Abstracts

Oral presentations

Transcranial photobiomodulation for mood and cognitive disorders

Dan V. Iosifescu

Transcranial photobiomodulation (t-PBM) with near-infrared light penetrates into the cerebral cortex and is absorbed by the mitochondrial enzyme cytochrome c oxidase, stimulating the mitochondrial respiratory chain and leading to increased ATP production. t-PBM also significantly increases cerebral blood flow and oxygenation. Antidepressant effects and pro-cognitive effects of t-PBM have been reported in animal models and in humans.

Dr. Iosifescu will present data on the effects of t-PBM in several neuropsychiatric disorders. Most of these studies have been conducted at NKI. In a recent study in patients with major depressive disorder (MDD), different parameter combinations of t-PBM resulted in divergent effects on cerebral hemodynamics (measured with fMRI BOLD) and on clinical symptoms of depression. He will additionally present the effects of several doses of t-PBM on brain temperature (measured with 1H-MRS chemical shift). Dr. Iosifescu will also present data on the effects of t-PBM in early stages of Alzheimer's' disease, including from a recently completed large study. In the same subjects, the fractional amplitude of low-frequency fluctuation (fALFF) in the fMRI BOLD signal tracked metabolic responsiveness to tPBM, with lower baseline metabolism predicting larger neural modulation.

In aggregate, these data support the role of t-PBM as a novel neuromodulation technique with unique biological and clinical effects in neuropsychiatric disorders. Moreover, imaging biomarkers integrated with the clinical data can serve to establish dose-dependent neural effects and can guide the development of more precise, mechanism-based interventions such as t-PBM.

Treatment resistance removes the differential effects of dopamine binding levels on speech patterns in schizophrenia

Jean-Pierre Lindenmayer, Anzalee Khan, Beverly Insel, Vikram Ramanarayanan, Hardik Kothare, Michael Neuman, Danyah Nadim, Rachael Mishkind

Aim: Antipsychotics differ in their dopamine D2 receptor (D2R) affinity, with first-generation agents such as haloperidol generally exhibiting high affinity, and most second-generation agents showing lower affinity. Prior research suggests that high D2R affinity antipsychotics are associated with greater negative language disturbances, particularly increased speech pausing compared with lower affinity drugs, in patients who respond to treatment. The impact of D2R affinity on speech patterns in treatment-resistant schizophrenia (TRS) remains unclear. The present study examines this differential effect

using digitally recorded speech during a standardized, avatar-driven short interview in a large sample of patients with TRS and controls. Method: 67 participants with TRS and 63 healthy controls (HC) completed two standardized, 10-minute avatar-driven interviews on the Modality AI digital platform. 8 acoustic speech measured were retained for analysis. TRS participants were categorized based on the D2 receptor (D2R) occupancy of their primary antipsychotic: low D2R occupancy drugs (clozapine, quetiapine, paliperidone, olanzapine) versus high D2R occupancy drugs (haloperidol). We also calculated the total median antipsychotic drug dosage in chlorpromazine equivalents for correlation with our speech measures. TRS patients' daily antipsychotic dose was converted to CPZ equivalents. Patients were classified as high when their CPZ equivalent dose was above the median and as low when the CPZ equivalent was below the median dose level. Nonparametric one-way ANOVA (NPAR1WAY) procedure was performed to evaluate whether the acoustic speech measures varied by high D2R occupancy vs low D2R occupancy groups. Spearman rank-order correlations were conducted to examine relationships between acoustic speech features and total daily CPZ equivalents. Results: Across the 67 participants with TRS, none of our 8 acoustic speech measures (Reading_CPP; Reading_mfa; Reading percent pause duration; Reading speaking time; Reading stdev_f0; Spontanous speech_CPP; Spontanous speech speaking time; Spontanous_stdev_f0) demonstrated significant differences between patients treated with high D2R affinity antipsychotics (haloperidol) versus low D2R affinity antipsychotics (clozapine, quetiapine, paliperidone, olanzapine). Similarly, there was no significant effect of the CPZ equivalent dose on acoustic speech patterns. Conclusion: Our data show that in TRS patients, the level of D2 affinity and the CPZ equivalent dose does not have a significant differential effect on patients' acoustic speech patterns. These findings contrast with prior observations in treatment-responsive patients, where high D2R affinity antipsychotics were linked to more pronounced negative language disturbances. The absence of differential effects on acoustic speech patterns in TRS may support the hypothesis that TRS patients lack the hyperdopaminergic state typically observed in antipsychotic-responsive schizophrenia, suggesting that D2R-mediated mechanisms may play a reduced role in speech alterations within this population. These results highlight the need to consider distinct neurobiological and pharmacodynamic profiles when evaluating speech-based biomarkers in treatment-resistant versus treatment-responsive schizophrenia.

Poster Presentations

1. Effects of Transcranial Direct Current Stimulation (tDCS) on Symptoms and Brain Changes in Patients with Autism

   Robert C Smith

   Background: Patients with autism spectrum disorder (ASD) have severe social deficits and behavioral and educations treatments have limited effectiveness. There is preliminary evidence that tDCS can improve some symptoms in patients with ASD. Previous studies

have shown that synaptic E/I ratios are significantly elevated in the medial prefrontal cortex (mPFC) of autism-like mouse models. Methods: This was a randomized double blind study of the effects of tDCS in patients with ASD.36 patients with ASD in Changsha, China were randomized to receive either 1.5 mA anodal tDCS or Sham tDCS for 20 minutes 2 times/day for 7 days delivered to the mPFC. Resting state EEG recordings were analyzed to assess changes in power spectral density (PSD) slope and the functional excitation-inhibition balance (fE/I) ratio. The primary clinical outcome measure was change in the Ohio State University Autism Rating Scale for DSM-5 (OARS-5) and there were several secondary clinical and safety measure scales. Analysis of the clinical data used linear mixed models in Stata 19 and SAS 9.4. Correlations were used to assess relationship of clinical change and EEG measure changes. Results: The active tDCS group showed significant greater decrease than sham, in OARS total score (P<.01) and social functioning sub-score (P<.03) after the 7 days to tDCS treatment and some of the differences in OARS scores persisted at an assessment 3 weeks later. There was a significant increase in slope ($p = 0.004$) and a significant decrease in fE/I ($p = 0.011$) from baseline to post week1 in the active tDCS group, with no significant changes observed in the sham group. Correlational analyses indicated that reductions in fE/I ($r = 0.377$, $p = 0.044$) and increases in slope ($r = -0.447$, $p = 0.015$) were significantly associated with improvements in OARS-5 social functioning scores. Conclusions: Our results suggest that tDCS to mPFC may be effective in reducing some symptoms associated with ASD, and induce changes in excitation-inhibition balance in the brain as analyzed from resting state EEG analyses. Correlations suggest that the changes in OARS scores may be influenced by changes in fE/I and slope brain measures.

2. Bayesian Deconvolution Reveals Cell-Type-Specific Effects of Early-Life Experience in the Hippocampus

Brian Hurwitz, Yotam Sagi, Paolo De Angelis, Janet Chang, Dani Zelli BS Betty Bigio, & Carla Nasca* (*co-senior authors)*

Psychiatric disorders are strongly influenced by early-life experiences, which can alter the structure and function of brain circuits involved in emotion, memory, and stress responses. The dentate gyrus of the hippocampus is a key hub for these processes, but the contribution of individual cell populations remains difficult to fully resolve. Here, we implemented a “transcriptomic repurposing” of existing bulk RNAseq databases using advanced bioinformatic approaches to infer cell-type-specific transcriptional programs from bulk tissue. Using a mouse model (BDNF Val66Met) that naturally varies in maternal care, we performed high-resolution bulk RNA sequencing of the dentate gyrus and applied a Bayesian single-cell inference method to virtually separate transcriptional profiles of excitatory neurons, inhibitory neurons, and astrocytes, referencing single-cell RNA sequencing data from the Allen Brain Atlas. Using this approach, we found that differences in early-life nurturing were associated with distinct transcriptional patterns across cell types, including uniquely regulated genes in metabolic pathways. In astrocytes, for example, high-nurturing conditions were associated with a shift from ketone body

metabolism toward carbohydrate metabolism, alongside lower susceptibility of adult animals to stress. Our findings suggest that early-life experiences leave lasting, cell-specific transcriptional signatures in the hippocampus, with consequences for brain architecture and behavior, and demonstrate that computational single-cell inference can be used to address questions that have previously been inaccessible in complex brain tissue.

3. Rapid Estimation of Sensorimotor Control in the Continuous Performance Critical Stability Task Predicts Cognitive Ability, Academic Achievement, and Cardiorespiratory Fitness

   Daniel Garcia-Barnett, Yunglin Gazes, Anna MacKay-Brandt, Stan Colcombe

   Objective: The Continuous Performance Critical Stability Task (cpCST) calibration phase is a brief sensorimotor paradigm adapted from Jex et al. (1966). Participants control a drifting stimulus while system instability (λ) increases systematically across 10 trials until control fails. We hypothesized that performance on this two-minute calibration, tapping sensorimotor integration, would predict cognitive performance and cardiorespiratory fitness. Participants and Methods: Data came from 217 participants (ages 10–76 years, M=47.6, SD=19.3; 64.5% female) from the Nathan Kline Rockland Sample II. The λ values at failure were fit to a decay curve to estimate asymptotic performance (95th percentile). Regression models examined associations between asymptotic λ, Woodcock–Johnson (WJ) composites (Brief Intellectual Ability [BIA] and Brief Achievement [ACHBRF]), and submaximal VO_2, controlling for age and sex. Results: Approximately 90% of participants reached stable performance within five trials (~two minutes). Higher asymptotic λ predicted both BIA ($t=3.26$, $p<.001$) and ACHBRF ($t=3.26$, $p<.001$), independent of age and sex. Higher asymptotic λ also associated with greater submaximal VO_2 ($t=2.61$, $p<.01$). Conclusions: Despite being a sensorimotor task, asymptotic λ demonstrated associations with cognitive ability, academic achievement, and cardiorespiratory fitness. This aligns with evidence that sensorimotor paradigms (e.g., grooved pegboard, multisensory integration, gait) predict clinically meaningful cognitive outcomes. Such 'low-level' probes may reflect CNS efficiency or tap multisystem neural integrations predictive of behaviors from simple to higher-order functioning. This brief two-minute calibration yields a scalable, non-verbal index of integrated sensorimotor control with predictive value across cognitive and physiological domains, supporting its use as a practical assessment tool for lifespan research, mobile testing, and repeated-measures designs in clinical and community settings.

4. Insights from PIP-seq into early hyperexcitability in an Alzheimer’s disease mouse model

   Gabriel Stephens, David Alcantara-Gonzalez, Helen Scharfman

   Rationale: Hyperexcitability is Alzheimer’s disease (AD) has captured attention because it appears to occur early in the disease and contribute to cognitive impairment and increased amyloid (A). In our prior work with AD mouse models, we found

hyperexcitability extremely early in life, just 1 month of age. In vivo, aberrant activity emerged mainly as interictal spikes (IIS) in sleep, with later onset of rarer seizure events. Silicon probe recordings suggested IIS were generated in the dentate gyrus (DG). In vitro patch-clamp studies identified that there was increased activity in some of the cell types in the DG at the 1 month age, but why this elevated activity occurred was not clear. Methods: To gain insight, we examined DG gene expression in wild type (WT) vs. Tg2576 mice, which overexpress a mutant form of the precursor to Abeta (APPSwe). Single-nucleus RNA sequencing (snRNA-seq) was performed using DG from slices of 1 month-old WT and Tg2576 mice (n=3/group). We used Particle-templated Instant Partition Sequencing (PIP-seq) from the NYU Genome Technology Center, which also processed and sequenced the isolated DG nuclei. High quality nuclei were then selected and annotated using validated marker genes that identify 9 major DG cell types. Results: We found similar proportions of the 9 cell types in both Tg2576 and WT mice at nuclei yields consistent with prior studies. Notably, differentially expressed gene (DEG) analysis identified thousands of DEGs, many of which may be involved in regulation of excitability, including known risk genes for AD and epilepsy. Surprisingly, a set of shared genes that can regulate excitability were altered across all 9 major cell types. Conclusion: We have identified gene regulatory programs and gene expression alterations that may promote or inhibit early-disease hyperexcitability in the dentate gyrus in the context of AD. Many of these genes across cell types match those that show altered expression in AD and epilepsy patient hippocampal proteomics studies. These findings will help develop hypotheses for drivers of DG hyperexcitability and could provide new insights into hyperexcitability in clinical AD.

5. Postnatal ethanol vapor exposure disrupts EZH2-dependent epigenetic regulation and promotes neurodegeneration in neonatal mice

   Balapal S. Basavarajappa

   Prenatal alcohol exposure is a primary cause of fetal alcohol spectrum disorders (FASDs), which are characterized by neurobehavioral abnormalities and intellectual disability. However, the molecular mechanisms underlying alcohol-induced neurodevelopmental defects remain poorly understood. In this study, we investigated the effects of postnatal ethanol vapor exposure on EZH2-dependent histone modifications and their relationship to neuronal apoptosis in neonatal mice. Using an established ethanol vapor exposure paradigm, both dams and pups were exposed to ethanol for 3 hours daily from postnatal day (P) 4 to P9, resulting in peak blood alcohol concentrations of 240 ± 25 mg/dL in P9 pups. Neuronal apoptosis and histone modifications—H3K27ac, associated with active transcription, and H3K27me3, associated with gene repression—were assessed in the prefrontal cortex (PFC) and hippocampus (HP). In addition, we examined ethanol-induced alterations in EZH2 expression and EZH2-dependent histone modifications in relation to neonatal neurodegeneration. Our results demonstrate that P4–P9 ethanol vapor exposure induces significant neuronal apoptosis, increases EZH2 expression, enhances H3K27me3, and reduces H3K27ac levels in both the PFC and HP. Significantly, pre-administration of the EZH2-specific inhibitor EPZ-6438 prevented ethanol vapor–induced neonatal

neurodegeneration and restored the balance between H3K27me3 and H3K27ac levels. Collectively, these findings indicate that postnatal ethanol exposure disrupts EZH2-dependent histone post-translational modifications, thereby promoting neurodegeneration in the developing brain. Ongoing studies aim to elucidate further the persistent molecular pathways mediating these ethanol-induced epigenetic and neurodevelopmental alterations. Acknowledgments: Funded by NIH/NIAAA grant AA029686.

6. Postnatal Ethanol Vapor Exposure Enhances EZH2 Expression and Promotes Neurodegeneration, Synaptic, and Behavioral Abnormalities in Mice

   Shivakumar Subbanna, Madhu Shivakumar, Balapal S. Basavarajappa

   Alcohol abuse during pregnancy contributes to neurobehavioral abnormalities in offspring, resulting in cognitive deficits collectively termed fetal alcohol spectrum disorders (FASDs). However, the molecular mechanisms underlying these brain abnormalities remain poorly defined. In this study, we investigated the effects of postnatal ethanol vapor exposure on EZH2-dependent histone modifications and their relationship to neuronal apoptosis in neonatal mice and cognitive dysfunction in adult mice. Using an established ethanol vapor exposure paradigm, both dams and pups were exposed to ethanol for 3 hours daily from postnatal day (P) 4 to P9, resulting in peak blood alcohol concentrations of 235 ± 30 mg/dL in P9 pups. Neuronal apoptosis and histone modifications—H3K27ac, associated with active transcription, and H3K27me3, associated with gene repression—were assessed in the prefrontal cortex (PFC) and hippocampus (HP). We further examined ethanol-induced alterations in EZH2 expression and EZH2-dependent histone modifications in relation to neonatal neurodegeneration and their persistent effects on synaptic and behavioral functions in adult mice. Our results demonstrate that P4–P9 ethanol vapor exposure induces significant neuronal apoptosis, increases EZH2 expression, enhances H3K27me3, and reduces H3K27ac levels in both the PFC and HP. Importantly, pre-administration of the EZH2-specific inhibitor EPZ-6438 prevented ethanol vapor–induced neonatal neurodegeneration, restored the balance between H3K27me3 and H3K27ac, and rescued ethanol-induced synaptic and behavioral abnormalities. Collectively, these findings identify EZH2-mediated epigenetic dysregulation as a critical mechanism linking early-life ethanol exposure to long-term neurodevelopmental deficits, and suggest EZH2 inhibition as a potential therapeutic strategy for FASD-related impairments. Acknowledgments: Funded by NIH/NIAAA grant AA029686.

7. Cutting through the Matrix: Comparative Analysis of Enzymatic Methods for Brain Extracellular Vesicle Isolation

   Galit Blecher, Logan Jones, Chris Goulbourne, Monika Pawlik, Yun-Juan Chang, Pasquale D'Acunzo, Efrat Levy

Methods for isolating brain extracellular vesicles (EVs) from the extracellular matrix (ECM) rely on tissue dissociation with proteolytic enzymes, risking cellular damage, contamination with intracellular components, and EV protein degradation. In our laboratory we established a protocol utilizing papain, a commonly used enzyme for the generation of primary brain cells, including neurons, astrocytes, and microglia. Papain effectively releases interstitial fluid while preserving cellular integrity, given that it has a broad proteolytic activity, potentially degrading EV surface proteins, thus hindering the identification of physiologically important EV-associated proteins. In order to identify the whole range of EV surface proteins, we compared EV isolation efficacy and protein cargo using 11 enzymatic treatments of mouse brain tissue: hyaluronidase, chondroitinase, elastase, dispase (neutral protease) trypsin, collagenase types 1/2/3/4, pure collagenase, and papain. Preliminary findings indicate that although the brain ECM is enriched in hyaluronic acid and chondroitin sulfate proteoglycans, hyaluronidase treatment yielded very small amounts of EVs, while chondroitinase failed to yield detectable EVs. Collagenase treatments, differing in residual nonspecific enzymatic activity, exhibited variability in the number and purity of EVs. Interestingly, elastase, targeting elastin primarily found in the brain blood vessels' ECM, yielded relatively high EV amounts without significant cellular contamination. Dispase showed similarly promising results. Our preliminary data show that dispase and elastase treatments yield high EV numbers with minimal cellular contamination, similar to papain. Western blot analyses of brain EVs isolated using the three enzymes followed by fractionation with a high-resolution density gradient showed comparable results in the separation of ectosomes, exosomes, and mitovesicles. Analyses of the EV proteome from samples obtained by digestion using these three enzymes by liquid chromatography-mass spectrometry have the potential to identify novel, physiologically relevant proteins in brain EVs.

8. Acute anti-PrPC Treatment Rescues Synaptic Integrity, Improves Cognitive Function, and Reduces Anxiety in Advanced-stage Alzheimer's Disease Models

Xutong Guo, Tong Zhao, Julia Janknecht, Xiaoyi Yang, Thomas Wisniewski, Shuo Chen

Background: Alzheimer's disease (AD) is the most prevalent cause of dementia in the elderly. AD immunotherapies utilize antibodies to inhibit the function of pathology-associated molecules such as amyloid-β (Aβ) and tau. Our group, along with others, has recently demonstrated a novel AD immunotherapy targeting cellular prion protein (PrPC), a cell-surface receptor mediating the neuronal toxicity of Aβ and tau oligomers. Long-term anti-PrPC treatments have been shown to improve cognition in middle-aged AD models. However, whether anti-PrPC also has an ameliorating effect on the symptoms of old AD mice where Aβ pathology has been extensively developed remains unknown. To address this question, we tested a novel monoclonal anti-PrPC developed in our laboratory that targets the PrP 94–108 epitope. Method: Two different AD models, APP/PS1dE9 and SWDI, were used. Geriatric mice (18-24 months old) were intraperitoneally injected with anti-PrPC, while control mice received only saline. Behavioral tests including anxiety in

open field and elevated zero maze (EZM), locomotor activity, and T-maze were performed 2 hours post-injection. After behavioral testing is completed, acute hippocampal slices were prepared and subjected to in vitro physiology. For in vivo calcium imaging, adeno-associated virus expressing GCaMP8f was injected into hippocampal CA1, above which a GRIN lens was implanted. Four weeks later, real-time calcium transients of single CA1 neurons were recorded during spatial navigation tasks. Result: Acute anti-PrPC treatment resulted in significant cognitive improvement for both mouse lines. While the treated mice did not show differences in locomotor activity, significantly enhanced cognitive performances in T-maze tests were observed. Anti-PrPC also significantly reduced anxiety in the open field and EZM. We found that hippocampal slices from treated animals showed enhanced Schaffer collateral long-term potentiation, suggesting rescued synaptic plasticity. Finally, our in vivo calcium imaging data suggested significant anti-PrPC-driven modification of CA1 neural dynamics for spatial encoding. Conclusion: Our results suggest that acute anti-PrPC administration rescues synaptic plasticity, cognitive decline, and anxiety in old AD mice where extensive Aβ pathology has been developed. Our finding opens the possibilities to apply the strategy of targeting PrPC for alleviating advanced-stage AD symptoms in addition to its application in middle-aged individuals.

9. Decoupled surrogate networks for efficient background input optimization in biophysical circuit models

Nikita Novikov, Scott McElroy, James Chen, Charles Schroeder, Stephan Bickel, Monica N O'Connell, Salvador Dura-Bernal, Samuel Neymotin

Brain circuits operate in distinct regimes depending on various conditions, including the behavioral state and ongoing task demands. Accordingly, biophysical circuit models require a systematic approach for tuning them for various operating regimes. A natural target for adjustment is the background inputs that mimic the influence of brain areas and modulatory systems not explicitly included in the model. Since biophysical models are highly nonlinear, mapping background inputs to population firing rates requires computationally expensive simulations. With many populations involved, exhaustively exploring a high-dimensional input space is impractical. A common approach is to break the optimization into simpler, low-dimensional problems. We propose a method that creates, for each original population P, a surrogate population P' composed of random spike generators firing at the target rate for P. In the surrogate network, every original connection P1→P2 is replaced by P1'→P2, preserving synaptic properties. The result is a set of independent subnetworks: each original population receives surrogate recurrent inputs matching the desired firing rates, but the populations are no longer dynamically coupled. This decoupling allows us to treat each population separately: we sweep through multiple background intensities and choose the one that yields the population firing rate best matching the target value. We tested the method on our existing biophysical model of the auditory thalamocortical circuit (A1) which includes 43 neural populations. We added AMPA-mediated background noise to each neuron, whose conductance follows an independent Ornstein-Uhlenbeck (OU) process. Each population was parametrized by a

mean OU value, and the standard deviation of OU was derived linearly from the mean. With downscaled synaptic weights, our method successfully predicted the background parameters that produce population firing rates close to the target values. With stronger weights, the error increased due to inter-population activity correlations not captured by our method. We suggest that it could be compensated by other optimization algorithms, using our prediction as the initial guess. Our approach to background regime tuning paves the way for reproducing attentional modulation in the A1 model and offers a general framework for exploring state-dependent activity in other biophysical models.

10. Low Levels Of Anxiety Associated With Enhanced Cognitive Functions In A Cohort Of Cognitively Unimpaired Elderly

Andrew Orefice, Nunzio Pomara, Chelsea Reichert Plaska

Introduction: Anxiety increases the risk of cognitive decline and Alzheimer's disease (AD), which may be influenced by AD-risk factors like APOEε4 allele and female-sex. Subsyndromal, or low levels of anxiety (SSA), are common in community-dwelling elderly compared to syndromal anxiety. However, few studies have examined the effect of SSA on AD-risk. This prompted us to examine whether SSA is associated with impaired cognition in elderly. We hypothesized that elderly with SSA would have worse cognition compared to those without SSA. We also examined the influence of sex and ε4-status. Methods: Participants enrolled in the Memory Education and Research Initiative (MERI) program and completed a comprehensive evaluation, including Hamilton Anxiety Rating (HAM-A) and Depression (HAM-D) scales. MERI participants were included if: MMSE>23, age 50-85, and HAM-D<18. SSA was defined as HAM-A: 2 to 10 and No-SSA defined as HAM-A: 0 or 1. Analysis of variance (ANOVA) were conducted to examine influence of SSA, sex and genotype status (ε4-positive/negative) on HAM-A/HAM-D and on cognition. Pearsons's correlations were run to examine associations with HAM-A/HAM-D. Results: Females had significantly higher HAM-A ($p=0.023$) and HAM-D ($p=0.014$) than males. There were negative associations between HAM-A ($rho=-0.268$, $p<0.001$) and age as well as HAM-D ($rho=-0.207$, $p<0.001$). These HAM-A associations were strongest in females. There were no interactions of sex and ε4-status and no main effect of ε4-status (HAM-A: $p=0.596$, HAM-D: $p=0.472$). SSA had higher HAM-D ($p<0.001$) than No-SSA. HAM-A and HAM-D were more strongly correlated in SSA ($rho=0.567$, $p<0.001$). When controlling for HAM-D, age and education, SSA had significantly better episodic memory (AVLT-Total: $p=0.015$, $\eta2=0.019$; -Delayed: $p=0.020$, $\eta2=0.017$) and executive function (TMTB: $p=0.002$, $\eta2=0.30$) than No-SSA. There was a significant interaction of sex and SSA on episodic memory ($p=0.026$, $\eta2=0.016$); females with SSA performed better than all other groups. Conclusion: Contrary to our hypothesis, elderly with SSA, particularly women, performed better on tests of episodic memory and executive function, as compared with individuals without SSA. These findings may reflect tau pathology, which is more prevalent in women, and early disruption of locus coeruleus whose compensatory hyperactivity may result in both enhanced memory and anxiety in preclinical AD.

11. Psilocybin induced synaptic plasticity in ACa neurons that feedback to visual areas

    Molly A Hornick, Lital Rachmany, Fumiyasu Imai, Jordan P Hamm

    Psilocybin is a serotonergic psychedelic that has shown therapeutic potential in psychiatric disorders. The neurobiological mechanisms underlying this potential remain unclear. Direct study of cell- and circuit-level functions in humans is challenging, highlighting the need for mouse models to evaluate the effects of psilocybin. Recent work in mice demonstrates that psilocybin leads to growth of synapses in the cerebral cortex, mirroring the effects of other antidepressant and antianxiety treatments. Which cells and circuits exhibit this synaptic growth, and which downstream functions are impacted by this plasticity, remain unknown and may still hold the key to elucidating on- and off-target therapeutic mechanisms. In this project, we employed simple and complex visual oddball paradigms and focused on visual mismatch responses (vMMN), as they reflect integrative sensory processing that depends on distributed cortical circuits and may be sensitive to alterations in neural plasticity. In mice, the anterior cingulate area (ACa) is a higher-order medial prefrontal region that sends feedback projections to the primary visual cortex (V1) to support vMMN. Specifically, ACa projections target superficial layers of V1 and modulate sensory processing in a context-dependent manner during oddball paradigms. Our past work has shown that suppression of ACa inputs to V1 abolishes vMMN in both simple and complex predictive processing paradigms. To evaluate the effects of psilocybin on these feedback circuits and feedback-dependent functions, we examined dendritic spine formation in ACa neurons that project to V1 areas using GFP, and found that spine density increased following psilocybin treatment. In addition, we expressed the inhibitory DREADD receptor hM4Di in ACa neurons, enabling analysis of the role of psilocybin-induced neuronal activity in spine formation. Finally, we assessed the effects of psilocybin on the vMMN paradigm using LFP recordings in both ACa and V1. We found that 24 hours after treatment with psilocybin, ACa neurons projecting to V1 exhibited changes in spine density and/or size in a sex-dependent manner. Complex forms of vMMN (prediction error during a global/local paradigm) – but not simple vMMN (during a classic oddball) – were altered in this time range, while feedback modulation of V1 was reduced and feedforward drive (V1 to ACa) was enhanced. Together, these results suggest that psilocybin-induced spine growth may serve to reset the balance of top-down versus bottom-up dynamics in the cortex in a manner that alters how sensory data are processed in context.

12. Grid-cell-driven reinforcement learning enables multi-goal maze navigation in spiking neuronal networks

    Gozde Unal, Christopher Earl, Hananel Hazan, Samuel A Neymotin

    Animals must often navigate environments where feedback about progress toward a goal is sparse or delayed, requiring internal representations of space and memory of prior experience. The hippocampal-entorhinal system is believed to support this capability by integrating spatial and idiothetic signals to form cognitive maps that guide behavior.

However, many computational models of these circuits focus primarily on reproducing neural dynamics rather than demonstrating how such representations support learning of goal-directed tasks. We present a biologically inspired spiking neuronal network (SNN) model that combines grid cell-like spatial inputs with a reinforcement learning mechanism derived from temporal-difference Q-learning. Synaptic plasticity is governed by a reward-modulated Hebbian rule driven by changes in predicted long-term value (ΔQ), enabling learning in sparse reward environments. Association cell populations form distributed place-like representations of location, while a context-modulation mechanism enables the network to learn multiple navigation policies within a shared architecture. Across two maze environments designed to isolate key challenges of biological navigation, the model demonstrates robust spatial encoding, efficient optimization of long action sequences, and goal-conditioned generalization across multiple paths. These results show that biologically grounded SNNs can support flexible navigation behavior while maintaining local learning rules, providing a bridge between mechanistic circuit models and functional reinforcement learning.

13. Elucidate the role of mitochondria-derived extracellular vesicles in the higher risk for sporadic Alzheimer's disease associated with the apolipoprotein E4 allele

Maria Luisa Valle, Mallory Downs, Elentina K. Argyrousi, Monika Pawlik, Ottavio Arancio, Pasquale D'Acunzo, Paul Mathews, Efrat Levy

INTRODUCTION: Alzheimer's disease (AD) is characterized by progressive cognitive decline and distinct neuropathological features, including mitochondrial dysfunction. Our group previously described a novel type of small extracellular vesicles (EVs) derived from mitochondria, named mitovesicles, whose number and content are altered in brains with mitochondrial dysfunction. We are comparing the generation, content, and secretion of mitovesicles and other EVs in the brain of apolipoprotein E4 (APOE4) homozygous targeted-replacement mice, given that the presence of the APOE4 allele is a major genetic risk-factor for the development of late-onset sporadic AD, with EVs isolated from brains of APOE3 mice (the disease neutral-risk allele) and APOE2 (associated with a lower risk for sporadic AD). In addition to EV characterization, we studied differential functional changes elicited by mitovesicles, positing that APOE2 mitovesicles are beneficial for cognition, while APOE4 mitovesicles impair memory consolidation. METHODS: EVs were isolated from the brains of APOE2, APOE3, and APOE4 homozygous mice and characterized by electron microscopy, nanoparticle tracking analysis, and Western blotting. Wild-type hippocampal slices were perfused with APOE2, APOE3, and APOE4 mitovesicles and long-term potentiation (LTP) was assessed. RESULTS: APOE2 murine brains contained the highest levels of brain endosomal-derived exosomes. The lowest levels were found in APOE4, while APOE3 mice showed an intermediate phenotype between APOE2 and APOE4 mice. Preliminary data show a similar trend for mitovesicles, with higher levels of mitovesicle markers in APOE2 mice compared to the other groups. Nevertheless, the lowest levels of protein acetylation (a marker of mitochondrial stress) were found in APOE2 mitovesicles, suggesting that higher level of mitovesicle secretion more effectively

clear mitochondrial toxic substances. Administration of physiological levels of mitovesicles from the different APOE mouse brains differently impacted LTP in the hippocampal slices of wild-type mice, altering synaptic function in circuits that are thought to be important for memory formation. CONCLUSIONS: Mitovesicle secretion is a novel hotspot in mitochondrial quality control through which cells remove damaged mitochondrial components and restore mitochondrial homeostasis. Findings from this work will elucidate mitovesicle protective and pathogenic roles associated with different APOE genotypes, demonstrating the role of mitovesicles in AD.

14. Biophysical model of auditory thalamocortical circuit reveals GABAB-dependent control of N1 deficits in Schizophrenia

    Ethan Irby, Nikita Novikov, Scott McElroy, Andrea Balla, Charles Schroeder, Salvador Dura-Bernal, Monica Noelle O'Connell, Daniel Javitt, Samuel Neymotin

    Auditory processing deficits are a core feature of schizophrenia (SZ) currently under investigation. The N1 component of the auditory evoked potential (AEP) is reduced in patients with SZ, and N1 refractory curves, which describe increasing N1 amplitudes with longer inter-stimulus intervals (ISIs), suggest dependence on slow synaptic mechanisms, including GABA type B (GABAB) and NMDA channels. In this study, we employ a biophysical model of the macaque primary auditory cortex (A1) and thalamus to examine how GABAB and NMDA modulation shape N1 dynamics, and whether GABAB modulation can counteract N1 amplitude reductions under NMDA hypofunction. The model includes the medial geniculate nucleus (MGN), thalamic reticular nucleus (TRN), and primary auditory cortex (A1). A1 is represented as a cortical column with over 12,000 neurons and ~25 million synapses. The model captures multiscale activity, including laminar local field potentials (LFPs), current source density (CSD), and neuronal firing rates. Simulated LFPs are used to derive CSD, and resulting patterns are compared with in-vivo macaque data for validation. Brief thalamic stimulation evoked CSD sink events in A1 granular layers closely matched in-vivo macaque responses. The model reproduced the N1 refractory curve, with CSD amplitude and multi-unit activity increasing with longer ISIs. GABAB conductance was found to be a strong governing factor for N1. Increasing GABAB by 25% reduced N1 amplitude across cortical layers, most prominently in supragranular and infragranular layer groups. In contrast, decreasing GABAB enhanced N1 responses. NMDA conductance modulation produced comparatively modest effects. Since reducing GABAB conductance enhances N1 responses, this suggests a potential compensatory mechanism for N1 reductions associated with NMDA hypofunction. These findings point to an important role for GABAB in auditory processing deficits observed in SZ. Future work will extend this modeling framework to more complex auditory responses, including mismatch negativity, which is also disrupted in SZ, with the goal of further probing the circuit mechanisms underlying auditory dysfunction in the disorder.

15. Human single-unit recordings in globus pallidus externus (GPe) reveal preparatory switch-selective activity during reversal learning in OCD patients

Amber Kiely, Martijn Figee, Brian H. Kopell, Zarghona Imtiaz, Ha Neul Song, Sonia Olson, Abigeal Kiros, Helen S. Mayberg, Allison C. Waters, Ki Sueng Choi, Vincenzo Fiore, Andrew H. Smith

Obsessive-compulsive disorder (OCD) is marked by impaired behavioral flexibility. The basal ganglia indirect pathway is hypothesized to be hyperactive in OCD, promoting rigid behavior, and the globus pallidus externus (GPe) is a central but understudied node in this pathway. Human GPe single-unit activity during behavior has never before been reported. Intraoperative single-units from anterior (limbic) GPe were recorded using an Alpha-Omega microelectrode system. OCD patients performed a probabilistic reversal learning task during recordings, and spikes were isolated in MATLAB. Population firing rates were computed using sliding-window peristimulus time histograms (PSTHs) and analyzed aligned to reward receipt and choice point. Single-unit recordings from the GPe were obtained from 6 OCD patients during DBS surgery (22 neurons total; 11 neurons ≥2 Hz). Reward-aligned population PSTHs showed no significant differences between win and loss trials. In contrast, choice-aligned PSTHs revealed significantly higher GPe firing rates preceding switch versus stay choices (−250 to −150 ms; $p < .05$). Individual neurons exhibited heterogeneous response profiles. Human GPe neurons exhibit switch-selective activity preceding choice during probabilistic reversal learning, while showing no population-level modulation by reward outcome. These findings suggest that the human GPe preferentially encodes preparatory signals associated with behavioral flexibility rather than reward receipt, highlighting a potential neural mechanism contributing to impaired adaptability in OCD.

16. Loneliness and Suicidal Ideation and Behavior in Schizophrenia and Depression

Michael Kuhl, Jewel Bell, Julia Chafkin, Kate Collins, Heather Doherty, Kelly Kwong, Stuti Munjal, Tyler Pia, Sara Rose Shannon, Anthony Ahmed, Faith Gunning, Dan V. Iosifescu, Matthew Hoptman

Background: Loneliness is a known risk factor for suicidal ideation and behavior (SIB) in both Schizophrenia Spectrum Disorder (SSD) and Major Depressive Disorder (MDD). We predicted loneliness would be higher in people with High vs. Low SIB in a preregistered report (AsPredicted Report #256,603). Methods: Participants (N=34) had Major Depressive Disorder (MDD; n=22) or Schizophrenia Spectrum Disorder (SSD; n=12) per DSM-5 MINI. Participants were administered Columbia Suicide Severity Rating Scales (C-SSRS) covering the past 3 years and lifetime SIB and were divided into low and high SIB groups. Low SIB (MDD n =14, SSD n=6) scored 0-1 on suicidal ideation over the past 3 years and had no lifetime suicidal behaviors. High SIB (MDD n=8, SSD n=6) answered “yes” to actual or aborted or interrupted attempt(s) AND to preparatory acts or behaviors, or 2+ lifetime actual attempts on the C-SSRS. Participants also completed the UCLA 3-Item Loneliness Scale (UCLA-LS). Results: In the SSD group, a one-tailed Mann-Whitney U test found a significant difference in UCLA-LS scores between the high and low SIB groups, U =

29.00, p = 0.035. In the MDD group, one-tailed Mann-Whitney U test found no significant difference in UCLA-LS scores between high and low group, U= 72.5, p = 0.133.
Conclusions: High SIB groups showed elevated loneliness in both disorders, significantly so in SSD. Screening for loneliness may help identify individuals at risk, especially in SSD. These findings are preliminary given the small sample size, and further research is needed to confirm disorder-specific patterns.

17. Spontaneous reactivation of TikTok video experiences during external sustained attention

Hyun-Woong Kim, Teddy Hoppe, Jenna Lembo, Karl-Heinz Nenning, Alexandre Franco, Stanley Colcombe, Michael Milham, Arielle Tambini

Spontaneous reinstatement of neural representations during offline periods such as sleep and rest is thought to support memory stabilization. We recently showed that spontaneous memory reactivation during wakeful rest preferentially occurs during internally versus externally oriented brain states. Brief internally oriented states arise intermittently during sustained attention to external stimuli, yet it remains unclear whether these states preferentially promote reactivation at the expense of external task engagement. In addition, spontaneous reactivation has rarely been examined using naturalistic stimuli such as TikTok video content. Here, we tested whether reactivation of recently encoded TikTok videos is coupled to specific brain states during sustained attention, and whether this coupling relates to fluctuations in task performance. Ten adults completed multiple fMRI sessions including a psychomotor vigilance task (PVT) and short-form video (SFV) viewing. Each session began with a baseline PVT (9 min), followed by six SFV runs (7 min each), each paired with an immediate post-encoding PVT (3 min). For each SFV, we derived a neural representation by averaging z-scored voxel-wise BOLD responses across the video. Memory-related cortical ROIs sensitive to SFV content were identified using whole-brain searchlight inter-subject pattern correlation. Reactivation events during post-encoding PVT were defined as time points when ROI activity patterns resembled those evoked during SFV viewing. To characterize brain states, we applied k-means clustering to whole-brain activity during the baseline PVT, yielding recurring coactivation patterns, and assigned each post-encoding PVT time point to the most similar state. We then compared reactivation rates across brain states during periods of high versus low response time variability. We identified three pairs of brain states. One pair captured internal versus external processing modes, contrasting default and dorsal/ventral attention networks. Naturalistic SFV reactivation in retrosplenial and medial parietal cortex occurred preferentially during the internally oriented state (vs. externally oriented state, $p < .005$). In retrosplenial cortex, this coupling was stronger during periods of high response variability ($p = .004$). These findings suggest that brief internally oriented states emerging during sustained attention provide privileged windows for spontaneous reactivation of recent naturalistic experiences, with a trade-off between memory-related internal processing and stable external engagement.

18. Image Guided Cell Sorting In Silica Reveals Transcriptomic and Proteomic Differences Between Pathology States of a 5xFAD Transgenic Mouse Model

    Christopher Bare, Phil Stavrides, Sandip Darji, Ralph Nixon

    The ability to quantify transcriptome and proteome at a granular level drives discovery. For decades, the ability to enrich for phenotypically defined cellular pathology states has involved tissue dissociation and flow cytometry, often with significant loss of fidelity, microenvironment, and morphometric information. Laser capture technology attempts to overcome this loss but is a labor intensive manual process prone to high background and limited characterization dimensionality. Recent advances in spatial profiling of tissue sections has improved sample refinement but often at the expense of output data plexity. Here we describe the application of multidimensional phenotyping of specific pathology states in mouse brain sections and the subsequent high plexity quantification of transcript and protein. In addition, a novel image segmentation technique incorporating multiple fluorescence channels is described as a key step in generating highly concordant data.

19. Reward-Modulated Delay Learning in Spiking Neural Networks for Adaptive Control in Pong

    Rachel Dynkin, Christopher Earl, Gozde Unal, Hananel Hazan, Samuel Neymotin

    Spiking neuronal networks (SNNs) provide a biologically grounded framework for studying learning and decision-making through temporally precise neural activity. Prior work has demonstrated that reward-modulated spike-timing-dependent plasticity (STDP) can support adaptive motor control in simulated environments such as CartPole and simplified racket-ball tasks. In these models, synaptic weights are adjusted based on the relative timing of neuronal spikes and modulated by reward signals, allowing networks to learn action policies through interaction with the environment. However, scaling weight-based reinforcement learning in SNNs to visually complex and dynamically changing tasks remains challenging due to difficulties in temporal credit assignment, sensitivity to reward scaling, and instability in synaptic updates driven by variability in spike timing and firing rates. Building on these foundations, this project investigates SNN-based control in the Atari Pong environment using the BindsNET simulation framework. Visual input is processed to extract key features of the game state, including the positions and motion of the ball and paddle. These features are used to generate intermediate shaping rewards that supplement sparse environmental feedback, improving the temporal alignment between neural activity and reinforcement signals. Eligibility traces associate delayed rewards with earlier spike events, enabling more consistent learning in a temporally extended control task. Results show that structured reward signals and improved temporal credit assignment enhance behavioral stability relative to reward-modulated STDP alone, while continuing to demonstrate sensitivity to parameter tuning and reward scaling. A central goal of this work is to extend these insights toward an alternative learning paradigm based on weightless spiking neural networks, in which memory is

encoded in spike timing relationships rather than synaptic strength. In this delay-based framework, learning occurs by modifying synaptic transmission delays so that neural activity becomes temporally aligned with successful behavioral outcomes. This approach may provide a more stable and scalable mechanism for reinforcement learning while preserving biological interpretability. The present study therefore serves as a bridge between established reward-modulated STDP approaches and emerging delay-based learning methods, using Pong as a benchmark task to evaluate how temporal coding strategies can support adaptive behavior in biologically inspired neuronal systems.

20. Individual, Cultural, and Neighborhood-Level Buffers: Differential Effects on Physical and Emotional Outcomes of Posttraumatic Stress in Black and Puerto Rican Americans

Kerstin Pahl, Xinyu Ding, Navin Sanichar, Joelle Floyd, Sharifa Z. Williams

While the impact of trauma exposure on health is well studied, less is known about the long-term effects of post-traumatic stress and the role of resilience resources on holistic well-being. Most research focuses on individual-level protective factors, with limited attention to systemic-level strengths, particularly in relation to broader indicators of positive functioning, such as subjective physical health and positive emotional states. These gaps are especially pronounced for Black and Latinx populations, where culturally relevant strengths and community resources remain understudied despite disproportionate trauma exposure. This longitudinal study examined how resilience resources across multiple domains moderated the relationship between post-traumatic stress symptoms (PTSS), measured by the PCL-S (Weathers et al., 1993), and subjective well-being among Black and Latinx adults (n=306 43% Black American; 57% Puerto Rican 66% female; 34% male). We investigated whether PTSS (measured at mean age 36) predicted subjective physical (i.e., disturbed sleep, subjective health concerns; SHC) and emotional well-being (i.e., anger, happiness) in participants' early 40s. We explored moderators across four domains: individual adaptation (i.e., active coping), relational resources (i.e., social support by friends), cultural strengths (i.e., ethnic/racial belonging), and community resources (i.e., access to safe neighborhood recreational space; ASRS). PTSS was significantly associated with increased SHC ($\beta=0.13$, $p<0.001$), disturbed sleep ($\beta=0.01$, $p<0.001$), anger ($\beta=0.03$, $p=0.005$), and decreased happiness ($\beta=-0.004$, $p=0.003$). In adjusted analysis controlling for gender and race/ethnicity, active coping and ASRS weakened the relationship between PTSS and disturbed sleep ($\beta=-0.01$, $p<0.001$; $\beta=-0.01$, $p=0.048$) and PTSS and SHC ($\beta=-0.14$, $p=0.001$; $\beta=-0.15$, $p=0.006$). The effect of PTSS on anger ($\beta=-0.04$, $p=0.033$) and happiness ($\beta=0.01$, $p=0.030$) was attenuated by a greater sense of belonging. Social support from friends showed no significant moderation. Findings suggest that active coping and access to safe recreational spaces contribute to subjective physical well-being, while a sense of cultural belonging enhances emotional well-being, reducing anger and increasing happiness, among those who have experienced PTSS. These differential patterns of risk and protection underscore the importance of considering a range of resilience-conferring characteristics and resources at different

contextual levels when examining dimensions of well-being in the context of post-traumatic stress in Black and Puerto Rican adults.

21. Visual contrast manipulation in the digit symbol substitution test reveals the role of early visual processing in greater cognitive dysfunction in schizophrenia

    Maxwell Greisberg, Antigona Martinez, Maria B. Aburto-Ponce, Kristin Micceri, Daniel C. Javitt

    Impairments in early visual processing, particularly reduced contrast sensitivity, are well-established in schizophrenia and contribute to broader cognitive dysfunction. The Digit Symbol Substitution Test (DSST) is a widely used measure of processing speed and cognitive performance in schizophrenia; however, it does not explicitly account for the contribution of visual processing in task performance. The present study examines how manipulation of visual contrast within the DSST influences behavioral performance with the goal of isolating the contribution of early visual deficits to cognitive outcomes in schizophrenia. A modified version of the DSST was implemented with both a standard condition and a low contrast condition. During task performance, eye-tracking data was collected to quantify fixation duration and saccadic patterns while behavioral performance was indexed by total correct responses. Cognitive functioning was independently assessed using relevant subscales from the MATRICS Consensus Cognitive Battery (MCCB). Across both healthy controls and individuals with schizophrenia, DSST performance decreased under low contrast conditions. This was accompanied by longer fixation durations and fewer fixations and saccades. Critically, performance and eye movements in healthy controls under low contrast conditions approximated those observed in individuals with schizophrenia under standard conditions. [MA1.1] Correlations were calculated across behavioral, eye-tracking, and cognitive measures. Within these analyses, positive relationships were observed between contrast DSST behavioral performance and measures of working memory and visual learning. These findings support the hypothesis that early visual processing deficits contribute meaningfully to cognitive impairment in schizophrenia. [MA2.1]By parametrically manipulating contrast, this paradigm provides a more mechanistic framework for dissociating perceptual from higher-order cognitive contributions to task performance. This approach may also offer a sensitive assay for detecting subtle visual-processing abnormalities that could serve as early indicators of disease risk.

22. Defective Rab5-dependent NGF endocytosis and signaling lead to Cholinergic Neurodegeneration in Frontotemporal Dementia Tauopathy Mouse Model

    Kuldeep Sachdeva, Martin J. Berg, Sandip Kumar Darji, Chris Goulbourne, Cynthia Bleiwas, Philip H. Stavrides, Erica Engelberg-Cook, Monica Castanedes-Casey, John F. Smiley, Mala V. Rao, Dennis W. Dickson, Ralph A. Nixon

Frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) tauopathy is a rare, autosomal-dominantly inherited disease caused by MAPT mutations, leading to abnormal tau accumulation, neuronal dysfunction, and progressive cognitive, motor, and behavioral decline. FTDP-17 is an early-onset disease, typically presenting between 45-65 years, with occasional earlier onset. Despite its clinical impact, the molecular mechanisms underlying cognitive decline in FTDP-17 remain unclear. Cholinergic neurons, which are essential for memory and cognition, remain poorly studied in this context. Using the PS19 tauopathy mouse model expressing mutant human MAPT (MAPT^P301S), we examined choline acetyltransferase (ChAT)-positive neurons in the medial septal nucleus (MSN) region and observed a progressive, non-developmental cholinergic neurodegeneration. Since retrograde transport of nerve growth factor (NGF) axonally from hippocampi to MSN is critical for the survival of cholinergic neurons, we examined NGF synaptic uptake and levels in the cell bodies of MSN cholinergic neurons. PS19 mice showed impaired synaptic NGF endocytosis in hippocampal synaptosomes and reduced NGF levels in MSN cholinergic cell bodies, indicating disrupted trophic support. In contrast to Alzheimer's disease (AD), where Rab5 hyperactivation driven early endosome (EE) enlargement disrupts retrograde NGF trafficking, PS19 mice exhibited smaller and fewer EEs due to reduced neuronal Rab5 activation. Similar Rab5 deficits were observed in postmortem FTDP-17 human brains, supporting the disease relevance of this phenotype. Mechanistically, the pathological interaction of Tau with Rab5 and loss of Rab5 activator- Rabgef1, contributes to neuronal Rab5 under-activation in PS19 mice. Altogether, these findings identify defective Rab5-dependent NGF endocytosis and impaired NGF signaling as key drivers of cholinergic vulnerability in FTDP-17 tauopathy, highlighting a mechanistic divergence from AD and suggesting restoration of Rab5 activity as a potential therapeutic strategy in FTDP-17 primary tauopathy.

23. Coordinated thalamocortical ensemble fluctuations during intermodal selective attention

Chase A. Mackey, Samuel Neymotin, Annamaria Barczak, Charles E. Schroeder, Monica N. O'Connell

There is a long tradition in neuroscience examining how variability in sensory evoked responses predicts perceptual choices. However, evoked responses often have relatively weak predictive power, which is attributed to variability in intrinsic (as opposed to evoked) neural activity. Intrinsic fluctuations form the excitability context within which sensory signals are processed, and accumulating evidence implicates slow (< 0.1 Hz) fluctuations in rhythmically gating sensory gain and attention. Critically, however, much remains to be discovered about the circuits generating intrinsic fluctuations - particularly those operating at infraslow timescales (< 0.1 Hz) due to common temporal constraints in controlled experimental settings. We addressed these gaps by recording simultaneous thalamic and laminar cortical activity in the auditory system of two nonhuman primates performing an intermodal audiovisual selective attention task, using linear array multielectrodes. Pre-stimulus alpha-band (9–14 Hz) bursts reliably predicted attentional lapses at the single-trial level. Strikingly, these lapses recurred quasi-periodically at ~4

mHz (~250-second cycles), linking trial-level neural dynamics to an infraslow organizational rhythm of the kind increasingly recognized as a fundamental feature of large-scale brain network operation. Laminar analyses suggest that lapse-related alpha bursts propagate from the thalamus to supragranular cortical layers, which implicates thalamic projections in the generation of intrinsic cortical excitability fluctuations. These results form the foundation for future studies of intrinsic fluctuations in humans, and of their dysfunction in disease states.

24. Cross-Species Alignment of Duration Mismatch Negativity Using a Unified EEG Analysis

    Yukta Jetalpuria, Andrea Balla, Antigona Martinez, Daniel C. Javitt

    Mismatch negativity (MMN) is an electrophysiological marker of auditory deviance detection that reflects pre-attentive sensory processing and is consistently reduced in schizophrenia (SZ), making it a promising translational biomarker. However, direct cross-species comparisons using aligned paradigms and analytical approaches remain limited. We examined duration MMN (dMMN) in humans and mice using parallel experimental designs and a unified analytical pipeline. Human EEG data were collected from healthy control and individuals with SZ during auditory oddball paradigms. Event-related potential (ERPs) and time-frequency analyses (TFA), including inter-trial coherence (ITC) and spectral power, were used to characterize neural responses. In Parallel, intracranial EEG recordings were obtained from freely moving mice, implanted with electrode arrays targeting multiple auditory cortical regions under matched paradigms. Identical preprocessing, artifact rejection, and spectral decomposition procedures enabled direct cross-species comparison. Both species showed robust deviance-related responses. In humans, controls exhibited significant dMMN accompanied by increased alpha/theta power and enhanced ITC for deviant relative to standard stimuli. In contrast, individuals with SZ showed attenuated dMMN amplitudes and reduced ITC. Mice exhibited comparable deviance-related responses with enhanced spectral power in homologous frequency ranges and similar phase-locking patterns in auditory cortex. Additionally, increasing interstimulus interval (ISI) was associated with progressively stronger theta/alpha band power and ITC across both species. These findings demonstrate cross-species convergence in the temporal and oscillatory signatures of dMMN, supporting the use of rodent models to probe circuit-level mechanisms underlying MMN deficits in SZ.

25. A High-Resolution Bioinformatics Pipeline for Identifying Genotypic and Maternal Choline Supplementation Induced Changes Within the Gut Microbiome of a Down Syndrome Mouse Model

    Harshitha Pidikiti, Melissa J. Alldred, Stephen D. Ginsberg

    The gut-brain axis is a critical regulator of homeostasis. Understanding interactions between the CNS and gut microbiome may help inform underlying mechanisms driving brain development, cognition, and emotion, as well as help understand the onset and

progression of neurodegenerative disorders. Individuals with Down syndrome (DS) develop a neurodegenerative brain profile in early mid-life, which is partially recapitulated in the DS mouse model. To characterize components of the fecal microbiome within relevant mouse models, we used a robust bioinformatic pipeline to identify genotypic and maternal choline supplementation (MCS) induced shifts during disease progression. Utilizing QIIME2, 16S rRNA sequences obtained from fecal samples, derived from normal disomic littermates (2N), Ts65Dn (trisomic), MCS trisomic, and MCS disomic were denoised with DADA2. This bioinformatic pipeline allows for detection of rare taxa as well as changes in the abundance of taxa across genotypes and maternal diets, while ensuring data integrity with the use of linear mixed-effects models to account for batch effects. This pipeline provides a foundation for evaluating the impact of MCS on the microbiome during disease progression. The analysis concentrates on identifying distinct microbial signatures that differentiate Ts65Dn from 2N littermates, in the context of maternal diet. Preliminary results pinpoint changes in microbial richness and the differential abundance of key taxa, including Firmicutes and Bacteroidota. These taxa may be vulnerable in trisomic mice, and alterations due to MCS may change the stability of the major taxa and trigger bloom of rare taxa such as Camplyobacterota and Proteobacteria. Such shifts are linked to stressors including inflammation and mucin degradation. Further, functional potential was predicted using PICRUSt2 to identify metabolic pathways associated with disease and the impact of maternal diet. This study provides an initial understanding of genotype effects and MCS driven microbial signatures, offering insights into potential targets for improving gut health in neurodevelopmental as well as neurodegenerative conditions, including Down syndrome and Alzheimer's disease.

26. Do mice prefer FM or AM tone?

Andrea Balla, Yukta Jetalpuria, Monica- Noelle O'Connell, Daniel C. Javitt

Deficits in auditory event-related potentials (aERP) Mismatch Negativity (MMN) and N1 generation are all well established in Schizophrenia (Sz) and have been mapped to dysfunction within early sensory, or even subcortical, auditory regions. Auditory ERP are well- suited for parallel rodent/human studies given the relatively conserved pattern of primary auditory function across species relative to that of other brain regions. Our goal is to develop an appropriate mouse analog using time-frequency (TF) approaches that can be used to establish homology to MMN for exploring electrophysiological and neurochemical disturbances seen in Sz. While MMN-like responses have been demonstrated in mice using simple oddball paradigms, although it was found inconsistently across studies, more complex and ethologically relevant stimuli have not yet been evaluated. Method: Multi-electrode recordings were conducted in freely moving mice to characterize local generators of auditory responses. In addition to standard oddball paradigms, we introduced novel deviant stimuli, including frequency-modulated (FM) "chirps" and amplitude-modulated (AM) tones. We also tested additional control sequences to differentiate stimulus-specific adaptation vs. deviance detection models of MMN generation like roving-standard, jittered standard. TF measures, including inter-trial

coherence (ITC) and spectral power, were analyzed across auditory cortical regions. Results: FM deviant stimuli elicited a significant increase in ITC within theta and alpha frequency bands, as well as a strong enhancement in delta-band ITC relative to standard stimuli. A corresponding increase in alpha-band power was also observed. These effects are localized primarily to secondary auditory cortices and the granular/supragranular layers of primary auditory cortex. Analyses of amplitude-modulated (AM) tone responses are ongoing.

27. Neural Correlates of Self-Processing in Obsessive-Compulsive Disorder and Major Depressive Disorder

    Madison Sakalosky, Caroline Palermo, Goi Khia Eng, Jeanmarie R. Harvey, Katherine A. Collins, Emily R. Stern

    Obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) are internalizing disorders associated with repetitive negative thoughts often involving the self. While more negative representations of self have been linked to MDD, few studies have examined self-representations in OCD and compared brain circuitry during self-processing between the disorders. 68 OCD, 67 MDD, and 19 healthy control (HC) participants performed a self-processing fMRI task where they rated how much positive and negative trait adjectives described themselves (1-5 scale from “not at all” to “very much”). Brain activity during self-ratings was compared between the groups separately for positive and negative traits ($p<0.005$, $k>20$). Compared to HC, OCD and MDD rated themselves as having more negative traits ($p<0.01$), while MDD additionally rated themselves as having fewer positive traits ($p=0.03$). All three groups showed similar patterns of activation in fronto-parietal, sensorimotor, occipital, salience network, and basal ganglia regions when making positive and negative self-ratings. OCD showed less activation than MDD and HC in dorsolateral prefrontal, sensorimotor, anterior cingulate, and inferior parietal cortices. In contrast, MDD had increased insula activation compared to HC for both positive and negative traits, with a larger increase for negative. In conclusion, OCD and MDD participants had more negative self-representations than healthy controls. Although activation patterns were similar overall, OCD patients showed reduced cognitive control-related activation whereas MDD patients showed greater interoception-related activation, specifically for negative traits. These findings demonstrate differential brain circuitry associated with self-processing in OCD and MDD despite both groups showing a similar negative self-bias.

28. Development of a Next Gen 9.4 T Magnetic Resonance system for Translational Neuroscience

    Wasif Zia, Alexandre R. Franco, J. Thomas Vaughan Jr.

    The Nathan S. Kline Institute, Columbia University, and General Electric (GE) are collaborating to develop a next-generation MRI scanner, supported by National Science

Foundation award #2117823. We will discuss 3D rendered videos of the new 9.4T building extension that New York is constructing at NKI. Once completed, the scanner will serve as a shared resource for the tri-state region and approximately fifty research groups across the East Coast. The system will operate at a magnetic field strength of 9.4 T, enabling direct comparison with many preclinical scanners used worldwide but for humans. It will incorporate GE's high-performance gradient system, delivering 140 mT/m gradient strength and slew rates of 810 T/m/s, providing unprecedented imaging performance. The system's core components are currently being assembled. The eight channel 2 kW RF amplifiers have been delivered, and the HG4 gradient system is ready for integration. We are now working to increase its mechanical stiffness with a dual-purpose ribbed shim assembly designed to function effectively within the 9.4 Tesla field strength and further improve magnetic field homogeneity. The system design incorporates service end axial stops, a water manifold, integrated wire guides, and vibration damping wedges at the patient end and along the length. Furthermore, the patient bed features a cantilevered design without a conventional bridge, which is intended to minimize vibration transfer to the subject. This system will enable in vivo imaging and spectroscopy across humans, non-human primates (NHPs), and small laboratory animals, supporting both comparative and translational research within a single platform. Key performance targets include: (1) in-plane spatial resolution of 50 microns for brain structural imaging; (2) temporal resolution for functional MRI (fMRI) capable of detecting connectivity events under 100 ms; (3) spatial resolution for fMRI in the hundreds of microns range; and (4) high-resolution spectroscopic measurements of about two dozen metabolites and neurotransmitters in the human brain comparable to those previously achievable only in small-animal models at similar or higher field strengths. Our overall goal is to establish a state-of-the-art MRI platform and development hub, delivering unprecedented human MRI capabilities at 9.4T.

29. Decoding Oscillatory Burst Features Reveals Population-Level Structure of Human Brain Activity

Alan Díaz-Montel, Idan Tal, Noah Markowitz, Shany Grossman, Elizabeth Espinal, Gelana Tostaeva, Charles Schroeder, Ashesh Mehta, Sam Neymotin, Stephan Bickel

Transient oscillatory bursts are increasingly recognized as fundamental units of neural computation, yet their functional role at the population level remains poorly understood. In this study, we introduce an information-theoretic and machine learning framework to quantify how burst-level features encode behaviorally relevant information in human intracranial electrophysiology (iEEG) recordings from epilepsy patients. We analyzed high-frequency activity (70-150 Hz) and extracted discrete burst events characterized by multiple features, including amplitude, duration, latency, and phase. Using two complementary dataset representations, we first preserved electrode-level structure to assess how spatially distributed burst features relate to experimental conditions. We then constructed an event-level representation, pooling burst features across electrodes to capture the statistical structure of neural activity independent of anatomical constraints. To quantify information content, we computed mutual information between burst

features and stimulus labels, alongside entropy-based measures of variability and conditional structure. This allowed us to dissociate whether information is carried by the presence of bursts, their feature values, or their joint structure across electrodes. We complemented this analysis with Random Forest classifiers to evaluate decoding performance and identify the most informative features across subjects. Our results reveal that burst features carry significant, non-redundant information about experimental conditions, with distinct contributions from feature identity and spatial organization. Notably, the joint distribution of burst features across electrodes enhances decoding performance beyond single-feature representations, suggesting that neural information is embedded in a distributed, population-level geometry rather than isolated local events. These findings support a view of brain activity in which transient oscillatory events form a structured representational space, bridging concepts from spike-based coding and population geometry. By linking burst dynamics to information encoding, this work provides a new framework for understanding how large-scale neural signals support cognition and behavior, with implications for both basic neuroscience and clinical applications.

30. Transcranial random noise stimulation of the secondary visual cortex: Effects on facial emotion recognition and motion processing in autistic adults

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The social communication challenges characteristic of autism spectrum disorder (ASD) include reduced facial emotion recognition (FER). Autistic individuals display elevated extrastriate V2 recruitment during visual processing, and hyper-engagement of secondary visual cortex (V2/V3) in ASD is associated with reduced FER and heightened social challenges. This study evaluated whether V2/V3-targeted transcranial random noise stimulation (tRNS) modulates activation of secondary visual regions to facial stimuli and improves motion processing and FER accuracy in ASD. Tolerability of tRNS was evaluated as tRNS is unexplored in ASD. Adult autistic male participants (N=10; mean [SD] age = 31.3 [7.1]; mean [SD] full-scale IQ = 97.6 [17.3]) received up to 4 mA tRNS delivered to a visual processing network anchored in V2/V3 using 5 high-definition ring electrodes. Targets were personalized using current-flow modeling based on participants' fMRI activation maps during an audio-visual task. Participants completed a random dot kinematogram (RDK; 20%, 25%, 75% motion coherence) task and FER task with static and dynamic components during sham, active, and post-tRNS. During fMRI on a 3.0T Siemens TIM Trio, participants completed bimodal audio-visual and static and dynamic facial emotion stimuli tasks under sham and active tRNS. Outcomes included RDK and FER accuracy and V2/V3 BOLD activation. Stimulation was well-tolerated. At 25% coherence on the RDK task, accuracy marginally improved from 62.8% during sham stimulation to 76.1% during active tRNS ($p=.094$, $dz=0.63$), with accuracy remaining elevated post-tRNS (72.2%). Recognition of afraid and angry expressions improved with tRNS, with greater improvements for

dynamic than static faces. BOLD activation indicated that active tRNS decreased V2 activity relative to sham during the bimodal audio-visual and dynamic facial stimuli tasks, and greater improvement in RDK accuracy was associated with greater V2 activation changes. Results support the feasibility of V2/V3-targeted tRNS in autistic adults. Individualized tRNS can reduce activation in a hyperactive secondary visual region, and V2 modulation may improve motion detection implicated in FER. These findings warrant further exploration of social processing benefits of visual network modulation in ASD, particularly for processing of dynamic fear and anger stimuli.

31. Quality of Sleep and Antipsychotic Dose both Impair Cognitive Performance in Individuals with Chronic Schizophrenia

Anzalee Khan, Beverly Insel, Jean-Pierre Lindenmayer

Background: Individuals with schizophrenia exhibit substantial neurocognitive deficits, which predict poor functional outcomes. Sleep disturbances are common in this population, yet their impact on cognitive performance, particularly during cognitive interventions, is underexplored. Treatment with antipsychotics dose, may interact with quality of sleep to further influence cognitive outcomes. This study examined both sleep measures and CPZ-equivalent dosing as interacting covariate of cognitive performance in patients with chronic schizophrenia enrolled in computerized cognitive remediation therapy (CRT). Methods: Fifty-one inpatients with schizophrenia and aggressive behavior completed baseline neurocognitive assessment using the MATRICS Consensus Cognitive Battery (MCCB). Sleep measures, hours of sleep prior to testing, sleep interruptions, and use of PRN medications for sleep, were extracted from medical charts. Daily antipsychotic doses at the time of cognitive testing were converted to CPZ equivalents. Linear regression models were conducted for each MCCB domain with sleep measures and CPZ equivalents as predictors. Interaction terms between CPZ equivalents and sleep measures were included to assess moderation effects. Significant interactions were explored using simple slopes analysis to quantify the combined impact of sleep and antipsychotic dose on cognition. Results: Participants were predominantly male (84%), Black (49%), with DSM V diagnosis of schizophrenia or schizoaffective disorder and had a high school education or less (75%), with a mean age of 38 years. Sixty-one percent had ≥8 hours of sleep, 67% experienced uninterrupted sleep, and 63% received PRN medications for sleep. Regression analyses indicated that insufficient sleep (<8 hours), interrupted sleep, and PRN sleep medication use were associated with lower MCCB scores across most cognitive domains, except for Social Cognition. Higher CPZ-equivalent doses were independently associated with lower cognitive performance. Interaction analyses revealed that the negative effect of poor sleep on cognition was significantly stronger among participants on higher CPZ-equivalent doses (e.g., for MCCB Composite score: ß interaction = -0.45, p = 0.02), indicating a combined effect of sleep disruption and higher antipsychotic load. Covariate analysis confirmed that both sleep quality and CPZ-equivalent dosing contributed independently and interactively to variability in cognitive performance. Conclusions: Sleep quality and antipsychotic dose are critical interacting covariates of

cognitive performance in individuals with chronic schizophrenia. Poor sleep amplifies the cognitive impact of higher antipsychotic doses, highlighting the importance of monitoring both factors in clinical care and trials of cognitive interventions. Inclusion of sleep assessments and CPZ-equivalent dosing as covariates may improve sensitivity to treatment effects and support the development of more personalized cognitive remediation strategies.

32. Comparison between different early life stress models and their effects on neurodevelopment

    Andrea Martinez-Verdu, Fabiula F. Abreu, Victoria Walker, Masago Ishikawa, Brandon Marino, Catia M. Teixeira

    Environmental factors have profound influence on brain plasticity during early life. Early-life stress (ELS) has been linked to multiple neurodevelopmental and neuropsychiatric disorders. Maternal care is an important environmental factor influencing brain development and later vulnerability to maladaptive behaviors. Our previous study revealed that the mother's presence or absence regulates the activity of the PFC in 11-day-old (P11) rat pups through the serotonergic system. We also observed that PFC inhibition in early life led to cognitive deficits and immature-like physiological responses similar to those observed during maternal separation. In the present study we used C57Bl/6J (N=70) males and female mice to evaluate how different ELS models (P2-P17) lead to similar/distinct behavioral and developmental deficits. Maternal Separation (MS; P2-P5, 4 h/day and P6-P16, 8h/day) and Low Bedding Nest (LBN; restricting access to bedding and nesting materials) groups were tested in Delay non-match to sample (DMNS), in Operant Conditioning (OC) procedure and Social Interaction (SI) task approximately P80. Perineuronal net (PNN) analysis revealed differences in PFC maturation between groups. MS and LBN groups presented behavioral deficits in distinct paradigms. PNN studies suggest differential rates of PFC maturation as a result of early-life stress. These results help to understand how different stressors affect cognition and PFC function and are helpful in modeling how diverse stressors may change brain maturation rates.

33. Workplace Racial Discrimination as a Psychosocial Hazard: Work Stress and the Protective Role of Family Support among Black and Latinx Workers

    Xinyu Ding, Sankhepo Ndhlovu, Sharifa Williams, Kerstin Pahl

    Background: Workplace racial discrimination is a critical social determinant of health, yet the mechanisms linking discrimination to adverse health outcomes and the protective factors that might buffer this association remain underexamined among Black and Latinx workers. This study investigates whether work-related stress mediates the relationship between workplace racial discrimination and depression and anxiety symptoms, and whether social support moderates this pathway. Method: Participants were 290 Black and Latinx adults (mean age=44; 66.5% female) from the Harlem Longitudinal

Development Study. Workplace racial discrimination was assessed using a 4-item scale capturing unfair treatment due to race by supervisors or coworkers. Work-related stress was measured using three work-focused items adapted from the Daily Hassles Scale-Revised (DHS-R; Holm & Holroyd, 1992), reflecting concerns about job satisfaction, supervisor hassles, and coworker interactions. Structural equation modeling tested whether work-related stress mediated the association between workplace racial discrimination and mental health outcomes and whether social support moderated the association between discrimination and work-related stress, adjusting for sex, self-rated health, and daily hassles unrelated to work. Result: Higher workplace racial discrimination was strongly associated with increased work-related stress ($\beta=0.66$, $p<.0001$), which in turn predicted greater depression and anxiety symptoms ($\beta=0.31$, $p<.0001$). The direct association was non-significant ($\beta=0.03$, $p>.05$) after accounting for work-related stress. Family social support significantly buffered the discrimination and work-related stress association ($\beta=-0.38$, $p<.0001$), whereas friend and partner support were not significant moderators. Conclusion: Findings identify workplace racial discrimination as a significant psychosocial hazard that harms mental health by increasing work-related stress. Family social support emerged as a uniquely protective resource for Black and Latinx workers experiencing workplace racial discrimination. Organizational responsibility remains critical: workplace policies such as transparent reporting systems and cultural humility training are needed to prevent racial discrimination and promote equitable workplaces.

34. Bi-Directional Chain of Chirality Transfer in Biological Evolution. Ignoring biological geometry and algebra is wrong way to go.

    Victor Dyakin

    Overlooking fundamental trends in biological sciences during experimental design is not merely inefficient but actively detrimental to human health and the optimal utilization of intellectual and financial resources. The biological relativity principle (BRP) is inherently associated with prevalent biological chirality (PBC). PBC—the exclusive use of one mirror-image form of molecules (L-amino acids, D-sugars, and right-handed DNA I) is linked to BRP through a "genome-centric" flow of chiral information, where initial small asymmetries (symmetry breaking) are amplified across multiple hierarchical levels of biological evolution. Under this framework, homochirality is not a fixed, independent phenomenon, but an essential "boundary condition" that flows from genomic RNA to proteins and metabolism. Elementary Mathematical Formulation of BRP: BC = Bio-Molecular Chirality (BMC) + Pyramidal Neuron (PyrN) + Bilateral Briain (BLB) BC = BMC+ PyrN + BLB. Bi-Directional (<>) Biological Chain of Chirality Transfer (BCCTr) across hierarchical levels of biological evolution (BE). BMC < > PyrN < > BLB. Conclusion: Adopting the principle of biological relativity provides a promising foundation for advancing affordable and accessible diagnostics, contributing to global efforts to mitigate key biological markers associated with neurodegenerative and psychiatric conditions. The predominant form of DNA chirality is a right-handed sugar-based double helix (B-DNA), which is essential for efficiently storing, replicating, and transcribing genetic information.

This structural uniformity ensures stable, predictable interactions with enzymes, which are themselves chiral (L-amino acids), allowing proper molecular recognition. Abbreviations: Biological evolution (BE); Biological relativity principle (BRP); Prevalent biological chirality (PBC); Bio-Molecular Chirality (BMC); Pyramidal Neuron (PyrN); Bilateral Briain (BLB); Biological Chain of Chirality Transfer (BCCTr).

35. Short-form Video Consumption Synchronizes Brain Activity and Enhances Vigilance

Jenna Lembo, Teddy Hoppe, HyunWoong Kim, Samuel Louviot, Eduardo Gonzalez-Moreira, Karl Heinz-Nenning, Alexandre Franco, Michael Milham, Arielle Tambini

The widespread use of media platforms like TikTok and Instagram Reels has made short-form videos (SFVs) a dominant form of media consumption (Pew Research Center, 2025). Given high levels of SFV consumption worldwide, understanding the impact of SFV exposure on behavior and brain activity is critical. To characterize how SFV consumption influences brain activity and behavior, here, we exposed healthy participants to SFVs with varying levels of engagement during fMRI. To assess how SFV watching impacts subsequent behavior, participants performed the Psychomotor Vigilance Task (PVT), a measure of sustained vigilance (Baumann et al., 2014), for three minutes after viewing. SFVs were downloaded from TikTok, and varying levels of SFV engagement blocks were created from viewer engagement metrics. To measure subjective experience during SFV viewing, participants completed an SFV Immersion Questionnaire (adapted from Rigby et al., 2019), assessing constructs such as enjoyment, captivation, and awareness. Principal component analysis (PCA) of questionnaire responses isolated a component reflecting video captivation and enjoyment, consistent with Rigby et al. (2019). To determine how SFV engagement and immersion affect subsequent PVT behavior (response times and hits), mixed linear models (MLM) were conducted with predictors of preceding SFV conditions and nuisance covariates. Exposure to higher-engagement SFVs increased hits after SFV watching. Similarly, greater SFV immersion improved performance after SFV exposure (higher hits and faster response times). These findings suggest that consuming engaging and immersive SFVs induced a state of increased vigilance and attention to external stimuli, which persisted for up to three minutes. To test this hypothesis, we calculated inter-subject correlations (ISC) of fMRI data during SFV watching as a proxy for externally-oriented, stimulus-driven processing. Higher SFV engagement drove ISC across widespread sensory and higher-level cortical regions, while SFV immersion specifically drove ISC in the auditory cortex and dorsal parietal somatosensory regions. ISC in the left fronto-polar cortex during SFV watching was positively correlated with subsequent PVT performance, suggesting that stronger SFV-driven brain activity is linked with enhanced vigilance following SFV exposure. Given that SFVs induce externally-oriented brain states and alter subsequent behavior, continued research is warranted.

36. Predicting Clinical Response to iTBS in Young Adults with MDD and NSSI: A Go/No-Go fMRI Study

Vicente Cotanda, Gabriel Behr, Laissa Harumi Furukawa, Giovanna Bertoldi, Ricardo Boff, Inais Andrade, Nicolas Stanton, Luiza Costa Silva, Mirna Portuguez, Jaderson Costa da Costa, Lucas Spanemberg, Alexandre Franco

Major Depressive Disorder (MDD) and Non-Suicidal Self-Injury (NSSI) are highly prevalent in young adults and associated with significant impairments in cognitive control and response inhibition. While Transcranial Magnetic Stimulation (TMS) to the left dorsolateral prefrontal cortex (dLPFC) has shown efficacy in treating depression, objective biomarkers are needed to predict clinical trajectories, particularly for behaviors associated with impulsivity. This clinical trial investigates the impact of intermittent Theta Burst Stimulation (iTBS) in a sample of 40 young adults (18–39 years) diagnosed with MDD and comorbid NSSI. Participants are randomized to receive 20 sessions of active iTBS or sham stimulation during a period ranging from 4 to 6 weeks. A central component of this study is the use of a Go/No-Go (GNG) functional MRI paradigm to quantify activation within the cognitive control circuit (dLPFC–dACC). Drawing on recent evidence (Tozzi et al., 2024), we hypothesize that baseline task-evoked functional profiles within this circuit characterize a biotype of "cognitive dyscontrol" that predicts clinical and behavioral response to dLPFC-TMS. Crucially, we investigate how GNG activation patterns and behavioral performance metrics relate specifically to the severity and frequency of NSSI symptoms. Given that deficits in response inhibition are a core neurobiological feature of the impulsivity underlying self-harm, we expect that baseline dLPFC–dACC dysfunction will serve as a specific predictor of NSSI clinical improvement. Integrating clinical assessments with task-based neuroimaging, this research aims to validate a targeted approach to psychiatric care, identifying those most likely to achieve both circuit-level modulation and the reduction of high-risk self-injurious behaviors.

37. In vivo 7 Tesla MRI of Intracortical Microvascular Architecture and Blood Flow Velocity in Macaque Monkey Brain

    Yuqi Feng, Jianbao Wang, An Ping, Feiyan Tian, Yipeng Liu, Yi-Chang Hsu, Jonathan R. Polimeni, Anna Wang Roe

    Intracortical arterioles are key locations for blood flow regulation and oxygen supply in the brain and are critical to brain health and neuropsychiatric disorders. However, imaging such small (<100-µm-sized) vessels in humans is challenging. Here, using non-human primates (macaque monkey) as a model, we developed a capability for imaging microvasculature in vivo with a clinical 7 T MRI scanner. Using simulations, we identified parameters for imaging intracortical vessels with slow flow and combined this with high-resolution (64 × 64 µm2 in-plane) time-of-flight magnetic resonance angiography. Across large swaths of occipital, parietal, and temporal cortex, arrays of intracortical arterioles and venules were observed in gyral crowns and deep within sulcal folds. Systematic arteriole-venule patterns revealed potential architecture of input-output flow relationships. Using quantitative phase-contrast MRI, we further measured blood velocity in these small intracortical vessels at the same in-plane resolution, enabling

quantitative characterization of microvascular flow dynamics at the level of individual vessels. This study establishes a new MRI technology for mapping microvascular architecture and for providing fundamental and quantitative knowledge regarding microvascular flow in the neurovascular tree. This also introduces a macaque monkey model as a basis for studying cortical vascular dynamics. These capabilities open doors for tracking vascular health in humans, investigating their disruption in neurodegenerative and neuropsychiatric disorders, and provide a human-similar animal model for developing and assessing interventional methods. [cf. Wang 2025 Neuron, doi: 10.1016/j.neuron.2025.05.028].

38. Infrared Neural Stimulation in V1 Produces Intensity-Dependent Perceptual Biases in Awake Macaques

Anna Wang Roe, Sunhang Shi, Meixuan Chen, An Ping, Feiyan Tian, Jianfeng Fu

Electrical microstimulation of cerebral cortex is a neuromodulatory tool which can be used to achieve systematic shifts of behavioral curves. However, in humans and primates, it is still difficult to reliably achieve selective effects on single perceptual parameters (such as color, orientation, motion, and depth perception), as electrical microstimulation is accompanied by current spread in tissue, making it more difficult to maintain single functional columnar specificity. Optogenetic stimulation offers exquisite cellular specificity but requires viral transduction and is more difficult to implement in humans. Here, we explore a new approach, called Infrared neural stimulation (INS). This method delivers tiny heat boli (via optical pulse trains at 1875 nm near peak of water absorption) and has been shown to be capable of selectively and safely activating single cortical columns and their connected networks. Here, we examine its effect on behavior in monkeys performing a choice task. Two macaque monkeys performed a 2-alternative forced-choice (2AFC) contrast-discrimination task (one side fixed at 30% contrast, opposite side 10–60%). In half the trials, the fixed-contrast side received INS (at 2 intensities: 0.3 J/cm² or 0.7 J/cm²); the remaining trials were visual-only controls. Across tens of sessions, 20,000 valid trials, and 5-10 stimulation sites in V1 using two intensity levels. Behavior was analyzed using parametric statistical framework. We assessed a few different paradigms of INS stimulation (pulse number, duration, relative timing). INS at a single columnar site induced systematic shifts in points of subjective equality (PSE or inflection point) and sensitivity (slope), revealing a perceptual bias of the stimulated side. Using parametric statistical framework, the modulation scaled with stimulation intensity, demonstrating a parametric effect of INS on perception. These behavioral signatures reflect highly focal contrast-gain–like shifts in PSE and sensitivity-gain–like changes in slope within early visual cortex. Our findings suggest that INS can be used as a causal, parametric neuromodulation technique capable of evoking single-column (and therefore featurally specific) perceptual biases in awake primates. INS thus complements electrical and optogenetic approaches and can be developed for functionally precise behavioral effects in future closed-loop neuroengineering.

39. Orexins as anxiety modulators in instrumental safety-seeking

Cristina Siller-Perez, Erika C. Andrade, John Smiley, Christopher K. Cain, Robert M. Sears

To shed light on human anxiety, it is necessary to identify the neuromodulatory systems that orchestrate adaptive coping behaviors. A central orchestrator in this context is the hypothalamic orexin (hypocretin) system, which modulates behaviors critical to survival in large part via projections to the dopaminergic ventral tegmental area (VTA). The VTA plays a crucial role in reinforcing behaviors that lead to desirable outcomes, but its involvement in reinforcing threat-motivated instrumental behaviors, such as signaled active avoidance (SigAA), remains unclear. Previous research in our lab utilizing a SigAA shuttling task indicates that avoidance is positively reinforced by response-produced safety signals (RPSS). Based on this, we hypothesized that the LH-orexin to VTA modulates avoidance behavior by invigorating avoidance responses reinforced by RPSSs. To examine this, we used an orexin-specific viral vector in adult Sprague-Dawley rats to express an inhibitory opsin (AAV1-Ple112-Arch3.0-eYFP) in perifornical/lateral hypothalamus neurons and implanted optic fibers in orexin axon fields in the VTA. After incubation, animals were trained in SigAA where rats learned to shuttle during a white noise warning stimulus (WS) to prevent mild foot shocks. Explicit feedback cues (pure tones) were delivered immediately after successful avoidance responses (i.e., RPSS). Rats received 15 trials per day until they reached a pre-defined avoidance criterion. In shock-free test sessions, inhibition of orexin at VTA axon terminals during feedback cue presentations gradually impaired avoidance, whereas the no-laser and virus control groups showed high levels of avoidance. Preliminary results suggest that inhibition during the inter-trial interval may also reduce avoidance; potentially, orexin signals an extended safety period beyond RPSS, maintaining avoidance. This finding suggests that orexinergic modulation of VTA is crucial for processing safety signals as valued instrumental goals during threats. It also provides additional evidence that active avoidance is positively reinforced by safety. Future research will explore the orexin system's role in adaptive coping behaviors and may pave the way for innovative treatments targeting maladaptive coping strategies beyond anxiety.

40. Religious Engagement and Meaning-Seeking as Coping Pathways During COVID-19

Alexandra Kohl, Anna MacKay-Brandt

During the COVID-19 pandemic, individuals relied on diverse coping mechanisms to manage heightened stress and psychological distress. We examined associations between religious engagement, meaning-seeking, and coping strategies using baseline measures from the NKI-Rockland Sample (NKI-RS) COVID Extension Survey (N = 553; 366 women, 187 men; aged 18 - 90 years) collected via an online survey between May and September 2020. Participants completed surveys assessing religious/meaning variables (prayer frequency, religious importance, meaning-seeking, perceived life purpose) and distress indicators (coping, intolerance of uncertainty, trait worry). Correlational

analyses revealed distinct associations linking these constructs. Religious engagement showed specific associations with emotion-focused coping: prayer frequency was positively correlated with emotion-focused coping ($r = 0.21$, $p < .001$), as was rating religion as important ($r = 0.16$, $p = .01$). Meaning-seeking demonstrated a broader pattern of associations, correlating with total coping ($r = 0.35$, $p < .001$), emotion-focused coping ($r = 0.31$, $p = .01$), and avoidant coping ($r = 0.25$, $p = .03$). Notably, meaning-seeking was independent of religious engagement measures ($r = -0.01$ to 0.01, ns), suggesting these represent distinct psychological resources during pandemic stress. Intolerance of uncertainty—but not trait worry—was significantly associated with feeling that life lacks purpose ($r = 0.37$, $p < .001$). Meaning-seeking also correlated with this sense of no purpose ($r = 0.16$, $p = .03$), suggesting that individuals experiencing hopelessness actively engaged in meaning-seeking. Women reported significantly higher prayer frequency and religious importance than men (both $p < .001$), and also reported higher coping strategy use across all types. These findings highlight religious engagement and meaning-seeking as functionally distinct responses to pandemic distress. Religious practices are specifically linked to emotion-focused coping, while meaning-seeking operates as a broader adaptive response. The association between intolerance of uncertainty and both meaning-seeking and hopelessness suggests that the search for meaning during crisis may reflect active psychological engagement with one's sense of purpose rather than simple anxiety reduction.

41. Examining functional connectivity during urge suppression in individuals with obsessive-compulsive disorder and unaffected siblings

    Goi Khia Eng, Jeanmarie R. Harvey, Katherine A. Collins, Russell H. Tobe, Dan V. Iosifescu, Emily R. Stern

    Background: Obsessive-compulsive disorder is a familial and heterogeneous disorder. Many individuals with OCD often report uncomfortable or aversive sensory-based urges preceding their compulsions. Using an eyeblink suppression task to model sensory urges, we previously showed that OCD patients had greater activation than healthy controls in sensorimotor network regions. Here, we seek to further elucidate these mechanisms by examining functional connectivity involving sensorimotor regions during blink suppression in probands with OCD and unaffected siblings. Methods: 24 healthy controls and 24 matched OCD probands with their unaffected siblings performed an fMRI eyeblink-suppression task, with eyeblinks measured using an eye-tracking device. Eight blocks of alternating blink-suppression (60s/block) and free-blinking (30s/block) were presented. Generalized psychophysiological interaction analysis examined seed-to-voxel functional connectivity during blink suppression using 10 ROIs of 5mm-spheres centered around sensorimotor network regions of Yeo’s atlas. Results: Unaffected siblings and healthy controls demonstrated better blink suppression than probands. Compared to probands, unaffected siblings showed less connectivity of sensorimotor regions with orbitofrontal cortex, superior frontal gyrus, insula, and supramarginal gyrus during suppression, and greater connectivity with inferior parietal and inferior frontal

gyrus regions. Compared to healthy controls, unaffected siblings showed less connectivity with caudate, putamen, and mid-cingulate and greater connectivity with prefrontal regions (superior, medial, and inferior frontal). Conclusion: OCD patients showed greater sensorimotor connectivity with regions involved in somatosensory and emotional processing during urge suppression, while unaffected siblings had greater connectivity with areas involved in cognitive flexibility and inhibition. These differences may reflect protective factors that might mitigate OCD symptom development.

42. Top-down inputs show context-selective synchronization with V1 spiking following focal N-methyl-D-aspartate receptor blockade

    Connor G. Gallimore, Jay Abraham, Adam Hockley, Jordan P. Hamm

    Basic sensory processing deficits are a core feature of psychosis-related psychopathologies, such as schizophrenia. Among the most reliable is that of a pre-attentive, unconscious brain response termed the "mismatch negativity" (MMN) signal—an event-related potential that is enhanced when environmental regularities, such as a repeated sight or sound, are violated. MMN has been linked to impaired N-methyl-D-aspartate receptor (NMDAR) functioning in humans, as well as “analogous deviance detection” (DD) responses in rodents, and primates, implicating deficient excitatory neurotransmission as one major axis of dysfunction. Mice have provided a powerful model system to tease out the cell and circuit roles of NMDARs in predictive processing, with some studies showing increases in top-down suppressive axonal input to lower sensory areas, yet aspects of its influence during real-time sensory processing have remained unclear. Here, we sought to address this by measuring extracellular potentials (16-channel multielectrode probes) in the V1 and ACa of mice (n=10) during visual oddball sequences of full-field oriented square-wave grating stimuli (redundant, p=.9; deviant, p=.1) both before and after V1 NMDAR block via local application of MK-801. We show that multiunit spiking activity (MUA) in infragranular layer 5 showed the greatest context-selective reductions during perception of both predictable and deviant stimuli. With respect to oddball versus control trials, the magnitude of MUA was significantly more modulated by the theta phase of frontal local field potentials from the anterior cingulate area (ACa; n=6). These data concord with past work demonstrating a suppressive input onto V1 from the ACa, potentially suggesting a bias of perceptual circuits towards internally-generated models when bottom-up signaling is disrupted.

43. Topography of tuning to acoustic bandwidth across the supratemporal plane in macaques

    Yoshinao Kajikawa, Chase A MacKey, Ian Chong

    Sensory cortices represent the organization of sensory organs in topographic maps. For instance, the positions on the body and retinal surfaces are represented in 2-dimensional somatotopic and retinotopic maps, respectively. In the auditory system, the

cochlea's representation of sound is tonotopic, i.e. sound frequency is mapped from low to high. This tonotopic representation is maintained throughout the primary auditory system, including auditory cortex, where frequencies are mapped low to high. Auditory cortex also represents periodicity orthogonal to the tonotopic gradient, forming multidimensional topographic representations similar to other sensory modalities. While many auditory studies focus on periodic sounds (e.g., pure tones or complex tones, harmonic or inharmonic), many natural sounds are aperiodic or fricative with different spectral envelopes. A feature common to different types of sounds, regardless of their periodicity, is the bandwidth. In this study, we address a possibility that tuning to the bandwidth of sound is represented in the direction perpendicular to the tonotopic gradient in macaque auditory cortex. The perimeter of the supratemporal plane (STP) was mapped bilaterally in a macaque monkey, in order to identify the mediolateral extent of auditory cortex for a project (RF1NS133972). At each site, responses to pure tones of different frequencies were examined to find the best frequency (BF). To examine the bandwidth tuning, pure tones at BF, and bandpass noise centered around the BF, with varying bandwidth, were presented in random order at 60dB SPL. Medially, all cortical columns responded least to pure tones and responded better to wider bandwidth sounds in both hemispheres. In contrast, most of the lateral columns responded best to pure tones and less to sounds of wider bandwidth. Though mapping in this study was sparse, the results suggest the possibility that macaque auditory cortex has mediolateral gradient exhibiting a map of the bandwidth of sound.

44. A Pharmacy-Based Opioid Use Disorder Care Model: Implementing Participant Navigation

Zoe Bertone, Xinyu Ding, Helen-Maria Lekas, Babak Tofighi, Crystal Fuller Lewis

Background: This study examines the implementation of PharmLink/VBC+, a pharmacy-based care model integrating on-site patient navigation with a Virtual Buprenorphine Clinic (VBC) providing telehealth opioid treatment and HIV services access in two independent pharmacies in the Bronx, a NYC neighborhood disproportionately affected by opioid use and overdose. A core implementation feature examined in this analysis was the pharmacy and research staff experience linking study participants to critically needed services (e.g., SNAP, CityFHEPs) to help reduce health disparities. Methods: Using community-based approaches, we recruited 30 individuals 18 and older who reported current opioid use and were not engaged in buprenorphine treatment but open to initiating treatment through telehealth. Research staff field notes were collected at each survey visits baseline, 6-week, and 12-week). Additionally, field notes were collected at documented participant encounter throughout the study. The findings below stem from the thematic analysis of the field notes. Results: Engagement in buprenorphine and HIV treatment is undermined by immediate social needs, including housing instability, domestic violence, limited access to public assistance, and untreated comorbid mental illness. Although participants described mistrust of healthcare systems due to stigma, discrimination, and bureaucratic barriers (e.g., long waitlists and

restrictive drug treatment programs), they expressed trust in pharmacy and research staff contributing to the intervention's feasibility. Delivery of patient navigation to begin addressing participants' high-acuity needs was achieved through close collaboration between research and pharmacy staff. However, competing workflow and time demands, limitations engaging in harm reduction approaches, and challenges in supporting individuals with significant social and clinical needs constrained pharmacy staff's capacity to fully engage in navigation activities. Conclusion: Findings underscore the need for comprehensive harm reduction- and social determinants-oriented pharmacy staff training to support their effective integration into low-barrier care models that aim to engage a socially and clinically precarious population in buprenorphine and HIV treatment.

45. Investigating the laminar signatures of mismatch negativity to frequency-modulated sweeps in macaque auditory cortex

    Ian Chong, Renee Hartig, Noelle O'Connell

    Mismatch negativity (MMN) is a robust cortical event-related potential associated with deviance detection and predictive coding. It is also among the most validated neurophysiological biomarkers of cognitive dysfunction and functional outcome in schizophrenia. Yet, despite its translational relevance, the laminar and circuit-level mechanisms that generate MMN remain incompletely defined, particularly in non-human primates (NHPs). Here, we investigated MMN generation in awake macaques using laminar electrophysiological recordings in primary auditory cortex (A1). Current source density analysis enabled precise delineation of cortical layer boundaries. Tonotopic mapping was first performed to identify each site's preferred frequency. We then employed a deviant-oddball paradigm in which upward or downward frequency-modulated (FM) sweeps served as standard stimuli, with the opposite sweep direction presented as the deviant. FM sweeps spanned 2-12 kHz over 100 ms (~26 octaves/s), providing a dynamic and ethologically relevant stimulus compared to traditional pure-tone paradigms. Simultaneous recording of local field potentials, multiunit activity, heart rate, and eye movements were obtained in a head-fixed configuration to assess the physiological correlates of auditory processing. Analyses included traditional amplitude-based comparisons of evoked responses as well as spectral characterizations of oscillatory dynamics underlying MMN. As part of a broader cross-species effort to develop spectrally defined rodent and NHP homologs of human MMN, this work supports direct comparison of deviance-related signals across species, advancing a mechanistic, cross-species framework for MMN generation.