit hyperexcitability and WM disruption remain unclear. To address this, we use the infraorbital nerve transection (IONX) mouse model, which permanently removes sensation from one set of whiskers, to examine adaptations within callosal circuits of primary somatosensory barrel cortex (S1BC). Unilateral IONX produces the cortical hyperexcitability and reduced WM integrity similar to that observed after limb loss. Because WM integrity is comprised of proper myelin formation and nodal distributions along healthy axons, we hypothesized that chronic hyperexcitability in S1BC leads to dysregulated neuronal and axonal health following denervation. We characterized the gene expression, electrophysiological profile, and nodal distribution on the axons of callosally projecting neurons at acute and chronic timepoints after IONX. These neurons expressed high levels of stress-associated genes (*Ddit3*) at both timepoints after IONX, while the expression of myelin-associated genes (*Plp1*) was reduced at chronic timepoint. Electrophysiological recordings revealed that these neurons remain hyperexcitable up to two months after IONX, with blunted and less dynamic action potential kinetics. In addition, we observed structural remodeling of nodes of Ranvier: nodal gap length (*Nav1.6*) and overall paranode-node-paranode length (*Caspr-Nav-Caspr*) were reduced 2 weeks after denervation, indicating nodal plasticity that may alter axonal conduction. Together, these findings demonstrate that unilateral denervation induces coordinated neuronal and WM integrity functional adaptations within callosal circuits. Disruption of interhemispheric connectivity may contribute to persistent cortical hyperexcitability following injury and represents a potential target for improving recovery after traumatic sensory loss.

KEYWORDS: *Electrophysiology; Molecular/Cellular Neuroscience; Monitor Neural Activity; Neuroimaging (invasive, non-invasive imaging)/Radiology; Synaptic Plasticity; Integrated Approaches*

Regulation of neuron identity by UNC-42/Prop1 cooperative binding

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A major outstanding question in homeobox transcription factor-mediated gene expression regulation is how gene regulatory specificity is achieved when all homeobox transcription factors bind the same consensus motif-TAAT. For a subset of homeobox transcription factors this is partially achieved through cooperatively binding DNA as a homodimer. Several Paired-like class homeobox transcription factors bind as a homodimer to P3 sites with a consensus motif of TAATNNNATTA. The Gebelein lab has identified eleven rules for identities of homeodomain residues that determine whether a Paired-like homeobox transcription factor can bind the P3 motif as a homodimer. Two of these rules are that homeodomain residue 28 cannot be an arginine and that residue 44 cannot be a glutamine. Conversion of either residue to the incompatible amino acid is predicted to result in severe loss of cooperative binding, but neither mutation is predicted to affect monomer binding to DNA. In *Caenorhabditis elegans*, one of the top Paired-like homeobox transcription factors predicted to bind the P3 site as a homodimer is UNC-42/Prop1. *unc-42* has been well-studied as a terminal selector for a set of interconnected neurons in the *C. elegans* nervous system. We are studying the role of UNC-42 cooperative binding to the P3 site in regulating neuron identity. We have used CRISPR-Cas9 to mutate *unc-42*, converting either homeodomain isoleucine 28 to arginine or arginine 44 to glutamine. Both of these residues are conserved from *C. elegans* UNC-42 to human PROP1. Mutating arginine 44 to glutamine recapitulates a human disease-associated allele. We are examining the effects of these mutant alleles on the expression of a set of neuron identity genes using CRISPR-inserted, nuclearly-localized transcriptional reporters co-expressed with these genes. So far, we have found that *unc-6*/Netrin expression is affected by loss of *unc-42* cooperative binding in a subset of neurons affected by a null allele of *unc-42*. This effect is partially recapitulated in cis-regulatory mutant alleles of *unc-6* that disrupt P3-like sites predicted to be bound by UNC-42. These results indicate that in a subset of neurons *unc-6* is regulated in part by UNC-42 cooperatively binding these P3-like sites.

KEYWORDS: *Cell Type/Interactions; Genetics/Genomics; Molecular/Cellular Neuroscience*

SLUGBOT V2: An Aplysia-inspired robotic grasper with improved anatomical accuracy

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The sea slug, *Aplysia californica*, is a well-studied animal model in neuroscience. Its tractable neural system allows for studies of musculature and neural circuitry. In particular, the feeding behavior performed by the muscular buccal mass, located in the animal's head, serves as a model of adaptable control and multifunctional grasping behavior. A previous Aplysia-inspired robot, the Slug-Like Uniaxial Grasping roBOT (SLUGBOT), qualitatively captured the animal's feeding behavior. However, its morphology was not fully accurate to the animal. This work presents SLUGBOT V2, a second iteration of the previous Aplysia-inspired robot. In the new version, we reduced the robot's size and modified the robot's actuators to better capture Aplysia's morphology. Furthermore, we redesigned the grasper protractor (I2) muscle to better capture the muscle properties in Aplysia. The redesigned Aplysia-inspired robot reproduces key kinematics during swallowing that more closely resemble the animal, a significant improvement over SLUGBOT V1. This robot can serve as an Aplysia testbed that will allow scientists and roboticists to investigate specific neuromechanical hypotheses, and to develop neural-based controllers of soft robots.

KEYWORDS: *Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering*

Age-dependent changes in brain vasculature in the bat (*Carollia perspicillata*)

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Changes in systemic vasculature occur with age, frequently in association with chronic disease such as hypertension or diabetes. Some changes, such as vessel elasticity, wall thickness, endothelial damage have a direct impact on blood delivery to tissues. Systemic consequences of micro- and macrovascular changes can be severe and can compound vascular derangements.

We are developing a model for studying the progression and mechanism of age-dependent changes in brain vasculature based on Seba's short-tailed fruit bat, *Carollia perspicillata*. Bat species are known for their longevity and several species do well in captivity—offering a platform to study elderly animals free from predators.

We have identified changes in the expression of alpha smooth muscle actin (a-SMA) in *Carollia* brain vasculature. a-SMA is a marker of arterial and arteriolar vessel smooth muscle.

Vascular changes with age may contribute to neurodegeneration observed in multiple *Carollia* brain regions and derangements of neurovascular coupling. An accurate timeline for vascular changes based on age (in progress) can be correlated with and serve as a potential therapeutic target to prevent age-dependent neuronal losses.

KEYWORDS: *Integrated Approaches; Molecular/Cellular Neuroscience*

DACx: An energy-based framework for building “digital twins” of the auditory cortex

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The mammalian auditory cortex processes input in real-time with unparalleled temporal resolution, detecting millisecond-scale changes in sound frequency and power. This temporal precision facilitates a range of critical cognitive functions, from maintaining rhythmic movements such as walking to decoding speech against background noise. A key obstacle to understanding the mechanisms behind this precision is the lack of a model which can integrate data on macro-level behaviors, meso-scale circuit motifs, and low-level molecular pathways. DACx, or digital auditory cortex, will fill this gap. DACx is a framework for building “digital twins” of the auditory cortex consisting of hundreds of thousands of simulated spiking neurons. DACx provides a protocol for building complex three-dimensional and spatially extended circuit topologies from simple motifs specified in terms of cortical layers, cortical columns, and cortical cell types. The spiking activity of the resulting network, connecting auditory input to behavioral output, is modeled via a biologically grounded analysis of cellular and network energy usage. This “growth transform” approach, as it’s called, enables using backpropagation-less learning algorithms to infer the relationship between (1) input-output associations between sound stimuli and network behavior, (2) network topology and cell-type composition, and (3) molecularly defined synaptic and membrane electrical properties. DACx will allow researchers to infer any one of these three from the other two, e.g., inferring cortical responses to sound from network topology and synaptic electrical properties. Thus, DACx will enable bringing together various kinds of data, including population-level neuron recordings (e.g., Neuropixel, two-photon calcium imaging), single-cell patch-clamp, traditional stain-based histology, and modern transcriptomics and proteomics (e.g., patch-Seq and various spatial imaging technologies). The upshot is not only deeper insights, but an ability to predict outcomes at one level from an intervention at another. For example, DACx will allow for making precise predictions about how network responses to different classes of sound stimuli will change in response to genetic or pharmacological interventions. Thus, DACx will allow not only for deeper theoretical insight, but will also accelerate the search for treatments to hearing loss.

KEYWORDS: *Behavioral Sciences/Psychology; Circuit Diagrams; Computational Biology/Modelling; Connectome; Molecular/Cellular Neuroscience; Neural Networks (topology, etc.)*

Profiling potential new pain therapeutics within the NIH HEAL Initiative® Preclinical Screening Platform for Pain (PSPP) program

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NINDS, NIH

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The Preclinical Screening Platform for Pain (PSPP) program was developed as part of the National Institutes of Health Helping to End Addiction Long Term InitiativeSM, to accelerate the discovery and development of non-opioid, non-addictive pain therapeutics.

The program accepts small molecules, biologics, natural products, and devices from industry, academic, or government asset owners for evaluation, at no cost to the asset owner. Researchers from academic institutions, industry, including small businesses, and government institutions, are eligible to submit novel non-opioid, non-addictive, small molecules, biologics, natural products, or devices ("assets") for evaluation of efficacy in pain-related endpoints. The PSPP program is not grant-based but operates through a contract mechanism with no set receipt dates.

PSPP has set up a preclinical paradigm for evaluating potential novel therapeutics for pain in collaboration with PsychoGenics, Inc. (Paramus, NJ, USA). The PSPP program uses a stepwise approach to evaluate experimental assets. Initial asset evaluation uses in vitro functional human-based screens to rule out activity at known targets associated with risk for abuse liability or safety concerns. Evaluation is then performed in pharmacokinetic studies and to understand potential neurological side effects. Following these studies, assessment for efficacy in pain-related models, using two endpoints per model, is performed. Assets with demonstrated efficacy are evaluated for abuse liability in vivo, using either intravenous self-administration or conditioned place preference. The platform is validated by evaluating clinically used drugs and negative controls. Currently, the program also continues to evaluate other potential human-based approaches, including new approach methodologies (NAMS), to incorporate appropriate paradigms into the profiling of novel assets for pain. The program will be highlighted with examples of efficacy data obtained with clinical compounds.

In summary, the PSPP program offers a preclinical evaluation platform for validating novel assets for efficacy in pain, including headache. PSPP has developed a public-facing website featuring information on evaluation within the program, including methods for assays, models, and endpoints, and highlighting data generated with clinically used drugs and CNS active compounds. The ability to evaluate novel assets from asset owners will be highlighted.

KEYWORDS: *Behavioral Sciences/Psychology; Human Neuroscience, Clinical Science, or Public Health; Synaptic Plasticity*

Tardigrades use Neuroligin-4 to fortify their nervous system, rendering them resilient to large-scale anisotropic volumetric changes during anoxic and hyperosmotic stress responses

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Extremotolerance, the ability to survive environmental extremes, is a rare convergently evolved adaptation found across all kingdoms of life. A premier example is found in tardigrades, which are renowned for their broad extremotolerant repertoire, including resistance to ~1,000 times the human lethal dose of ionizing radiation, hyperosmotic stress, near-complete desiccation, and near-complete anoxia. The tardigrade nervous system consists of an estimated few hundred neurons, yet supports a diverse behavioral repertoire, including sensory-motor navigation, associative learning, and complex gaits. We assessed the anatomical, behavioral, and molecular changes that the tardigrade nervous system undergoes during transitions into and recovery from extreme osmotic (500 mOsmol, 2 hours), anoxic (0.05 ppm D.O., 16 hours), and freezing (-20°C, 1 hour) stressors. Via immunohistochemical analysis of synapsin-stained animals, we observed a nearly twofold expansion in the anisotropic volume of the central brain and ventral nerve ganglia under anoxic conditions. A similar magnitude of volumetric expansion was also observed during recovery from osmotic stress. Beta-tubulin staining revealed contraction, folding, and coiling of interganglion connectives in the osmotic stress state, and their robust extension under anoxic stress. Despite these large-scale neuroanatomical changes, animals recovered to baseline velocity and locomotion within minutes, as monitored by our new behavioral tracking module. Furthermore, complex motor tasks such as self-righting were unaffected in both rate and motor program, as compared to pre-stress and unstressed controls. These observations suggest that these anatomical alterations and the subsequent tensile and shear forces arising during stress exposure have minimal impact on tardigrade nervous system function. To assess the molecular mechanism of this resilience, we identified synaptic and synaptogenic proteins that are highly upregulated in response to stress and found that RNAi knockdown of Neuroligin-4 significantly increased death rates and resulted in severe, prolonged motor dysfunction in animals that did survive. Together, our data provide the first evidence that the tardigrade nervous system is dramatically remodeled during transitions into cryptobiotic states, in part by using Neuroligin-4-dependent fortification to prevent significant loss of neural circuit function and ultimately enabling rapid recovery from extreme stressors.

KEYWORDS: *Developmental/Systems Biology; Molecular/Cellular Neuroscience; Synaptic Plasticity*

Plant-derived volatiles modulate chemosensory-guided avoidance in an insect model

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Animals continuously evaluate chemical information in their environment and convert sensory cues into adaptive behavioral decisions. The house cricket, *Acheta domesticus*, provides an accessible neuroethological model for studying how volatile plant compounds influence chemosensory-guided navigation, avoidance, and exploratory behavior. Although this species is found globally and is often considered an agricultural and stored-product pest, its behavioral responses to naturally occurring odorants also offer an opportunity to investigate how insect nervous systems encode complex chemical stimuli and translate them into approach or avoidance. In this study, we examined the behavioral effects of 27 plant-derived essential oils on *A. domesticus* using an open-arena entry assay. Crickets were introduced into an arena that allowed unrestricted movement, and a transparent plastic bottle containing an essential oil treatment was placed within the arena to provide a localized volatile cue. After a predetermined observation period, the number of crickets that entered the bottle was recorded, and percent entry was calculated relative to the total number of crickets in the arena. Reduced entry was interpreted as avoidance behavior, providing a quantitative behavioral readout of repellent potency.

The essential oils produced distinct behavioral profiles, ranging from weak or no repellency to strong avoidance. Nearly half of the tested essential oils elicited strong repellent behavior, whereas four essential oils and two synthetic repellents produced no significant repellent response. Four highly effective essential oils, peppermint, rosemary, cinnamon, and lemongrass, were subsequently tested across multiple concentrations and produced clear dose-dependent avoidance responses. These findings suggest that plant-derived volatile compounds can modulate sensory-guided decision-making in *A. domesticus* in a concentration-dependent manner. Beyond their potential use in environmentally sustainable pest management, these results provide a foundation for future brain-focused studies examining how insect olfactory systems detect essential oil constituents, how neural circuits assign valence to chemical cues, and how sensory information is transformed into avoidance behavior. Integrating behavioral assays with receptor-level, neural activity, and circuit-mapping approaches may help reveal broader principles of olfactory coding and chemically guided action selection across insects.

KEYWORDS: *Behavioral Sciences/Psychology; Chemistry; Developmental/Systems Biology; Human Neuroscience, Clinical Science, or Public Health; Integrated Approaches; Neural Recording & Modulation*

Integrative analysis of adaptive information processing and learning-dependent circuit reorganization in the auditory system

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The barn owl auditory localization pathway provides a powerful model for studying neuronal computation, population coding, and learning-dependent circuit reorganization. This project combines electrophysiology, connectomics, and computational modeling to investigate mechanisms underlying auditory space-map formation and adaptive plasticity in the owl midbrain. Specifically, this collaborative project focuses on space specific neurons (SSN) in the owl inferior colliculus. These neurons integrate auditory inputs across frequencies and are tuned by visual input during development to form an optimal topographic representation of auditory space. Based on previous work, we aim to bridge the gap between synapse-level reorganization, behaviorally relevant network functions, and learning-dependent tuning.

Large-scale whole-cell patch-clamp recordings from SSNs characterized synaptic integration and short-term plasticity across the map. Spatial patterns of synaptic facilitation were found to align with auditory tuning and binaural cue reliability, suggesting that developmental plasticity mechanisms may reflect expected sensory experience. Interestingly, facilitation was observed only under physiological calcium concentrations, whereas standard high-calcium recording conditions predominantly produced synaptic depression, indicating that standard approaches may obscure biologically relevant mechanisms.

To investigate local network organization of SSN inputs, three micro-connectomic datasets (volumetric EM) were generated from normal and prism-adapted owls. Reconstruction and analysis are ongoing. Data from the first volume already revealed diverse neuronal morphologies and extensive synaptic connectivity. We found a new form of “toric” dendritic spines with complex shapes and closed loops. A pipeline was developed for generating morphologically accurate neuronal models from volume reconstructions, including these toric spines, enabling data-constrained simulations. In parallel, a large-scale computational model of auditory input from the upstream pathway (approx. 15,000 neurons) reproduces experimentally observed response distributions.

Together, these results provide an integrated framework linking synaptic physiology, circuit architecture, population coding, and adaptive plasticity in the auditory system. Ongoing work will combine dense circuit reconstruction with data-driven computational models to test mechanisms of learning-dependent circuit reorganization.

KEYWORDS: *Connectome; Developmental/Systems Biology; Electrophysiology; Neural Networks (topology, etc.); Theory & Data Analysis Tools; Synaptic Plasticity*

Exercise improves motor coordination and alters brainstem neuronal excitability and excitatory input selectively in female mice

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Aerobic exercise boosts motor function across the lifespan and in the presence of motor disorders such as Parkinson's disease. Previous work using rodent models has revealed that changes exercise results in changes in multiple motor-related neural populations, including neurons impacted by PD such as the dopaminergic neurons of the substantia nigra pars compacta (SNc) and the cholinergic neurons of the pedunculopontine nucleus (PPN). However, there is a gap in our knowledge about how exercise alters the activity and intrinsic properties of these key neural populations. To address this question, we used the voluntary wheel running model in mice and performed behavioral analysis, ex vivo electrophysiology, and ex vivo optogenetics to determine the effect of one week of exercise on motor coordination and on intrinsic properties of SNc dopaminergic and PPN cholinergic neurons. We found surprising sex-specific effects of exercise: female mice who exercise exhibited enhanced rotarod performance, increased SNc neuron excitability, and increased spontaneous excitatory input to PPN cholinergic neurons, while male mice showed none of these effects. We also identified the lateral hypothalamus as a source of excitatory input to PPN cholinergic neurons that is potentiated by exercise in female mice. These results reveal exercise effects correlated across behavioral and cellular levels.

KEYWORDS: *Electrophysiology; Molecular/Cellular Neuroscience; Synaptic Plasticity*

Neuroanatomical and behavioral characterization of corticotropin releasing factor-expressing lateral habenula neurons in mice

PRESENTER: **E. Thomas**

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The lateral habenula (LHb) is a critical hub for value-based decision-making and stress-related behaviors. While the LHb is highly responsive to corticotropin-releasing factor (CRF), the specific sources of CRF inputs to this region have remained poorly defined. Here, we utilized high-resolution imaging, multiplexed RNAscope, and viral tracing to map CRF inputs to the LHb and discovered a novel, intrinsic subpopulation of LHb neurons expressing CRF (LHbCRF). Molecular characterization revealed that the majority of LHbCRF neurons are VGLUT2+, with a distinct rostral subpopulation co-expressing GAD2. Chemogenetic activation of LHbCRF neurons in both sexes did not alter conditioned place preference, locomotion, or general anxiety-like behaviors. However, LHbCRF activation selectively shifted defensive strategies toward passive responses during a Visual Looming Shadow Test (VLST). This was characterized by increased action-locking frequency and duration across both sexes, while specifically prolonging escape latencies in males and post-escape shelter stays in females. Using optogenetics and electrophysiology, we further identified significant sex-dependent divergence in the physiological phenotype of these neurons. While individual LHbCRF neurons in males are more numerous and intrinsically excitable, female LHbCRF neurons form significantly stronger local excitatory synaptic connections. These findings establish the LHbCRF population as a novel, sexually dimorphic component of the LHb's heterogeneous circuit architecture that could contribute to bias towards defensive strategy selection of action-locking under threat and may underlie the sex-dependent variations in escape latency and post-escape shelter seeking observed during the VLST.

KEYWORDS: *Cell Type/Interactions; Electrophysiology; Molecular/Cellular Neuroscience; Neural Recording & Modulation*

A spiking sequence generator for polar trajectories on neuromorphic hardware

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Neuromorphic controllers for size, weight, and power-constrained systems require neural architectures that are both energy-efficient and interpretable at the level of system dynamics. However, existing approaches either rely on end-to-end trained spiking networks with limited interpretability, or on converted classical controllers that fail to fully exploit neuromorphic dynamics. We present a spiking neural network (SNN) architecture for generating polar trajectories, using a winner-take-all (WTA) architecture with accessory populations that induce controlled transitions in neural activity. We demonstrate tuning rules for these population dynamics, and utilize a form of shunting inhibition to enable independent control of direction, speed, and radius of the resulting polar trajectories. We implement the network on the SpiNNaker2 neuromorphic processor and demonstrate a two to three orders of magnitude reduction in wall-clock step time and three to four orders of magnitude reduction in energy expenditure when compared to conventional computing platforms.

KEYWORDS: *Circuit Diagrams; Computational Biology/Modelling; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*

Neuromodulation outcomes of restless leg syndrome: Closed-loop cord stimulation NO-RLS study

PRESENTER: **M. Holland**

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Restless legs syndrome (RLS) is a common sensorimotor neurologic disorder characterized by an overwhelming urge to move the legs, typically worsening in the evening and disrupting sleep. RLS affects an estimated 5-15% of the general population, is associated with impaired quality of life and cardiovascular morbidity, and remains difficult to treat. Current pharmacologic therapies, including dopamine agonists, alpha-2-delta ligands, and opioids, provide incomplete relief for many patients and may be limited by augmentation, tolerance, or adverse effects. Although RLS pathophysiology remains incompletely understood, converging evidence implicates altered iron metabolism, peripheral nerve and microvascular dysfunction, impaired spinal sensory gating, and cortical sensorimotor hyperexcitability.

Spinal cord stimulation (SCS) is an established neuromodulation therapy for chronic neuropathic pain. Our group reported the first-in-human evidence that SCS produced durable improvement in severe RLS symptoms for more than 2.5 years in a patient treated with SCS for chronic pain. Subsequent reports from independent groups suggest a reproducible therapeutic signal, but prior cases have largely involved patients with comorbid neuropathic pain rather than treatment-refractory primary RLS.

The NO-RLS Study is a single-center feasibility trial evaluating the safety, patient acceptance, and preliminary effectiveness of closed-loop SCS for treatment-refractory primary RLS using the FDA-approved Saluda Medical Evoke system. This device records evoked compound action potentials and adjusts stimulation in real time, enabling physiologically informed therapy during wakefulness and sleep. The study will assess changes in International RLS Study Group Rating Scale scores and electrophysiologic markers of spinal gating and cortical sensorimotor excitability.

KEYWORDS: *Electrophysiology; Implantable Devices (probes, etc.); Neural Recording & Modulation*

Rapid cortical motor learning from subcortical demonstration

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In mammals, neocortex plays a critical role in many forms of motor learning. The high dimensionality of the musculoskeletal system allows flexibility but poses significant challenges for efficient learning. A key computational insight is to exploit pre-existing motor patterns to simplify the learning problem, but whether and how neocortex can utilize similar principles for efficient learning remains an open question. To address this, we developed an active avoidance paradigm in which head-fixed mice “jump” by extending against a counterweighted platform. Naive mice use a pre-existing jump motor pattern to escape a cold platform and can rapidly learn to jump predictively to avoid the cold. Optogenetic inhibition of frontal cortex blocked active avoidance, but left reactive escape jumps intact. Brainwide recordings revealed that persistent, movement-null activity in prefrontal cortex was critical for avoidance and coupled through motor cortex to control predictive jumping. Remarkably, mice covertly learned active avoidance even without trial-and-error exploration of cortically-mediated jumps. We propose that subcortically-mediated movements can “demonstrate” successful motor patterns to enable efficient cortical learning.

KEYWORDS: *Electrophysiology; Neural Recording & Modulation; Behavioral Sciences/Psychology*

Sleep to forget: Active control of consolidation and forgetting by slow-wave sleep dynamics

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Sleep supports both the consolidation of new memories and the forgetting of others, but how the brain flexibly controls these outcomes remains poorly understood. Our past work showed that two types of sleep oscillations may play distinct, competing roles during slow-wave sleep (SWS): slow waves actively consolidate memory traces, whereas delta waves promote their weakening. Here we used a biophysical thalamocortical network model equipped with spike-timing-dependent plasticity to investigate the synaptic mechanisms underlying this dissociation. By manipulating the intrinsic Ca^{2+} dynamics of cortical pyramidal cells, we generated both slow and delta waves within a single network. A trained and consolidated memory trace was subjected to random interference during SWS from new episodic memory traces encoded by hippocampal ripples. The model recapitulated the optogenetic dissociation: blocking plasticity during slow waves degrades the memory, while blocking it during delta waves enhances consolidation. Mechanistically, the model reveals that the longer duration of slow-wave Up states provides a spontaneous memory reactivation phase that follows the interfering input, during which the trained memory is selectively reactivated and protected. In contrast, the shorter delta-wave Up states do not provide this reactivation phase, thus allowing memory forgetting. The model predicts that the balance between consolidation and forgetting can be flexibly regulated by the relative proportion of slow and delta waves during SWS. We further find that delta waves produce sparser synaptic memory representations than slow waves. Together, these results suggest that the natural mixture of slow and delta waves observed during physiological sleep may provide an optimal balance between preserving memories and increasing the sparseness and efficiency of their cortical representations.

KEYWORDS: *Behavioral Sciences/Psychology; Computational Biology/Modelling; Integrated Approaches; Neural Networks (topology, etc.); Synaptic Plasticity*

Find it, see it: Spatial transcriptomics discovery and visualization at the Brain Image Library

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The Brain Image Library (BIL) is the BRAIN Initiative's home for light microscopy data. NIH-funded and built for the community, BIL holds more than 6 petabytes across thousands of public brain datasets spanning 14 species, most of them large 3D whole-brain volumes imaged at cellular and subcellular resolution.

Spatially resolved omics has emerged as a powerful approach across the BRAIN Initiative, and BIL now holds a growing number of these datasets. They bring demands that go beyond traditional imaging. Datasets differ from platform to platform, each measuring hundreds to thousands of genes at once. Two barriers keep these rich datasets underused. The datasets of interest are hard to find, because search has to reach the genes a dataset measures and the labels that describe individual cells, not just dataset-level metadata. And they are hard to explore, because visualizing and interacting with the data demands computational expertise.

BIL is evolving to serve these needs, working along both axes. To make datasets easier to find, we are developing search that reaches inside each dataset, by gene, cell type, or brain region. We will surface the annotations that depositors provide, and for datasets that lack them, we will generate cell-type annotations from established reference taxonomies. Each label will carry its provenance, whether depositor-submitted or automatic. To make datasets easier to explore, we are integrating MERFISHEYES into BIL, a browser-based tool built specifically for this domain. It renders these data as interactive points, coloring individual cells and transcripts by cell type or marker expression, and lets users move smoothly across scales, from whole-brain overviews down to single cells, filtering by gene or cell type.

Together, these tools will lower the barriers to finding and exploring spatial transcriptomics data, letting any researcher locate the datasets they need and examine them without specialized computing of their own.

Microsystems scanners for high-speed, 3D addressable neural imaging in moving mice

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Miniaturized microscopes capable of high-speed, three-dimensional imaging in freely moving animals require compact scanning technologies that provide both large optical range-of-motion and flexible control of the imaging region. We are developing thin-film piezoelectric microsystems scanners for implantable multi-photon microendoscopes to enable high-speed, addressable neural imaging over a large three-dimensional field-of-view. In this work, we present a piezoelectric scanning micromirror designed to provide two-dimensional region-of-interest (ROI) access by combining quasi-static beam steering with high-speed resonant scanning. The micromirror uses thin-film lead-zirconate-titanate (PZT) actuators configured for independent bend-up and bend-down motion, enabling large quasi-static angular displacement for positioning the imaging region, while a separate resonant actuator provides rapid scanning within the selected ROI. Preliminary testing demonstrates quasi-static mechanical tilt of approximately 7.8° and resonant operation near 5.4 kHz with approximately 3° mechanical tilt. The device is designed to support addressable raster scanning, allowing detailed imaging at arbitrary locations within the full field-of-view while reducing the need for mechanically repositioned optical components. These capabilities complement our broader development of lateral and axial microsystems scanners for implantable 3D multi-photon microscopes. Integration of addressable lateral scanning with large-range axial focusing is expected to enable high-speed volumetric fluorescence imaging with user-selectable imaging regions in moving mice, supporting real-time investigation of neural activity during behavior.

KEYWORDS: *Implantable Devices (probes, etc.); Monitor Neural Activity; Neural Recording & Modulation; Neuroimaging (invasive, non-invasive imaging)/Radiology; Physics or Microscopy/Optics; Software (analysis, etc.) and Engineering*

The George Washington University Nanofabrication and Imaging Center: A multiscale electron microscopy resource for the neuroscience community

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The George Washington University Nanofabrication and Imaging Center (GWNIC) was established in 2016 as an expansion of the university's previous imaging core, enabled by substantial institutional, federal, and corporate investment. The resulting state-of-the-art nanoscale imaging facility, located in the heart of Washington, DC, was deliberately designed to meet neuroscience research needs: for more than 20 years, the core has served the DC Intellectual and Developmental Disabilities Research Center (IDDR) and the broader Mid-Atlantic neuroscience community. A defining feature is that GWNIC is led and staffed by active neuroscientists, and its instruments are integrated to enable correlative light-electron microscopy (CLEM) and precise co-registration across zoom levels within a single common coordinate frame. These capabilities are particularly well suited to high-throughput EM analysis, targeted localization of structures under study, and preservation of the broader connectomic context.

The EM portfolio spans four complementary approaches: large-field 2D backscatter SEM (bSEM) for millimeter-scale cytoarchitectural context at nanometer resolution; in situ mechanical serial-block-face imaging on the Teneo VolumeScope 2; focused-ion-beam milling on the Helios NanoLab 660; and 200 kV axial tomography on the Talos F200X. High-resolution acquisitions are co-registered to broader contextual image sets, enabling precise structure/function assessment. Molecular profiling is accessible through CLEM workflows and through post-embedding immunogold on silicon wafers, detected by large-field 2D bSEM either as up to 8-micron-scale sections or as arrayed serial sections for 3D reconstructions.

Acquired volumes are formatted for direct integration into the Brain Observatory Storage Service and Database (BossDB) through an ongoing collaborative effort, ensuring datasets produced at GWNIC are compatible with the standards and tools used across the wider BRAIN connectomics community.

GWNIC offers end-to-end project support—from sample preparation through segmentation-ready volumes or targeted training in individual workflow steps. An annual collaborative workshop provides an entry point for investigators new to volume EM. Selected use cases relevant to the BRAIN Initiative strategic roadmap will be presented on the poster.

KEYWORDS: *Cell Type/Interactions; Dissemination & Open Science/Education; Neural Networks (topology, etc.); Physics or Microscopy/Optics*

Gene code concept modernization and AI

PRESENTER: **M. Uppaluri**

GA Medicine

AUTHORS: M. Uppaluri

The 1-23 loop makes a person vertical on axis, mid 3 lines as grid makes magnetism seen as loops in action are magnetic loops on the person. This is unlike the usual concept of the 3 lines of spinal system from the brain and to the brain in axis having 2 loop links set to work in action. The horizontal aspect of the human makes the 3D imaging has to be set to self than to the general body axis in the diagnostic devices and methods for procedures through assessments that are used to study the links to go to planned treatments.

The old school of thought is Vitruvian Man, who is actively used in learning the concepts in education to train the mind on the brain building mechanism for the medical students, which, when used on the professional self to use that as explicit side in working aspect, will give scope to study the patients in hand, to reach the type of mind on living lines of their person form the basics towards solving mentally driven bodily needs in medical terminology, on the level of CNS and PNS forms that are to be corrected for the person in need, as it is the sole source of living that being the gene code to totality in the 1-23 loop. The concept still gets the focus into the eye through the vision get into the connected acoustic system to the HEENT in the fully linked 1 code gene makeup it combinedly makes out of disease to self.

The thinking living life of Leonardo da Vinci is on the relished classically, publicly known paintings from abstract to a concept merged living he had in his own mind more to his own other side, known to be more of a scientist than artist.

The genes on brain makeup when are seen merged to a single combo are different on the 1-23 loop function on their dominant level of coding in the organ specific way makes the core in this abstract.

The specific dominant-to-recessive loop failure to main gene that makes it to sick state is on the broken links to receptor setting issues into calling for correction. This needs in vivo to in situ made medical preparations through extract procedures, when not applied together clinically on the needed tandem lines on these line and circumstances cannot be generalized to all, mainly in diseases such as the Alzheimer's disease.

The focus is on "I am thinking this way in my life," to the front.

Linked forensics level is on the clock and limbs to the Frankenstein effect in position on distorted images it makes.

KEYWORDS: *Circuit Diagrams; Dissemination & Open Science/Education; Genetics/Genomics; Integrated Approaches; Interventional Tools; Electrophysiology*

Dense dynamics instrumentation for test-time adaptation of EEG foundation models

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Test-time adaptation (TTA) is a common deployment mode for EEG foundation models, where a pretrained model adapts online to each new subject from the unlabeled test stream alone. TTA optimizes proxy objectives (e.g., entropy minimization, normalization-statistic alignment) in place of a supervised loss and is correspondingly prone to collapse, in which predictions concentrate on a single class. A related concern is hyperparameter transfer, where under Maximal Update Parameterization (μP), a learning rate tuned on a small, narrow proxy model transfers without retuning to a wider target model. This only happens when μP is implemented correctly, which has to be checked empirically, but no existing EEG benchmark instruments either the per-step TTA trajectory or the parameterization health of the model under test. We integrate dynlab, a measurement layer for early-training dynamics, into Meta's NeuralBench (36 EEG tasks, 94 datasets, 14 models).

Under TTA the whole run is the early regime (i.e., one gradient step per test batch with a single pass over the stream). dynlab registers one callback on the benchmark's Lightning Trainer, and logs per step predictive entropy, predicted-class marginal skew, drift of normalization-layer running statistics from their source-domain values, proxy-loss gradient norm, and parameter displacement from initialization. On a fixed probe batch it adds centered kernel alignment (CKA) to the pretrained representation, activation effective rank, and the top Hessian eigenvalues (loss sharpness). It also runs μP coordinate checks: instantiating the model at several widths for under 20 steps and confirming that per-layer activation magnitudes and their effective updates stay width-invariant, which is the condition under which a tuned learning rate transfers across width. All outputs serialize to Parquet, segregated from NeuralBench's test-split metrics.

dynlab integration governs dynamics-relevant axes (optimizer, learning rate, batch size, seed), while we use NeuralBench's architecture, data, and evaluation pipeline. We compare zero-shot inference against TTA modules we integrated into NeuralBench (TENT, TTT, ActMAD) on REVE, LaBraM, and MOMENT variants across EEG paradigms and subject-shift conditions. Across these, μP coordinate-check violations at initialization flag models whose TTA trajectories destabilize, and predictive-entropy velocity over the first few batches separates successful adaptation from eventual collapse.

KEYWORDS: *Dissemination & Open Science/Education; Informatics, Statistics, or Applied Mathematics; Neural Networks (topology, etc.); Software (analysis, etc.) and Engineering; Theory & Data Analysis Tools*