Abstracts Presentations:

1. Lifetime Achievement Talk: Perceptual and cognitive deficits in severe mental illness

Pamela Butler, PhD

Visual perceptual deficits are prevalent in people with severe mental illness, from the teen and early adult years of clinical high risk to first episode and more chronic schizophrenia. This presentation will discuss our research at the Nathan Kline Institute and with collaborators at other institutions, showing prediction of conversion to psychosis in high risk populations and the changes in visual perceptual deficits as the disease progresses. These deficits, including anomalous perceptual experiences, low-level impairment in contrast sensitivity and more mid-level impairment in perceptual integration are related to impaired cognition and social cognitive function. Indeed, difficulty perceiving the world, such as in fragments rather than holistically, affects face and object perception. Social interactions and function depend on accurate perception. We have recently found social reward learning deficits in schizophrenia, which are, in part, a function of impaired emotion perception. Understanding fundamental neural processes gone awry has allowed us to design visual remediations (i.e., a gamification of learning to detect contrast and contour) which have improved perceptual function as well as symptoms. Understanding basic neural processes provides ability to drive the field forward to develop remediations to help people function better in the world. This presentation will also briefly discuss changes in the field from a "bottom-up" vs. "top-down" view of brain function to more synergistic concepts such as predictive coding and Bayesian priors.

2. Racism Hurts: Race-based traumatic stress predicts bodily pain in midlife black and latinx americans

Maggie Ding*, Sharifa Williams, Navin Sanichar, Tine Pahl

Background: Trauma and stress are associated with physical pain. Repeated insults to a person's identity, such as exposure to racism, cumulatively influence pain-regulation processes. To date, little research has examined the association of pain and racism. We examined how race-based traumatic stress, a trauma response to a stressful racist encounter, relates to bodily pain in the context of self-reported general health (GH) and depressive mood, both related to pain.
Method: 303 (mean age = 44) Black and Latinx Americans (56.4% female) from the Harlem Longitudinal Development Study completed surveys between 2018-2023. RBTS was measured as the sum of a 14-item scale (Cronbach's alpha = 0.86) that assessed post-traumatic responses after a racist encounter. Bodily pain was the mean of 2 items (Cronbach's alpha = 0.86) that inquired about severity of bodily pain. GH was defined as the average of five items measuring self-reported health (Cronbach's alpha = 0.73). Depression was defined as the mean of an 8-item scale of depressive symptoms (Cronbach's alpha = 0.91). Pain was regressed on RBTS, adjusting for race/ethnicity (Black, Latinx), gender (male, female), GH, and depression.
Result: In the adjusted analysis, RBTS and bodily pain were significantly associated (beta=0.05, $p=0.014$), as were GH and pain (beta =-0.45, $p<0.001$) and depression and pain (beta=0.19, $p=0.046$). Our research thus demonstrates the unique contribution of racism-related trauma to elevated pain levels in Black and Latinx Americans.
Discussion: Findings illustrate the grave impact that racism has on Americans of color. Racism not only causes psychic pain; it also manifests as bodily pain, which severely impacts quality of life. This is of particular concern given the racialized disparities in the treatment of pain that affect Americans of color. Pain disparities thus seem to be another important manifestation of how racism "gets under skin."

3. tDCS-induced modulation of face emotion processing deficits in schizophrenia

Maria Aburto*, Pejman Sehatpour, Odeta Beggel, Daniel Javitt, Antigona Martinez

Background: Impaired face emotion recognition (FER) is a core feature of schizophrenia (Sz) which has been linked to atypical neuronal activity within visual cortex. In the visual system, FER depends upon coordinated functioning of subcortical and cortical regions including the pulvinar nucleus of the thalamus and motion-sensitive cortical regions (MT+) for processing of moving facial features. Abnormal processing of basic motion features (e.g., direction, velocity) is also consistently observed in patients with Sz and has been associated with FER deficits. In this ongoing study, we use personalized transcranial direct current stimulation (tDCS) delivered to MT+ in combination with behavioral measures of motion perception and FER, and concurrent EEG recordings and fMRI to evaluate effects on both behavior and associated EEG and fMRI activation patterns. Based upon prior work by us and others, we predicted that cathodal stimulation targeting MT+ would have the greatest beneficial effects on FER and motion perception.
Methods: Nine patients (mean 37 years) meeting DSM-IV criteria for Sz. For tDCS, MxN stimulation was combined with realistic head modeling to generate a personalized model per subject that maximized current flow within MT+. Subjects participated in 3 tDCS/EEG sessions separated by at least 1 wk, followed by a single tDCS/fMRI session. tDCS/EEG sessions consisted of either sham (30sec ramp-up/ramp-down condition), cathodal or anodal stimulation. For the tDCS/fMRI session we used sequential sham and cathodal stimulation. Behavioral measures of coherent motion detection were determined using random dot kinematograms (RDK) at pre-set coherent motion levels (20-25%). Dynamic emotional faces were used to assess FER accuracy. Behavioral variables were collected pre, during and post-stimulation during EEG sessions. For fMRI the same stimuli used in the RDK and FER tasks were delivered passively. Lastly, EEG data was analyzed in the time-frequency domain.
Results: We observed the predicted increase in the theta evoked power response to RDK stimuli during cathodal stimulation that was significant even in this small sample size ($t=3.45$, $p=.011$). Moreover, the increase correlated with improved motion sensitivity, which, in turn, correlated with improved FER ($p<.05$). In contrast, we observed decreases during and after anodal stimulation that were not significant in this sample size. Consistent with the EEG findings, we observed enhancement of the fMRI response in the cathodal vs. sham stimulation condition to both RDK and FER stimuli. For motion stimuli significant enhancements were observed within MT+ ($t=3.14p<.01$) and early visual regions ($t=2.31p<.05$). Additionally, we observed correlations between changes in MT+ activation and behavioral improvement ($p=.03$). For face stimuli we observed a numeric increase in superior temporal sulcus activation that was not significant in this sample size ($p=.08$).
Conclusions: The ability to recognize and respond to the emotional content of faces is crucial for social cognition and is impaired in SZ. The findings thus far from this study are consistent with previous work and support the hypothesis that deficits in motion processing contribute to social cognition impairment in Sz and support the feasibility of using combined tDCS/EEG/fMRI to evaluate the mechanisms underlying early sensory contributions to cognitive impairment in Sz.

4. Development of a next gen 9.4 T magnetic resonance system for translational neuroscience

Wasif Zia*, Yihe Hua SK Lee, Thomas Foo, Rory Warner, Alexandre R. Franco, J. Thomas Vaughan Jr.

Nathan S. Kline Institute, Columbia University, and General Electric (GE) are working together to build a powerful MRI scanner with National Science Foundation funding award # 2117823, which is currently in year 3. New York state is building a special facility for it and upgrading their animal facility and human experiment room. The scanner will be a shared resource in the Tristate area.
The scanner will have a magnetic field strength of 9.4 T. This particular field strength allows direct comparison with many pre-clinical scanners being used around the world and is coupled with high performance gradients from GE with a field strength and slew rates of 140 mT/m and 810 T/m/s, respectively, for unprecedented performance.
Currently, we are developing a 36-tray shim tube assembly based on magnet-gradient interaction (MGI) simulations to nest the high-performance gradient set and rigidly secure it into the 65 cm

bore magnet with axial stops in the service end. The service end will also have a water manifold and wire guides where each wire will carry ~900 A. The patient bed is a cantilever design without a conventional bridge to isolate the subject from vibrations.
With this system, we will acquire in vivo images and spectra from humans, NHPs, and smaller laboratory animals to facilitate comparative and translational studies on a single scanner. Targeted specifications include: 1) in-plane spatial resolution for brain structural imaging of 50 microns, 2) maximal temporal resolution of functional MR imaging (fMRI) measured connectivity events of less than 100ms, 3) maximal spatial resolution of fMRI of 100s of microns, and 4) high resolution spectroscopic measurement of metabolites and neurotransmitters in human brain comparable to values heretofore achievable only in small rodent models in high resolution systems of the same or higher field strengths.
To achieve the latter, we are also developing an ultra-high field laboratory to fabricate our own RF coils including Transverse Electromagnetic (TEM) coil and use the concept of B1 shimming. To manage B0 inhomogeneity we plan higher order shims to be integrated with our TEM coil. Our objective is to develop a state-of-the-art MRI system and development hub unprecedented human MR capability at 9.4 T.

5. Single cell multiomic hyperdimensional measurement platforms

Christopher Bare*

The cell is considered the finest viable subdivision of an organism, often colloquially termed the “building block” of the larger entity. A fundamental precept of precision medicine is the reduction of pathology and treatment to the granularity of the individual. Analytical technology for individual-specific assessment of multiple biological domains, often labelled multi-omic technology, has existed for decades within the research community. With the renewed focus on precision medicine and multimodal research verification, convergence of previously siloed discovery and analytical platforms with single cell resolution is providing larger troves of insight and exploration than before. The key element that defines a platform as multi-omic is the intrinsic ability to correlate readout domains. Transcriptomics is correlated to cellular morphology. Proteomics is correlated to organ architecture. Deep phenotyping is correlated to metabolomics.
NKI has implemented two discrete platforms that provide workflow to multi-omic endpoints from any input research material from any faculty laboratory. The use of fluorescence associated cell sorting (“flow”) and digital spatial profiling (“DSP”) facilitate new levels of exploration and unlocking key reservoirs of scientific data. While the platforms have both similarities and differences, they fundamentally transform research. Here we shall describe the basic functionality, requirements, and potential value of each platform.

Abstracts Posters:

1. Electrophysiological effects of mitochondria mitochondria-derived extracellular vesicles: novel implications for memory dysfunction in neurodegenerative disorders

Pasquale D’Acunzo*, Elentina K. Argyrousi, Jonathan M. Ungania, Yohan Kim, Steven DeRosa, Monika Pawlik, Chris N. Goulbourne, Ottavio Arancio, Efrat Levy

Background: Mitovesicles are a newly identified subtype of small extracellular vesicles (EVs) of mitochondrial origin. We recently developed a method to separate mitovesicles from other EVs after their isolation from the extracellular space of murine and human brain tissues. This method permits the study of the roles of mitovesicles in physiology and disease.
Given their origin, we hypothesized that mitochondrial dysfunction, a hallmark of both Alzheimer’s disease (AD) and Down syndrome (DS), could induce alterations in mitovesicles, thus perturbing

brain homeostasis and contributing to propagation of pathology. Therefore, we studied mitovesicle components and functionality after their isolation from the brain of a mouse model of DS (hereafter Ts2) as compared to diploid (2N) controls, as well as from frontal cortices of individuals with DS as compared to their age-matched 2N controls.
Methods: Brain mitovesicles were isolated and analyzed by Western blotting, electron microscopy, nanotrack analysis, and monoamine neurotransmitter degradation assay as recently described (D'Acunzo, et al., 2022, PMID: 35962195). Coronal hippocampal slices from wild-type mice were perfused with different subtypes of brain EVs, pretreated or not with clorgiline and pargyline (1 μM each), irreversible inhibitors of the monoamine oxidases type A and B (MAO-A and MAO-B), respectively. Long-term potentiation (LTP) induced at the level of the Schaeffer collateral fibers through a theta-burst stimulation.
Results: Mitovesicle number is higher in brains of DS individuals and of Ts2 mice and contain a higher MAO-B protein amount and enzymatic activity per EV as compared to diploid controls, suggesting a potential mitovesicle-dependent impairment of neuroamine homeostasis in DS. In agreement with that, Ts2 (but not 2N) mitovesicles stimulated a decreased LTP in recipient hippocampal slices as compared to vehicle control. This biological activity was abolished when MAO-B (but not MAO-A) was blocked. The other EV subtypes of both genotypes, microvesicles and exosomes, did not trigger an effect on LTP. DS changes were found to be sex independent.
Conclusions: Pathogenic mitovesicles are previously undescribed active players of the brain extracellular milieu by regulating LTP via MAO-B, and potentially contribute to memory formation deficiencies typically found in AD and DS.

2. Sulforaphane for the treatment of negative symptoms in schizophrenia

Robert C Smith*, Jing Huang, Hua Jin, John M Davis, Renrong Wu

Background: Negative symptoms persist in many patients with schizophrenia after positive symptoms are reduced by antipsychotic medication and are associated with persistent problems in social functioning and other functional outcomes in schizophrenia. There are few established treatments for negative symptoms in schizophrenia. Oxidative stress, inflammation and epigenetic modifications involving HDAC have been implicated in the pathophysiology of schizophrenia. Sulforaphane has antioxidant properties and is an HDAC inhibitor. The object of the current study was to determine the efficacy of sulforaphane in treatment negative symptoms in patients with schizophrenia who were stabilized on antipsychotics and had predominant negative symptoms.
Methods: This was a randomized double-blind placebo controlled study of patients (male and female) with schizophrenia who were stabilized on antipsychotic medication and had predominant negative symptoms (PANSS negative symptoms higher than positive symptoms) in Hunan China. Patients received daily doses of either 2 (1700 mg) tablets daily of Extra Strength Avmacol (Nutramax sulforaphane tablets glucoraphanin content 30 mg/tablet) or placebo tablets for 24 weeks. All other medication was stable thought the trial. Psychiatric symptoms were measured with PANSS scale and CGI. Side effects were assessed with TESS scale. Analysis used intent to treat mixed model analysis for symptom scores and Mann Whiney U Test for each side effect item scores.
Results: 53 patients treated with sulforaphane and 24 patients treated with placebo who had a least one post intervention outcome evaluations were analyzed. Sulforaphane treated patients showed a significantly greater decrease in PANSS negative symptom total score (P=.01) and PANSS Negative factor score (P=.02) than placebo treated patients with the most prominent difference occurring at 24 weeks (P≤.001) with large effect size at this time point (d=0.8). Sulforaphane's effect on decreasing negative symptoms was not mediated by change in scores of depression or cognitive factors on the PANSS. There were no significant differences between sulforaphane and placebo on change in the CGI scale. Sulforaphane was well tolerated and there were few differences between sulforaphane and placebo on items in the TESS side effect scale.
Conclusions: The results of this study suggest that add-on high dose sulforaphane may significantly reduce negative symptoms in stabilized schizophrenic patients on antipsychotic medications who have predominant negative symptoms. The pronounced effect may only be seen after several

months of treatment. The clinical meaningfulness of this reduction in negative symptoms needs further evaluation.

3. Rumination and psychosis: Exploring brooding, reflection, and dimensions of delusions

Kari Siu*, Zamfira Parincu, Katherine T. Evans, Umit Tural, Katherine A. Collins, Dan V. Iosifescu

Introduction: Previous research has demonstrated preoccupation and conviction as two relevant dimensions of delusions, and implicate rumination as a potential target for cognitive-behavioral intervention. However, the relationship between facets of rumination and dimensions of delusions have not been explored. The current analysis utilizes data from a community sample to investigate the relationship between brooding, reflection, and delusion preoccupation and conviction. We hypothesize that brooding will be positively associated with delusion preoccupation and conviction, but reflection will not be associated with delusional beliefs.
Methods: We analyzed data from the Nathan Kline Institute Rockland Sample (n = 375, age = 46.12 ± 15.43). The Peters et al. Delusions Inventory (PDI) and Ruminative Responses Scale (RRS) were used to assess dimensions of delusional beliefs and facets of rumination. Spearman's rank correlations were conducted to investigate the relationship between rumination and delusions.
Results: Brooding was positively associated with delusion preoccupation ($r=0.37$, $p<0.001$) and conviction ($r=0.33$, $p<0.001$). Reflection was also positively associated with delusion preoccupation ($r=0.09$, $p=0.01$) and conviction ($r=0.15$, $p=0.006$).
Discussion: Our findings replicate prior research by indicating a correlation between rumination and delusion. Notably, results revealed similar associations across brooding and reflection, such that increases in both were associated with greater delusion preoccupation and conviction: suggesting that despite reflection being regarded as more adaptive than brooding, it may be more effective to reframe self-reflection before it becomes unproductive. Future studies may examine neural correlates of these processes to identify potential novel interventions for delusions.

4. Gene expression profiles of frontal cortex pyramidal neurons across the Alzheimer's disease spectrum

Amanda Labuza*, Melissa J. Alldred, Harshitha Pidikiti, Andrea Heguy, Paul D. Coleman, Elliott J. Mufson, Stephen D. Ginsberg

Alzheimer's disease (AD) is an irreversible, age-related neurodegenerative disorder affecting an estimated 6.7 million Americans, and yet the underlying cause of AD is not understood. Current FDA approved treatments only slow the progression of disease but do not arrest or prevent the onset or progression of AD. Therefore, it is imperative to identify molecular and cellular mechanism(s) underlying AD, which would lead to novel therapeutics. Currently there are several approaches under development to evaluate changes at the transcriptomic, proteomic, and metabolic levels associated with AD. RNA sequencing (RNA-seq) provides an index of expressed genes as well as noncoding RNAs (ncRNAs) within a given cellular population. However, a limitation is that bulk-tissue resolution masks complex alterations occurring across different cell types. Here, we applied single population RNA-seq using laser capture microdissection (LCM) to isolate Nissl-stained layer III or layer V pyramidal neurons from the frontal cortex (BA9) from postmortem human brain tissue. Samples are taken from subjects across the AD spectrum ranging from no cognitive impairment (NCI, n=8), through mild cognitive impairment (MCI, n=5), ending in fulminant AD (n=7). A total of 600-900 Nissl-stained pyramidal neurons from each lamina were collected via LCM, RNA was isolated, converted to RNA-seq cDNA libraries, and analyzed on the Illumina NovaSeq platform at an average sequencing depth of 63 million reads per sample. Preliminary bioinformatic pathway analyses including IPA, KEGG, and GO were used to identify changes in differently expressed genes (DEGs) and canonical pathways between the AD and age-matched control cases. Total DEGs ranged from 1306 (MCI versus NCI in layer III pyramidal

neurons) to 3230 (AD versus NCI in layer III pyramidal neurons). Pathway analysis revealed several pathways were altered with disease progression, including pathways labeled “Alzheimer's disease” and “neurodegenerative diseases” as positive controls. Other pathways of interest included oxidative phosphorylation, mitochondrial dysfunction, and immune responses. We found differences in DEGs and pathways via bioinformatic inquiry across the AD spectrum from early to late stage. DEG and pathway changes seen exclusively between NCI and MCI can be targets for early intervention, while changes seen in early and late stages can be considered targets for biomarker analysis. Through this unbiased pathway analysis, we expect to identify and understand mechanistic changes in vulnerable pyramidal neurons that are integral to cortical circuitry and inform novel therapeutic strategies.

5. Persistent ΔFosB activity is required for seizure restriction and neuroprotection in the dentate gyrus of J20 APP mice

Gabriel S. Stephens*, Yi Zheng, Jin Park, Manuel Silva-Pérez, Andrew Eagle, Jason You, Chia-Hsuan Fu, Sumin Choi, Chiho Sugimoto, Shelly Buffington, Mauro Costa-Mattioli, Yin Liu, AJ Robison, Jeannie Chin

We reported that recurrent seizures in Alzheimer’s disease (AD) patients and mouse models promote memory deficits by inducing hippocampal accumulation of ΔFosB, a transcription factor that accumulates under recurrent seizures and can impair cognition via epigenetic regulation of target genes. ΔFosB binds to targets involved in excitability and neurotransmission in the dentate gyrus (DG) of amyloid precursor protein (APP) transgenic mice, suggesting ΔFosB binds to targets that could serve neuroprotective roles against hyperexcitability. To determine if persistent ΔFosB activity is required to maintain restrictions in seizure activity, we blocked ΔFosB activity in the DG of APP mice for 1 or 2-4 months. Unlike 1 month blockade, APP mice with 2-4 month blockade of ΔFosB showed increased mortality, seizure activity, memory deficits, DG hyperexcitability, and DG atrophy. In vitro studies confirmed that hippocampal neurons expressing AAV-ΔFosB showed reduced markers of excitotoxicity after NMDA challenge. Many ΔFosB target genes in APP mice relate to excitability and neuroprotection, and 3 month ΔFosB blockade can restore or destabilize target gene expression in APP mice, revealing discrete modes of ΔFosB target gene regulation. Our results indicate that persistent ΔFosB regulation of hippocampal target genes is necessary to restrict seizures and maintain neuroprotection in J20 APP mice.

6. Predicting the epileptic seizure onset zone with brain-wide alterations of temporal dynamics in fMRI

Karl-Heinz Nenning*, Erkam Zengin, Ting Xu, Gelana Tostaeva, Elisabeth Freund, Stanley J. Colcombe, Ashesh D. Mehta, Michael P. Milham, Stephan Bickel

Introduction: Epilepsy has been recognized as a network disease that can disturb brain regions beyond a focal seizure onset. Previous studies linked an altered autocorrelation function (ACF) of brain activation to disturbed brain dynamics in the seizure onset region and beyond. Here, we used preoperative resting-state functional magnetic resonance imaging (rs-fMRI) to quantify brain-wide ACF decay rates in medically refractory epilepsy patients with medial temporal lobe seizure onset. We evaluated how brain dynamics may be disrupted due to the underlying disease, and determined the potential use of ACF decay rates to identify seizure onset zones (SOZ) to inform intervention strategies.
Methods: We studied rs-fMRI data from 15 patients with unilateral mesial temporal lobe epilepsy (TLE; 10 left) that was confirmed by intracranial stereo EEG. For each voxel, we established a feature vector characterizing the temporal dynamics based on different ACF decay rate measures. We utilized data from a group of 652 healthy controls (Cam-CAN) as a normative baseline, and, for each patient and voxel, quantified the deviation of the ACF decay rates as a timescale anomaly

score (z-score based on the normative distribution). For each intracranial EEG electrode, we calculated the corresponding fMRI timescale anomalies and, using logistic regression, evaluated their predictive performance to classify electrodes that map the potential SOZ. Finally, we associated brain-wide timescale anomaly maps with outcome measures to examine the potential added value of preoperative rs-fMRI to guide neurosurgical intervention.
Results: Overall, we observed reduced ACF decay rates for electrodes that are located in brain regions associated with a seizure onset zone, suggesting a more constrained temporal dynamic. Brain regions that map to SOZ-related electrodes also show a reduced regional homogeneity, emphasizing disturbances in brain activity and functional connectivity. Importantly, in a leave-one-patient-out framework, we found that ACF decay rate measures were sensitive to focal alterations and predicted the electrodes identified as seizure onset well. In 13 out of the 15 patients, we observed a prediction performance of AUC > 0.7 and that was better than chance (prediction based on shuffled labels).
Conclusions: Our preliminary findings revealed widespread alterations of neural dynamics in patients with temporal lobe epilepsy. Brain regions in the seizure onset zone showed a more constrained activity (slower temporal autocorrelation decay rates) and lower regional homogeneity than regions located outside the seizure onset zone. These preliminary results indicate that alterations of temporal dynamics show promise for non-invasively delineating seizure onset zones from preoperative rs-fMRI. The observed alterations also emphasize the notion of epilepsy as a network disease, affecting brain regions beyond an obvious focal seizure onset. False positive classification remains a challenge that can likely be informed with patient outcomes to determine potential electrode mislabeling and latent seizure onsets.

7. Interoceptive dimensions in patients with obsessive-compulsive disorder with and without comorbid depression

Nicolette Recchia*, Pearl Kravets, Goi Khia Eng, Laura B. Bragdon, Katherine A. Collins, Emily R. Stern

Both obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) are associated with alterations in interoception, or the sense of the physiological condition of the body. Interoception comprises three dimensions: interoceptive accuracy (IAcc; i.e., ability to accurately identify bodily signals), interoceptive sensibility (IS; i.e., subjective sensitivity to body sensation), and interoceptive awareness (IAw; i.e., metacognitive awareness in interoceptive ability, operationalized as correspondence between actual IAcc and reported confidence in IAcc). Previous studies have separately investigated interoception in patients with OCD and MDD, but the nature and direction of interoceptive effects have been variable. The current study compares IAcc, IS, and IAw in individuals with OCD, MDD, and comorbid OCD/MDD.
Preliminary data were collected from 42 individuals with OCD, 34 individuals with MDD, 19 individuals with comorbid OCD and MDD (OCD/MDD), and 22 healthy controls (HCs). Reported confidence in interoceptive ability and IAcc was measured using a validated heartbeat tracking task (HTT). The Multidimensional Assessment of Interoceptive Awareness (MAIA, self-report) noticing subscale assessed IS. One-way ANOVAs explored group differences in IAcc, IS, and reported confidence in interoceptive ability. A mixed model ANOVA considering diagnostic group (4 levels: OCD, MDD, OCD/MDD, HC) and HTT performance (2 levels: IAcc, reported confidence in interoceptive ability) as factors evaluated IAw. Follow-up post-hoc independent sample t-tests determined significant group differences.
Diagnostics groups did not significantly differ in IAcc ($F(3,113)=0.972$, $p=0.41$). All patient groups showed significantly elevated IS compared to HC ($F(3,113)=4.9$, $p<0.01$), with all pairwise comparisons $p<0.05$. A significant interaction between HTT performance and diagnostic group ($F(3,113)=4.4$, $p<0.01$) was observed, driven by significantly lower confidence levels in the OCD group ($F(3,113)=4.1$, $p < 0.01$), with all pairwise comparisons $p<0.05$.
Our findings suggest that elevated subjective sensitivity to bodily sensation may be a feature of both OCD and MDD. While individuals with OCD had significantly less confidence in their interoceptive ability, the MDD, OCD/MDD, and HC groups exhibited similar confidence levels.

Accordingly, an altered correspondence between accuracy and confidence (IAw) was displayed by individuals with OCD. These preliminary results support therapeutic interventions addressing interoceptive distortions, specifically elevated IS in both OCD and MDD and diminished confidence in OCD. Future work in larger samples is needed to fully understand the relationship between interoceptive dimensions in OCD, MDD, and comorbid populations.

8. Flexible tracking of rhythmic acoustic streams in parallel thalamocortical circuits

Chase A. Mackey,* Annamaria Barczak, Sam Neymotin, Troy A. Hackett, Charles E. Schroeder, Monica N. O'Connell

The natural world is replete with acoustic signals displaying varying degrees of periodicity, such as animal vocalizations and speech. The auditory system's ability to track periodicity via oscillatory entrainment of the local field potential (LFP) has been well documented in humans and nonhuman animals, with animal models providing critical insight into the laminar circuitry involved. However, animal studies typically use isochronous (perfectly periodic) stimuli, while natural stimuli such as speech exhibit dynamics that are "quasi"-periodic. Moreover, humans readily comprehend time-compressed speech. These two features (tolerance for imperfect periodicity and time compression) suggest that speech processing is highly flexible. However, much remains to be discovered about the underlying circuitry related to such flexibility. Our previous work suggests that distinct cortical layers, and their thalamic inputs, play different roles in the entrainment process. "Matrix" (nonlemniscal) thalamic inputs targeting supragranular layers provide a modulatory influence on the processing of narrowly tuned information that is conveyed to the granular layer from the "core" (lemniscal) thalamus. This leads us to hypothesize that the ability to track the temporal structure of more naturalistic, quasi-rhythmic auditory stimulus streams may differ across core and matrix thalamocortical circuits.

To test this hypothesis, we evaluated the degree to which neuronal activity in macaque primary auditory cortex (A1) and medial geniculate body (MGB) tracks or entrains to 40 dB SPL band-pass noise that was progressively jittered around presentation rates corresponding to delta (1.6 Hz), theta (6 Hz), and alpha (11 Hz) frequencies. Neuroelectric activity was assessed at the level of the field potential (via current source density for cortex, and bipolar field potential for thalamus) and multi-unit activity (MUA). Entrainment was quantified using intertrial coherence (ITC), measuring the consistency of the field potential phase across trials. For each recording site, ITC was used to estimate entrainment's "tolerance for" or robustness to jitter and its flexibility across different repetition rates.

Across core and matrix circuits, entrainment decreased as jitter increased, and the tolerance for jitter decreased as presentation rate increased. The supragranular layers of A1 exhibited greater flexibility than the granular and infragranular layers in that their entrainment suffered less from increasing presentation rate. Consistent with this, at the highest presentation rate (11 Hz), matrix MGB exhibited greater tolerance for jitter than core MGB. These results suggest that parallel core and matrix thalamocortical circuits may have different roles in tracking temporal patterns present in natural sounds. Future analyses will incorporate spiking activity and modulatory influences, like attention and eye movements.

9. Involvement of the calcium-activated potassium channel (KCA3.1) in apoptotic neurodegeneration and neuroinflammation induced by ethanol in neonatal mice

Mariko Saito*, Shivakumar Subbanna, Zhang Xiuli, Nitesh Nandwana, John Smiley, Donald Wilson, Bhaskar Das

It has been shown that ethanol exposure in postnatal day 7 (P7) mice induces acute neurodegeneration in many brain regions, followed by long-lasting neuroanatomical and behavioral abnormalities, providing a third trimester model for fetal alcohol spectrum disorder. (FASD). Ethanol-induced acute neurodegeneration is accompanied by transient activation of microglia,

which phagocytose degenerating neurons. However, the following astrocyte activation persists until adult stages, suggesting secondary or chronic neuroinflammation. Activated microglia may not only phagocytose degenerating neurons but also produce pro-inflammatory mediators which activate astrocytes or induce neurotoxicity. If activated glia exert both beneficial and toxic effects, reduction in neurotoxic pro-inflammatory reactions without inhibiting the protective phagocytic activity may be a better treatment strategy for FASD. KCa3.1, which is highly expressed in immune cells, is indicated to contribute to microglia and astrocyte activation. KCa3.1 expression increases in activated microglia and astrocytes in several neurodegenerative diseases and nerve injuries, and KCa3.1 inhibitors ameliorate glial activation and promote neuroprotection. It is suggested that KCa3.1 inhibition blocks microglial neurotoxicity without affecting their neuroprotective phagocytic activity. To our knowledge, roles of KCa3.1 have not been tested in FASD models. We studied the possible involvement of KCa3.1 in P7 ethanol-induced neurodegeneration. P7 mice were injected with ethanol (2.5 g/kg) subcutaneously twice at a 2h interval, and the brain samples were taken 24h after the first ethanol injection. Western blot results showed that KCa3.1 protein levels were significantly higher (about 2 times) in the cortex and hippocampus of mice exposed to ethanol compared to the saline controls. Then, a KCa3.1 inhibitor BT563 (a TRAM-34 analogue), newly developed in Dr. Das's laboratory, was injected intracerebroventricularly (2.5μg/2μl in 10% DMSO) into P7 mice 30 min before ethanol injections. 24h after the first ethanol injection, brain samples were dissected out and analyzed by Western blots. The results indicated that BT563 inhibited P7 ethanol-induced cleaved-caspase-3 formation in the cortex and hippocampus. In microglial cell line (SIM-A9), BT563 partially inhibited LPS-induced NO formation, suggesting the anti-inflammatory effect of BT563. These results suggest that KCa3.1 may be involved in ethanol-induced neurotoxicity in the developing brain and considered as a target for future clinical applications for FASD.

10. Astroglial changes in the superior temporal cerebral cortex of subjects with major depressive disorder and schizophrenia

Brandon M. Marino*, Cynthia Bleiwas, Gopika Unnikrishnan, Vinod K. Yaragudri, Gorazd Rosoklija, Andrew J. Dwork, John F. Smiley

Changes in the number of glia and their molecular expression profile have been reported in major depressive disorder (MDD) and schizophrenia (SZ), especially in prefrontal and midline areas of cerebral cortex. In the present study we used stereological cell counting to evaluate astroglia and microglia in the superior temporal gyrus in 22 age and gender matched brain triads of MDD, SZ, and non-psychiatric control (Cntr) subjects. In Nissl-stained tissue, estimates of total neuron, glia, or endothelial cell densities were nearly identical across diagnostic groups. However, in immunolabeled sections, the cell density of astroglia identified with antibodies to glial fibrillary acidic protein (GFAP) was reduced in both MDD and SZ subjects. The reduction was prominent in astroglia evenly distributed throughout the cortical depth, consistent with a reduction of protoplasmic astrocytes. Using alternative astroglia markers, S100-beta immunolabeled cells were also significantly reduced in MDD brains, but glutamine-synthetase immunolabeled cells did not differ between diagnostic groups. In contrast to astroglia, the cell density of microglia did not differ between groups, and immunolabeling intensity of microglia with IBA-1, HLA-DR, or LN3 antibodies did not differ between diagnostic groups. The findings are consistent with reduced GFAP and S100b expression in protoplasmic astroglia especially in MDD subjects, but do not support obvious deficits in total glial number. Altered function of protoplasmic astrocytes is likely to contribute to disrupted metabolism and synaptic function in the cerebral cortex of MDD.

11. Increased excitability of dentate gyrus mossy cells occurs early in life in the Tg2576 model of Alzheimer's disease

David Alcantara-Gonzalez*, Meghan Kennedy, Chiara Criscuolo, Justin Botterill, Helen E Scharfman

Background: Hyperexcitability in Alzheimer's disease (AD) is proposed to emerge early and contribute to disease progression. The dentate gyrus (DG) is implicated in hyperexcitability in AD. Hence, we hypothesized that mossy cells (MCs), important regulators of DG excitability, contribute to early hyperexcitability in AD. Indeed, MCs are linked to hyperexcitability in epilepsy.
Methods: Using the Tg2576 model of AD and WT mice (~1 month-old), we compared MCs electrophysiologically, assessed the activity marker c-Fos, Aβ expression and a hippocampal-dependent memory task that is affected earlier in life.
Results: Tg2576 MCs exhibit increased spontaneous excitatory events (sEPSPs) and decreased spontaneous inhibitory currents (sIPSCs), increasing the charge transfer excitatory/inhibitory ratio. Additionally, Tg2576 MC intrinsic excitability was enhanced. Granule cells showed increased excitatory input without changes in intrinsic properties. Tg2576 MCs showed enhanced c-Fos expression, higher intracellular Aβ expression, and axon sprouting. The effects occurred before a change in the memory task, suggesting they are extremely early alterations.
Conclusions: Early electrophysiological and morphological alterations in Tg2576 MCs are consistent with enhanced excitability, suggesting an early role for MCs in DG hyperexcitability and AD pathophysiology.

12. Lysosomal dysfunction in Down syndrome and Alzheimer mouse models is caused by v-ATPase inhibition by Tyr682-phosphorylated APP βCTF

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Lysosome dysfunction arises early and propels Alzheimer's disease (AD). Herein, we show that amyloid precursor protein (APP), linked to early-onset AD in Down syndrome (DS), acts directly via its β-C-terminal fragment (βCTF) to disrupt lysosomal vacuolar (H+)-adenosine triphosphatase (v-ATPase) and acidification. In human DS fibroblasts, the phosphorylated 682YENPTY internalization motif of APP-βCTF binds selectively within a pocket of the v-ATPase V0a1 subunit cytoplasmic domain and competitively inhibits association of the V1 subcomplex of v-ATPase, thereby reducing its activity. Lowering APP-βCTF Tyr682 phosphorylation restores v-ATPase and lysosome function in DS fibroblasts and in vivo in brains of DS model mice. Notably, lowering APP-βCTF Tyr682 phosphorylation below normal constitutive levels boosts v-ATPase assembly and activity, suggesting that v-ATPase may also be modulated tonically by phospho-APP-βCTF. Elevated APP-βCTF Tyr682 phosphorylation in two mouse AD models similarly disrupts v-ATPase function. These findings offer previously unknown insight into the pathogenic mechanism underlying faulty lysosomes in all forms of AD.

13. Orexins as anxiety modulators in instrumental safety-seeking

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

Navigating threatening environments can elicit anxiety and stress responses. However, if adaptive coping strategies foster safety, stress and anxiety may be alleviated. Thus, dissecting the neuromodulatory systems orchestrating adaptive coping behaviors is critical to understanding human anxiety. The orexinergic system, originating in the perifornical (PFH) and lateral hypothalamus (LH), modulates cognitive and emotional functions critical to survival through projections throughout the brain. One crucial target is the dopaminergic ventral tegmental area (VTA), which is essential for reinforcing behaviors that result in desired outcomes. However, it is unclear if this circuit is important for reinforcing aversive instrumental behaviors such as active avoidance (AA) of threats. Evidence from other studies in the lab using the signaled AA (SigAA) shuttling task suggests that AA is positively reinforced by achieving safety. Thus, we hypothesized

that the LH-orexin to VTA projection would be required for safety-seeking, with safety being the 'rewarding' outcome. To test this hypothesis, adult Sprague Dawley rats received infusions of an orexin-specific viral vector containing an inhibitory opsin (AAV1-Ple112-Arch3.0-eYFP) into the PFH/LH, and optic fibers were implanted in orexin axon fields in the VTA. Following a 6-8-week incubation, rats were trained in SigAA. Animals were trained to avoid a foot-shock (1.0/0.7 mA males/females; 0.5 s) preceded by (and co-terminating with) a white noise warning signal (WS; 60 s). Rats were first trained with a single inescapable foot-shock delivered at the end of the 60 s WS presentation (Pavlovian trial). For all remaining trials, only failures to shuttle during the WS resulted in shock, which could be escaped by shuttling. If rats shuttled during the WS (an avoidance response), before the shock, a feedback (FB) cue was delivered (5 s, 80 dB). Thus, the FB cue becomes associated with safety—a safety signal. Rats received 15 trials per day until reaching a pre-defined criterion (80% successful avoidance); after, they were subjected to daily shock-free avoidance tests. Orexin to VTA axon terminals were inhibited (green laser 532 nm, 10 mW) during FB cue presentations only. On the first day, latency to avoid and avoidance responses were unaffected. However, inhibition on subsequent days increased latencies and impaired avoidance time- and session-dependent. These results suggest that 1) the FB cue is a reinforcer, perhaps through its association with safety, and 2) orexin communication with VTA is essential for safety-reinforced avoidance. Future studies will uncover the orexin system's role in adaptive coping behaviors and provide support for novel treatments of maladaptive coping, including active coping therapy combined with drugs to target the orexin system.

14. Endocytic anomalies in synapses precede amyloid pathology in an AD mouse model

Kuldeep Sachdeva*, Sandipkumar Darji, Martin Berg, Mala V. Rao, Aidong Yuan, Philip Stavrides, Chris Goulbourne, Evgeny Kanshin, Beatrix Ueberheide, Ralph A. Nixon

Synapses are the operational units for signal transmission between neurons, and dysfunction in synaptic transmission is an early pathological hallmark of Alzheimer's disease (AD), directly implicated in cognitive decline. Endocytosis is a process vital for synaptic function that notably undergoes alterations in AD, particularly within neurons. However, how this pathway is affected within synapses still remains elusive. To address this, we isolated synaptosomes from the hippocampus of a pre-pathological, late-life AD mouse model (APP51, 14 months old) and performed label-free quantitative mass spectrometry on both isolated synaptosomes and total hippocampal lysate. We focused on understanding the endocytic processes within hippocampal synapses and assessed levels of the endocytic proteins by employing Gene Ontology and SynGO-curated gene lists related to various endocytic uptake and trafficking pathways. Our findings revealed a significant upregulation of proteins involved in the endocytic uptake and trafficking pathways, including many associated with Retromer and HOPS complexes, essential for endocytic recycling and transport. An unbiased gene set enrichment analysis (GSEA) further supported the upregulation of these endocytic pathways. Most importantly, we confirmed the elevated endocytic uptake in APP51 hippocampal synaptosomes by conducting an ex-vivo uptake assay in isolated synaptosomes. Additionally, we found several AD risk-associated genes to be upregulated in the APP51 proteome. A Multi-marker Analysis of GenoMic Annotation (MAGMA) analysis revealed a significant association of these risk genes with endocytic uptake function, re-emphasizing the importance of endocytosis in AD pathology. Collectively, our results of this ongoing study shed new light on significant alterations in the endocytic pathway within synapses of an AD mouse model. These insights hold the potential for providing a mechanistic understanding of critical synaptic pathologies linked to AD, including synaptic loss and hyperexcitability.

15. $100 now or more money later? Comparing delayed discounting in obsessive compulsive disorder and major depressive disorder

Jeanmarie R. Harvey*, Goi Khia Eng, Rachael Moldow, Nicolette Recchia, Laura B. Bragdon, Katherine A. Collins, Emily R. Stern

Obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) are clinically heterogeneous disorders associated with altered reward processing and cognitive control. Experimentally, these processes can be investigated using the delay discounting (DD) paradigm, which shows that individuals prefer smaller immediate rewards over larger delayed rewards, a preference that increases as the length of the delay becomes greater. This study compared DD behavior in patients with OCD and MDD and examined its relationship with clinical symptom heterogeneity.

51 participants with OCD and 49 participants with MDD completed a delay discounting task. Clinician-rated scales assessed overall OCD and depression severity using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Inventory of Depressive Symptomatology (IDS), respectively. The Symptoms of Depression Questionnaire (SDQ) and Beck Anxiety Inventory (BAI) measured self-reported severity of depressive and anxious symptoms.

The adaptive DD task (available through the Many Brains Project, Inc.) assessed preference for immediate over delayed rewards across 46 trials over 7 temporal delays. For each temporal delay, immediate and delayed reward options begin at $500 and $1000, respectively. In each subsequent trial, the immediate reward increased or decreased based on the choice made previously. A discount rate, k, was calculated for each participant based on the choice made on each trial, the dollar amount of each option, and the length of the delay, with a higher discount rate reflecting greater DD (i.e., greater preference for immediate over delayed rewards).

As expected, both groups showed DD, preferring immediate over delayed rewards. The MDD group showed more overall DD (higher discount rate) compared to the OCD group at trend level ($p= 0.06$), a difference driven by greater discounting of short-term temporal delays of up to 6 months (all $p<0.05$). There were no group differences in DD for temporal delays of 1 to 10 years ($p>0.05$).

Within the OCD group, more severe anxiety (BAI) was associated with greater DD (all $r>0.29, p<0.05$), particularly at the 6-month temporal delay ($r=0.43, p<0.01$). Symptoms of anxiety and irritability on the SDQ were significantly associated with more DD for long-term delays of 1 or more years (all $r>0.30, p<0.05$).

The MDD group did not show significant associations between self-reported anxiety and DD. Greater anxiety and irritability symptoms on the SDQ were associated with less DD for long-term delays of 1 or more years (all $r>0.28, p<0.05$). Greater fatigue and mood disturbance symptoms on the SDQ were associated with less discounting of long-term delays within the MDD group.

Both OCD and MDD experienced delayed discounting although the magnitude differed based on temporal delay and group. The opposite pattern of relationships between DD and clinical symptom severity suggests different underlying mechanisms. Specifically, OCD patients showed a pattern of increased reward sensitivity and/or reduced cognitive control (greater DD) with increasing anxiety severity, whereas MDD patients showed a pattern of reduced reward sensitivity and/or increased cognitive control and future-oriented thinking in association with greater symptom severity. Future work using neuroimaging to probe the neurocircuitry of DD in these populations is needed to examine the associated neural mechanisms.

16. Interaction of sex and genotype on CSF marker of microglial activation

Chelsea Reichert Plaska*, Fatima Medrano, Giovanna Novi, Nunzio Pomara

Background: Major depressive disorder (MDD) is a risk factor for Alzheimer's disease (AD), but the mechanisms behind this association are still unclear. MDD has been associated with increased proinflammatory microglia activation. Although microglia play an initially protective role in the pathology of AD by internalizing and degrading pathological proteins, including brain amyloid (Aβ), persistent proinflammatory microglia activation diminishes microglia's capacity to clear the proteins, and may lead to increased Aβ production, deposition, and tau seeding associated with more advanced AD. CSF soluble triggering receptor expressed on myeloid cells 2 (sTREM2), a cleavage product of the TREM2 receptor expressed on brain microglia, is considered a proxy for TREM2-mediated microglial phagocytic activation, and may provide the link between MDD and Aβ deposition. We previously reported a reduction in CSF Aβ42 in MDD consistent with increased

brain Aβ burden as well as a reduction in CSF sTREM2, which suggests reduced microglial phagocytic activation in response to Aβ. Since sex and APOE-status are independent risk factors for AD, this prompted us to examine the interaction of these factors for sTREM2 status in a longitudinal study of cognitively normal older adults.
Methods: We examined the interactions of sex and APOE-status on CSF sTREM2 and AD markers (Abeta 40, 42, Tau and P-tau) from 49 individuals (29 MDD and 20 controls) who completed a lumbar puncture as part of a 3-year observational study. All study participants completed a clinical evaluation, physical and neurological evaluation, as well as a comprehensive neuropsychological test battery. Independent samples Mann Whitney U test were used to compare group differences. Analysis of Variance was used to examine interactions.
Results: This was an exploratory analysis, so all subjects with available data were included. There were no significant sex or APOE status-related differences on CSF sTREM2 or the AD biomarkers. Two-way analysis of variance with sex (male, female) and APOE-status (e4-positive, e4-negative) revealed a significant interaction between sex and APOE status on CSF sTREM2 levels, irrespective of diagnosis, $F(1,46) = 8.920$, $p = 0.005$. The effect size, calculated as eta squared (η^2), was 0.162, indicating a medium effect.
Conclusions: sTREM2 was lower for e4 Positive females and e4 Negative males. Neither Sex alone nor APOE-status alone influenced sTREM2 levels. Since both female sex and e4 positivity are risk factors for AD, the interaction of these groups may increase AD risk through impairment in TREM2-mediated microglial phagocytic activation. Future studies, with larger samples, should confirm these interactions.

17. Preliminary findings of virtual reality treatment of treatment refractory auditory hallucinations: Study design and intervention

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Background: Despite treatment with Cognitive Behavioral Therapy (CBT) and medication management, individuals with schizophrenia Auditory Verbal Hallucinations (AVH) often do not respond. AVH are pervasive sensory experiences of hearing voices without an external stimulus. Controlled clinical studies using structured avatar-virtual reality therapy (VR) have shown improvements of AVH. This method fosters a dynamic interaction between the patient, an avatar (embodying the AVH), and the therapist, facilitated by developing an avatar in a virtual setting that simulates the patient's reported features and voice of their AVH. The therapy is performed in the VR and progresses through phases of exposure, confrontation, and empowerment, with the aim to alter the patient's relationship with their AVH. The therapist engages the avatar by representing and mirroring the patient's AVH; patients learn to challenge and negotiate with the hallucinated voice to enhance their control and coping strategies with their AVH. The aim of the current study is to 1) test the feasibility of this novel approach in a long-term treatment setting, and 2) to replicate previous findings in a randomized clinical trial (RCT) to assess improvements in AVH in individuals with schizophrenia.
Methods: This is a randomized, single blind, 6-week two site clinical trial with a week 10 follow up in adults with schizophrenia or schizoaffective disorder who present with AVH at both the Manhattan Psychiatric Center and Weill-Cornell Westchester inpatient services. Thirty-two individuals aged 18-60 with distressing AVHs despite exhaustive pharmacological treatment will be randomized. Patients are included who: 1) are on antipsychotic medication and have AVHs for at least 3 months and recurring at least more than once per week, 2) can describe the voice(s), 3) score ≥ 4 on PANSS Hallucinatory Behavior, and 4) had no changes in antipsychotic treatment for 2 weeks prior to enrollment. Patients are excluded who: 1) are unable to identify a single dominant "voice," 2) received ECT, rTMS or deep brain stimulation (DBS) in the past 6 months, 3) have an AVH in a language not spoken by the therapist(s), 4) have active suicidal ideation within the last 6 months, and 5) have a diagnosis of organic brain disease. The primary endpoints are the Psychotic Symptoms Rating Scales (PSYRATS-AH-Distress), Positive and Negative Symptom Scale (PANSS), Revised Beliefs About Voices Questionnaire (BAVQ-R), and Voices Acceptance and

Action Scale (VAAS). Feasibility will be assessed using the Client Satisfaction Questionnaire (CSQ), Simulator Sickness Questionnaire (SSQ), and percent of patients who withdrawal or discontinue the trial.
After screening, participants are randomized to VR avatar therapy or VR geographical videos for 6-weeks; after completion of the VR AVH therapy, patients are followed-up at week 10 to assess persistence of symptom change. The VR used in this study is the Oculus Rift 2. Therapists have received a standardized comprehensive training on avatar therapy and receive supervision from an avatar therapy expert. The therapy is highly structured using a standardized curriculum and multiple safety assessments.
Results: Enrollment began in 2023, and 3 participants have completed the study thus far. For patients randomized to the VR AVH therapy a non-significant decrease was observed in PSYRATS scores from 3.36 at baseline to 3.18 at endpoint ($p > 0.05$), with no change in PANSS Hallucinatory Behavior Score. The first control patient's PSYRATS scores increased from 2.45 to 2.73 and the second control patient increased from 2.36 to 2.82, demonstrating an increase in mean scores. Both control and treatment groups reported enjoying the VR exposure and no discomfort with VR was reported. Additional data will be presented for the poster.
Conclusions: Preliminary findings demonstrate favorable implementation conditions, with positive reception from treatment users.

18. Hypothalamic theta modulation improves memory

Shuo Chen*, Linmeng He, Zhe Sage Chen, Thomas McHugh

Brain rhythms are fundamental features of coordinated neural activity underlying various brain functions and neural mechanisms. In the hippocampus the theta (4-12 Hz) rhythm is crucial for learning and memory, however, uncertainty about the anatomical origin and related circuitry that control theta rhythms remains. In particular, while ascending hypothalamic circuits are known to play a role in theta modulation, how this impacts learning has been understudied. Taking advantage of a transgenic mouse line that allows for specific gene expression in the hypothalamic supramammillary nucleus (SuM), we confirmed the SuM as a modulator of hippocampal theta oscillations. Optogenetic stimulation of the SuM that expresses channelrhodopsins robustly induced hippocampal theta oscillations. Furthermore, the entrained theta rhythm significantly enhances animals' learning of a hippocampal-dependent spatial memory task. To elucidate the physiological mechanism behind SuM theta modulation and associated impact on animals' behavior, we performed in vivo electrophysiological recordings under optogenetic SuM stimulation. We found that SuM-induced theta oscillations globally reshape hippocampal coding, e.g. place cell activity, at both single unit and population levels during different behavioral phases, in particular the synchronization of place cell activities. These results extend our previous findings of the SuM as a hypothalamic hub that routes novelty signals to the hippocampus for memory modulation by highlighting its important physiological role in modulating and synchronizing in vivo hippocampal activities.

19. Can you repeat that? I was ruminating. Internal-external attention switching in obsessive compulsive disorder

Rachael Moldow*, Goi Khia Eng, Emily R. Stern

Individuals with OCD are often internally focused, with their attention attuned to obsessions and mental compulsions. However, efficient functioning requires disengaging one's attention from internal focus toward external stimuli. The present study used an attention-switching task to investigate the associations between OCD symptom dimensions and internal-external attention switching. 47 participants who met DSM-V criteria for OCD completed the attention-switching task. Obsessive-compulsive symptoms dimensions were assessed through the self-report Dimensional

Obsessional-Compulsive Scale (DOCS). Overall OCD severity was assessed with the clinician-administered Yale-Brown Obsessive Compulsive Scale (Y-BOCS).
The attention-switching task involves performing a target detection (TD) task following an internally focused negative or positive event imagination condition, a rest condition, or a color-word conflict Stroop condition. Dependent measures from the task were mean reaction time (RT) on correct TD trials (corrRTmean), standard deviation of RT on correct TD trials (corrRTstd), percent commission errors on TD trials (accuracy), and percent omission errors on TD trials (no response). Measures were calculated separately based on whether TD blocks followed negative imagination (TD-IMneg), positive imagination (TD-IMpos), TD-Stroop, or TD-Rest.
Paired sample t-tests examined differences between conditions in the OCD group as a whole. Correlations assessed bivariate relationships between task measures (corrRTmean, corrRTstd, accuracy, omission) and DOCS subscales of Contamination (DOCS-C), Responsibility for Harm (DOCS-R), Unacceptable Thoughts (DOCS-UT), and Symmetry/Not-Just-Right-Experiences (DOCS-S). Additionally, correlations assessed bivariate relationships between task measures and total YBOCS scores, obsession and compulsion subscores, and individual items of time spent, distress, interference, resistance, and control.
DOCS-UT scores were negatively correlated with the percentage of omission responses during TD following IMpos ($r=-0.291$, $p<0.05$). DOCS-UT and DOCS-R scores were negatively correlated with standard deviation (variance) of RT during TD following Stroop ($r=-0.318$, $p<0.05$, $r=-0.408$, $p<0.05$). YBOCS obsession resistance, compulsion resistance, and obsession control (higher scores indicate more impairment) were also negatively correlated with commission error percentage during TD following IMneg ($r = -.344$, $p < .05$, $r = -.302$, $p < .05$, $r = -.425$, $p < .05$).
Our study revealed that patients who have more OCD-related impairment with less resistance to obsessions (i.e., more giving into obsessions) showed better ability to switch attention from negative event imagination to TD. These unexpected findings linking greater OCD severity to improved attention switching in a variety of conditions suggest that certain forms of cognition may actually be enhanced in OCD, perhaps in relation to the hyperactive fronto-striatal circuit so often linked to the disorder. Future work will address this question further by examining the relationship between fronto-striatal function and behavior in the task.

20. Early-life prefrontal cortex inhibition and early-life stress lead to long-lasting behavioral, transcriptional, and physiological impairments

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Early-life stress has been linked to multiple neurodevelopmental and neuropsychiatric deficits. Our previous studies have linked maternal presence/absence from the nest in developing rat pups to changes in prefrontal cortex (PFC) activity. Furthermore, we have shown that these changes are modulated by serotonergic signaling. Here we test whether changes in PFC activity during early life affect the developing cortex leading to behavioral alterations in the adult. We show that inhibiting the PFC of mouse pups leads to cognitive deficits in the adult comparable to those seen following maternal separation. Moreover, we show that activating the PFC during maternal separation can prevent these behavioral deficits. To test how maternal separation affects the transcriptional profile of the PFC we performed single-nucleus RNA-sequencing. Maternal separation led to differential gene expression almost exclusively in inhibitory neurons. Among others, we found changes in GABAergic and serotonergic pathways in these interneurons. Interestingly, both maternal separation and early-life PFC inhibition led to changes in physiological responses in prefrontal activity to GABAergic and serotonergic antagonists that were similar to the responses of more immature brains. Prefrontal activation during maternal separation prevented these changes. These data point to a crucial role of PFC activity during early life in behavioral

21. Probing sensory phenomena, interoceptive sensitivity, and neural patterns in individuals with obsessive-compulsive disorder and unaffected siblings

Goi Khia Eng*, Katherine A. Collins, Laura B. Bragdon, Nicolette Recchia, Jeanmarie Harvey, Russell H. Tobe, Emily R. Stern

Background: Obsessive-compulsive disorder (OCD) is a familial and heterogeneous disorder. Up to 70% of patients with OCD have prominent sensory symptoms (i.e., 'sensory phenomena') preceding or driving compulsions, regardless of a concrete fear. Previously, we found that patients with OCD experience greater subjective sensitivity to body sensation (interoceptive sensitivity; IS) compared to controls. Greater IS within the patient sample was also associated with more severe symptoms of sensory phenomena such as symmetry/ordering symptoms. However, it is unknown whether unaffected siblings share these traits, constituting a potential endophenotype. This study compared sensory phenomena and interoceptive sensitivity between unaffected siblings, individuals with OCD, and control subjects, and interrogated differences in patterns of neural connectivity between patients and unaffected siblings.

Method: 97 controls, 142 individuals with OCD, and 38 unaffected siblings underwent an 8-minute resting-state scan, of which 24 are proband-sibling pairs. Overall OCD symptoms were assessed through the clinician-rated Yale-Brown Obsessive-Compulsive Scale (YBOCS). Sensory phenomena were assessed using the clinician-rated University of São Paulo's Sensory Phenomena Scale (SPS) and self-reported symmetry/ordering symptoms using the Symmetry, Completeness, and Need for 'Just Right' dimension of the Dimensional Obsessive-Compulsive Scale (DOCS). IS was assessed using the self-reported Noticing subscale of the Multidimensional Assessment of Interoceptive Awareness (MAIA).

The full sample of OCD and unaffected siblings were compared on the metric of "local correlation", which measures how much a given voxel is connected with its immediate neighbors and is thought to reflect the local coherence of a brain area, using the CONN-fMRI Functional Connectivity Toolbox for SPM (FDR-correction $p<0.05$).

Results: Individuals with OCD had higher Y-BOCS than unaffected siblings ($p<0.05$), who did not significantly differ from controls. However, unaffected siblings had scores in-between controls and the OCD group on SPS, DOCS-Symmetry and IS (all $p<0.05$). Consistent with our prior work, higher DOCS-Symmetry symptoms were significantly associated with greater IS in the OCD group ($r=0.270$, $p<0.01$), however, this relationship was not observed in unaffected siblings ($p>0.05$).

In terms of neuroimaging findings, OCD patients had higher local correlation in sensorimotor/somatosensory regions than unaffected siblings, whereas siblings had higher local correlation in the anterior cingulate cortex (pregenual and subgenual), superior frontal gyrus, putamen, insula, and orbitofrontal cortex, regions involved in cognitive control/inhibition and emotion processing.

Discussion: Elevated sensory phenomena and IS in unaffected siblings is similarly found in OCD patients and thus may relate to disease vulnerability or risk. The lack of association between IS and sensory phenomena in unaffected siblings suggests that this relationship in OCD might be due to disease-specific progression or the presence of resilience or protective factors in the unaffected siblings, or possibly both. Additionally, higher local coherence in brain regions involved in cognitive control and emotion processing observed in unaffected siblings might reflect a compensatory mechanism conferring protection from symptom development.

Conclusion: This study revealed the existence of shared vulnerabilities between patients and unaffected siblings. Further work could focus on investigating protective mechanisms that might be present in unaffected siblings, which could inform treatment development for OCD.

22. High frequency oscillations (>250Hz) outnumber interictal spikes in preclinical studies of Alzheimer's disease

Christos Lisgaras*, Helen E. Scharfman

Interictal spikes (IIS) and seizures are well-documented in Alzheimer's disease (AD). IIS typically outnumber seizures, supporting their role as a prominent EEG biomarker in AD. In preclinical models, we showed that high frequency oscillations (HFOs>250Hz) also occur, but it is currently unknown how HFOs compare to IIS. Therefore, we asked whether the incidence of HFOs and IIS differed and if their rates of occurrences are differentially affected by behavioral state such as wakefulness and sleep.
We used three mouse lines that simulate aspects of AD: Tg2576, presenilin 2 knockout, and Ts65Dn mice. We recorded and quantified HFOs and IIS in the hippocampus during wakefulness, slow-wave sleep, and rapid eye movement sleep.
In all three mouse lines, HFOs were more frequent than IIS. High numbers of HFOs correlated with fewer IIS, suggesting for the first time possible competing dynamics among them in AD. Notably, HFOs occurred in more behavioral states than IIS.
In summary, HFOs were the most abundant EEG abnormality when compared to IIS, and occurred in all behavioral states, suggesting they are a better biomarker than IIS. These findings pertained to three mouse lines, which is important because they simulate different aspects of AD.

23. A digital platform to detect negative symptoms of schizophrenia through facial and acoustic analysis

Danyah Nadim*, Jean-Pierre Lindenmayer, , Anzalee Khan, Vikram Ramanarayanan, Kothare Hardik, David Paulter, Mohan Parak, Benedicto Parker, David Suendermann-Oeft

Background: Negative symptoms represent a transdiagnostic feature of serious mental illness, impacting communication and social interaction in patients with schizophrenia. Current assessments rely predominantly on verbal reports, lacking objective incorporation of behavioral observations. The automatic analysis of facial and acoustic expressions has yielded several clinical applications. One of these applications is the study of facial and speech productions in individuals with schizophrenia. The Neurological and Mental health Screening Instrument (NEMSI) presents an innovative tool for assessing negative symptoms, with the potential to enhance the reach, clinical impact, and scalability of assessments for individuals with schizophrenia. This study aims to assess the psychometric properties of NEMSI and to compare facial and speech metrics between individuals with schizophrenia and healthy controls. The results provide valuable insights into the validity and reliability of the instrument.
Methods: Hospitalized inpatients with schizophrenia (SZ: n = 74) and demographically matched healthy controls (HC: n = 75) completed a brief 8-minute assessment using the AI-driven NEMSI platform. Each participant was rated twice by the same rater within one week period in order to assess test-retest reliability. For the AI software, participants were each provided a valence-neutral sentence to read; participants then were engaged in free speech where they were asked open ended probes designed to be emotionally-ambiguous in valence and content (e.g., tell me about yourself?). For the SZ group, PANSS, BNSS, CDSS, CGI-S, AIMS, SAS, BARS were performed. Concurrent, convergent, divergent, and discriminative validity were assessed. For the HC group, individuals received the AI vocal/speech software only. Mann–Whitney test was used for comparison of AI features. Accuracy, sensitivity, specificity, and area under receiver operating characteristics-curve were measured as discriminatory indices of classifications of SZ vs HC groups.
Results: The mean age of individuals with SZ was 41.48 (10.41) and the HC group was 37.25 (8.51), and the mean PANSS total score at Time 1 was 80.43 (10.28). Comparison of all the

extracted features (54 facial and acoustic metrics) between SZ and the HC groups found 40 features to be significantly different ($p < 0.001$) mostly belonging to speech features (syllable alternating motion rate, loudness/articulation, speaking rate and pauses) and some facial features (e.g., average jaw acceleration, lip aperture). Session duration for the AI software was a mean of 8:30 min (min = 5:04 min, max = 13:39 min). Significant correlations were observed between PANSS Motor Retardation and the AI software speaking rate (r= -0.741) and average jaw acceleration (r = -0.828), PANSS Active Social Avoidance and syllable alternating motion rate (r = -0.820), PANSS Marder Negative symptom score and pauses during speech (r = -0.593), BNSS Blunted Affect Vocal Expression, and Blunted Affect Expressive Gestures were correlated with the AI software speaking rate (r = -0.778). The accuracy of classifying SZ from HC was 89.31%. Of the participants who completed the SUTAQ, most SZ (85.70%) and HC (93.70%) reported satisfaction with the AI-driven platform.
Conclusions: Speech and facial digital technology using AI could supplement negative symptoms clinical assessments as it affords precision of measurement of negative symptoms and can provide opportunities for tracking, understanding, and treating negative symptoms.

24. Functional localization of the primary taste cortex in the anesthetized macaque monkey

Renée Hartig*, Ali Karimi, Henry Evrard

The insular cortex is a recipient of direct thalamocortical inputs relaying sensory information from various bodily regions, including the oral cavity and gastrointestinal tract. This cortical region plays a pivotal role in regulating homeostasis related to feeding, digestion, and bodily functions. In this study, we utilized novel taste delivery systems to help pinpoint the primary taste area in both humans and macaques. Beginning with human psychophysical testing, followed by ultra-high field 7T fMRI in anesthetized macaques, we evaluated tastant stimuli at varying concentrations. Our findings consistently revealed activation in specific regions of the macaque insula, particularly highlighting the mid-insula dorsal fundus (ldfm) and dorsal anterior insular cortex (dAIC), alongside an additional activation cluster in the ventral anterior insular cortex (vAIC). Through comparisons with human functional homologs and neuroimaging meta-analyses, we aimed to discern the existence of a common gustatory area. Our translational investigation suggests a degree of homology between primate species, underscoring a notable resemblance, between the macaque and human insula and surrounding opercula, in the localization of fMRI voxel-wise activity correlated with gustatory processing.

25. Interaction between serotoninergic and dopaminergic signaling in a developmental model of SSRI exposure

Edenia C. Menezes, Lital Rachmany*, Fabiula F. Abreu, Catia M. Teixeira

Serotonin is known to regulate multiple systems, from food satiety to mood regulation. Multiple environmental factors affect serotonin levels during development including exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) antidepressants. In the US, it is estimated that between 5 and 10% of pregnant mothers take antidepressants during pregnancy with unknown effects on fetal development. It has been shown that altered levels of serotonin during development can lead to behavioral deficits in adult mice such as anhedonia and anxiety-like behavior. However, the mechanisms by which serotonin levels during development affect adult behavior are largely unknown. We hypothesize that early-life exposure to high serotonin levels, induced by SSRI exposure, causes alterations in the adult dopaminergic system and long-lasting dopamine-dependent behavioral changes. To manipulate developmental serotonin levels, we administered the SSRI fluoxetine from postnatal day (P)2 to P11 in mice. This period roughly correlated with the third trimester of pregnancy in humans in respect to serotonergic development. We found that early-life SSRI exposure leads to deficits in exploration and deficits in glutamatergic co-transmission between serotonergic and dopaminergic neurons. Interestingly, early-life SSRI exposure (PN-FLX)

and VGlut-3 knock-out in serotonergic cells led to similar phenotypes in the open-field, elevated plus-maze and light-dark box. Furthermore, using photometry and micro dialysis, in live behaving animals, we found a hypoactivation of the dopaminergic system in PN-FLX mice. Importantly, these mice showed reduced motivation in the progressive ratio in an operant task. To test whether we could rescue these deficits in adulthood, by acting in the dopaminergic system, we compared their response to an SSRI (fluoxetine) or a Dopamine-Norepinephrine Reuptake Inhibitors (DNRI; bupropion). We found that PN-FLX induced reduction in motivation could be reversed by adult administration of bupropion but not by fluoxetine. Furthermore, the PN-FLX impaired performance in the novelty suppressed feeding test, a recognized measure of anxiety-like behavior, was successfully ameliorated by administering bupropion in PN-FLX adult mice, while the administration of FLX did not yield similar results. In conclusion, we found that early-life fluoxetine exposure leads to deficits in serotonergic-dopaminergic signaling, deficits in dopaminergic response to rewarding stimulus, deficits in motivation and increased anxiety. There deficits could be ameliorated by enhancement of dopaminergic signaling in the adult.

26. Associations between prenatal stress-induced transcriptional changes and cognitive and anxiety behavior deficits in adolescent animals

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Long-term exposure to adverse environmental conditions has been associated with various neurodevelopmental and psychiatric disorders in both human and animal models. Our prior investigations into developmental alcohol exposure as an adverse environmental factor have revealed epigenetic alterations, including DNA methylation and histone modification at specific promoter regions of synaptic plasticity genes. Even brief stress episodes during early rodent life can impact crucial epigenetic markers and later behavioral regulation, potentially leading to adult pathologies such as cognitive impairment, altered social interactions, emotional responses, and repetitive behaviors. Establishing and validating preclinical models for prenatal stress (PS) exposure enables the exploration of underlying mechanisms and the evaluation of potential therapeutic interventions. In this study, we present an animal model involving the restraint of pregnant mice in transparent cylinders to induce PS. Our work aims to validate this PS procedure and elucidate its primary endpoints, consequences, and mechanisms. We evaluated cognitive-emotional functions and repetitive behaviors in adolescent male and female animals. Our findings demonstrate that transcriptomic changes associated with cognitive disturbances, heightened anxiety, and impaired coping with repeated stressful situations are evident following PS exposure. Given the profound impact of the PS procedure on offspring, this model offers ecological advantages and significant translational potential. Therefore, advancing our comprehension of the effects of PS on brain and behavioral development is essential for the current and future population's health and well-being.

27. Neural correlates of emotion regulation in psychosis with suicidal ideation and behavior

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The neural basis of suicidal ideation and behavior (SIB) in schizophrenia may relate to deficits in circuitry related to emotion regulation. SIB is highly elevated in schizophrenia compared to healthy individuals, with 5-10% of people with this diagnosis dying by suicide. This rate is as high or higher than that seen in major depression disorder. Emotion regulation refers to the strategies used to manage emotions and typically involve reappraising reactions to emotional stimuli (reappraisal) or suppression of responses to emotional stimuli (suppression. People with schizophrenia show significant deficits in emotion regulation, and we hypothesized that impairment in this ability would be associated with SIB. In particular, we reasoned that people with schizophrenia and higher levels of SIB would show abnormalities in circuitry related to emotion regulation during performance of an

emotion regulation task. We thus examined blood oxygen level-dependent (BOLD) activation during performance of an emotion regulation task in people with schizophrenia with high and low levels of SIB.
The Columbia-Screening Suicide Rating Scale was used to categorize people with schizophrenia into low SIB (n=16) and high SIB groups (n=14). People in the low SIB group had only passive suicidal ideation and no suicide attempts, whereas people in the high SIB group had at least active suicidal ideation (indicating a plan) and/or 2+ lifetime suicide attempts.
Participants were scanned using a Siemens 3T TiM Trio and a 32-channel head coil to assess emotion regulation using a task in which negative pictures from the International Affective Picture System were preceded by negative (NegNeg) or neutral (NeutNeg) spoken sentences. Neutral pictures were always preceded by neutral statements. After each picture, they rated the unpleasantness of the image (see Figure 1). There were 22 trials of condition over two task blocks. This task was originally developed by Foti & Hajcak (2008) and adapted for fMRI based on (Wang et al., 2017).
We used a multiband EPI sequence. T1-weighted images were collected for tissue-type segmentation and spatial normalization using an MPRAGE sequence.
First-level analyses were done using AFNI's afni_proc.py program to create a subject-wise script that applied motion correction, normalization to standard space, smoothing with a 4mm FWHM Gaussian kernel and detrending. Time series were corrected for 6 motion parameters, as well as signal in white matter, CSF (using anaticor for the latter).
Second level analyses were conducted with Group (Low,High) as a between subject factor. The contrast of interest was the NeutNeg-NeutNeut comparison. Images were thresholded using FSL's randomise tool and a threshold-free cluster enhancement, $p < .05$ two-tailed. A minimum cluster size of 40 voxels was applied to eliminate very small clusters.
Results: Participants reliably rated the NegNeg pictures as more unpleasant than the NeutNeg pictures, indicating that the task manipulation was successful ($p<1.3 \times 10$). The task activated emotion-regulation circuitry. Patients in the high SIB group showed reduced activation compared to those in the low SIB group in bilateral rostral anterior cingulate (RAcc), paracentral gyrus, and insula, as well as a number of right-sided regions: dorsolateral prefrontal cortex, superior temporal gyrus, precentral gyrus/Brodmann Area 6, medial frontal gyrus, and superior frontal gyrus.
Conclusions: In this preliminary study, patients in the high SIB group showed deficits in activation in emotion-regulation regions compared to those with low SIB. This suggests potential neural targets to improve emotion regulation and reduce SIB in schizophrenia.

28. Quantification, replication, and predictive utility of a relative brain age metric in the Nathan Kline Institute - Rockland sample

Olivia Ripley*, Yunglin Gazes, Jessica Cloud, Anna MacKay-Brandt, Stan Colcombe

The aging process typically leads to brain atrophy and cognitive decline, even without the influence of age-associated pathologies. Modifiable factors such as exercise or substance use are known to affect brain health and cognition; however, their relative influence across the lifespan and regarding the aging process is less well understood. Therefore, it is crucial to determine the standard progression of structural changes as the brain ages and what factors may accelerate or decelerate biological brain aging. This study identifies relative brain age (RBA) as a widely-utilizable measure of the brain's biological age. This metric is not confounded by chronological age, allowing for more accurate analyses of what modifiable health factors may influence the aging process. We trained a machine learning algorithm to derive the biological age of brains from high-quality T1 structural MRI images. The model based its calculations on a Joint and Independent Variation Explained (JIVE) analysis of 6 measures of brain health (thickness, cortical and subcortical volume, surface area, mean curvature, and travel depth). Then, the relationship between RBA and modifiable health factors was examined. We trained the algorithm on two large-scale data sets, Nathan Kline Institute - Rockland Sample (NKI-RS) and Human Connectome Project - Aging (HCP-A). The first model was based entirely on the NKI-RS sample, split into 1:1 age and sex-matched halves for training and testing the model. Three additional models were trained on the HCP-A dataset and forward

applied to the NKI-RS data to see if they would provide similar conclusions. In all models, acute drug use of tobacco, cannabis, and alcohol were associated with accelerated biological brain aging, though only chronic tobacco use displayed the same relationship across samples. Notably, there was a discrepancy between the association of self-reported and objective measures of health with brain aging; reliable associations were only obtained for objective measures. We found lower BMI, lower waist-to-hip ratio, and higher VO2 max were associated with decelerated biological brain aging. The successful forward application of models trained with the HCP-A sample indicates that the JIVE prediction algorithm can be trained on an independent dataset and effectively applied to smaller samples. Further, we note that two of the HCP-A models provided lower prediction errors similar to the NKI-RS model; one that was trained on the full data set, and another with harmonized data using ComBat to account for site differences. However, this had little impact on the predictive validity of associations among RBA metrics and health measures in the study sample. Our results demonstrate an RBA metric that can be derived from open-science data for forward application to novel samples to identify factors that may confer risk or resilience to accelerated brain aging across the lifespan.

29. Dentate gyrus granule cell resilience to amyloid β: potential roles of brain-derived neurotrophic factor and neuronal activity

Chiara Criscuolo*, Elissavet Chartampila, Stephen D. Ginsberg, Helen E. Scharfman

The accumulation of amyloid β (Aβ) in neurons is a hallmark of Alzheimer's disease (AD) pathology, contributing to neuronal dysfunction and cognitive decline. Remarkably, some types of neurons are more vulnerable to the accumulation of Aβ than others. In the course of other studies, we found that granule cells (GCs) of the dentate gyrus (DG) were resistant to Aβ accumulation in the Tg2576 mouse model. In these mice, the Swedish mutation of amyloid precursor protein (APP) is mutated and overexpressed by the hamster prior protein promoter. Aβ increases with age, and the mice develop increased electrical activity, sleep impairments, and cognitive deficits. We studied several ages taking in consideration both sexes: 2-3 months, characterized by intraneuronal Aβ in hippocampal neurons but no plaques, and 11-20 months, after plaque accumulation. Aβ was evaluated immunohistochemically using three antibodies to the first 6 amino acids of Ab (MCSA1, 6E10, 4G8). Thioflavin-S was used to assess plaques. Surprisingly, Aβ was not detected in GCs even at advanced ages when plaques were present around the GCs. In contrast, neighboring hilar neurons and hippocampal pyramidal cells exhibited robust Aβ accumulation even at 2-3 months. Because brain-derived neurotrophic factor (BDNF) is neuroprotective and expressed at high levels in normal GCs, we asked if GCs expressed BDNF in Tg2576 mice. Furthermore, given that BDNF expression is known to rise with increased neuronal activity, and considering the elevated activity levels observed in dentate gyrus GCs of Tg2576 mice, we also investigated a marker indicative of prolonged neuronal activity, ΔFosB. Our results revealed that Tg2576 GCs showed strong BDNF protein expression at all ages. We also found that ΔFosB was strongly expressed in Tg2576 GCs, and there was a correlation between BDNF and ΔFosB, regardless of sex. These results highlight the resilience of GCs to Aβ pathology and suggest that heightened activity and BDNF may be contributing factors.

30. Auditory striatum and medial geniculate body modulates mice auditory cortex through GABAB receptors

Andrea Balla*, Henry Sershen, Daniel C. Javitt

Background: Early auditory system dysfunctions in Schizophrenia were demonstrated at the beginning of 1980’s and shown to relate to higher-order auditory impairments. Neurophysiological measures, such as auditory event-related potentials (aERPs), became validated biomarkers of cognitive function across humans, primates, and rodent populations. P1/N1 refractoriness reflects

obligatory auditory responses to repetitive auditory stimulation when amplitude of P1 and N1 component depends on interstimulus interval (ISI). It also activates short-term “echoic” memory system, which maintains representations of simple physical features of auditory stimuli, such as pitch or intensity, for 10-30 s following stimulus presentation.
Method: In this recent project we are utilizing tetrode recordings (NeuroNexus) in primary auditory cortex (A1) parallel with drug infusion into the medial geniculate body (MGB) and /or into Auditory Striatum (AS). Responses were recorded in B6 freely moving male mice presented with different auditory paradigms to characterize the influence of subcortical sensory pathways on A1 through inhibitory GABAB receptors (GABABRs).
Data were analyzed by standard time-domain ERP and event-related spectral perturbation (ERSP) approach.
Conclusions: Thalamocortical circuitry component MGB modulates refractoriness function in A1 through GABABRs, affecting mostly beta, alpha, theta, and delta activity, and AS modulates predominantly gamma activity. Both regions reduced N40 amplitude, but AS also tunes N40 timing and reduced P20 amplitude.

31. Deep brain stimulation promotes white matter remodeling and is accompanied by functional changes to brain-wide networks

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Deep brain stimulation targeting subcallosal anterior cingulate cortex and adjacent white matter (SCC-DBS) is a promising therapy for treatment resistant depression. Indeed, SCC-DBS protocols report a 60 to 70% response rate even for the patients who do not respond to electroconvulsive treatment. However, it remains unclear how DBS stimulation of white matter functionally and anatomically alters brain-wide circuits to promote recovery from depression. Lacking this understanding impedes further optimization of this treatment which is essential to improve clinical outcomes. Thus, the aim of this study was to establish how SCC-DBS works in healthy brains, focusing on determining the brain-wide network-level anatomical and functional effects of white matter stimulation. Modeling the approach used to successfully treat TRD patients, we implanted SCC-DBS electrodes in two rhesus macaques. Specifically, we identified the confluence of the cingulum bundle, forceps minor, and uncinate fasciculus using diffusion tractography imaging (DTI). We then implanted a DBS lead unilaterally in this location, the other hemisphere serving as a control. One month after electrode implantation, stimulation (5mA, 130Hz, 90µsec) began and was maintained for 6 weeks. DTI and whole brain resting-state functional MRIs (rs-fMRIs) were acquired before electrode implantation and following 6 weeks of SCC-DBS stimulation to reveal the anatomical and functional effects of SCC-DBS. Functional data were analyzed using a seed-based comparative-connectome approach where SCC-DBS stimulation induced changes in functional connectivity (FC) were determined. Fractional anisotrophy (FA) was calculated from DTI data to investigate the anatomical white matter changes. Additionally, we investigated the histological changes using immunofluorescence staining of oligodendrocytes using the CC-1 antibody. Compared to before stimulation, we found that six weeks of chronic SCC-DBS enhanced white matter integrity in midcingulate portion of cingulum bundle (Figure 1). This white matter tract connects the stimulated SCC and posterior cingulate cortex, and we found a significant increases in FA and corroborated this effect by finding a significant increase in the numbers of oligodendrocytes in the mid-cingulum bundle. Additionally, we also demonstrated that SCC-DBS significantly changed the FC between stimulated SCC and multiple brain networks' hubs, mainly in the default mode network and the limbic network hubs which are connected by cingulum bundle projections. Our data unveiled the specific effects of SCC-DBS on myelin remodeling and brain network level functional changes providing insight into the neural mechanisms of DBS targeted to white matter, as well as the biological bases of depression pathology.

32. Investigating the relationship between eye movements and recall in an auditory list recall task

Christa Ouellette*, Daniel Garcia-Barnett, Anna MacKay-Brandt, Stan Colcombe

Memory foraging describes a cognitive process not unlike foraging for resources in a natural environment. Much like an animal foraging for berries in a patch of bushes, we exhaust “patches” of semantically related information before moving on to more distant clusters of information. This movement from cluster to cluster is best modeled by Levy flight patterns, a type of “random walk with memory” characterized by a greater frequency of short movements and fewer long movements. Memory foraging is often applied to verbal fluency tasks, but less is known about memory foraging in the context of a discrete list of semantically unrelated items. In these cases, item order in the presented list (rather than semantic closeness) may be used as a parameter for the clustering of information. Eye gaze may also provide insight into the mental environment in which memory foraging is employed. Prior studies have found a relationship between eye movements and recall, but tend to focus on visual stimuli (like an image) or auditory descriptions of images (with positional cue phrases such as “‘to the left’ or “in the center”). Here, we consider whether eye movements during episodic recall, with no visual stimuli, will reflect a spatial memory foraging pattern that is consistent with temporal recall patterns. Using preliminary data from NKI-Rockland Sample II’s Mobile Brain/Body Imaging protocol (MoBI; n = 24 participants, aged 18-45, M= 30.75), we examined eye fixations and item recall latencies during the Rey Auditory Verbal Learning Test. Eye tracking was conducted with an Eyelink 1000 Duo system; recall was digitized and transcribed for analysis. Temporal distance between items and spatial distance between eye fixations were compared. Results show a positive correlation for distance between items’ position in the original list and time between verbal recall of those items ($r(23) = .17$, $p < .001$), such that less time elapsed between recall of items near one another on the original list, and more time elapsed between recall of items farther from one another. The distance between items’ position in the original list is also positively correlated with spatial distance between eye fixations during said items ($r(23) = .11$, $p = 0.004$). There is also evidence of Levy flight patterns: right-skewed, heavy-tailed distributions are present for all distance parameters, with a greater frequency of short distances (for list position, time between utterances, and distance between eye fixations). These analyses provide evidence for memory foraging behavior in the context of discrete list recall tasks, and outlines an approach to consider these behaviors in memory tasks with no visual stimuli.

33. G-protein coupled receptor 55 (GPR55): Its expression and modulation of alcohol drinking behavior

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Alcohol abuse, particularly binge alcohol (ethanol) drinking, is a major public health concern and neuronal mechanism/s contributing to excessive drinking is not clearly understood. In this study we examined the role of a novel component of the endocannabinoid system, G-protein-coupled receptor 55 (GPR55) signaling in binge alcohol drinking in a mouse model. We examined the expression pattern of GPR55 in the brain, and effects of GPR55 targeted ligands on alcohol drinking phenotype and dopamine signaling. The immunofluorescence and western blot analyses revealed expression of GPR55 in various brain regions such as the prefrontal cortex, hippocampus, basolateral amygdala, striatum, and ventral tegmental area (VTA), and are colocalized with inhibitory (GABAergic) neurons. Interestingly, these receptors are mainly confined to the cell bodies unlike other cannabinoid (CB1 and CB2) receptors. In VTA, GPR55 are expressed in dopaminergic neurons. Our initial studies suggest that chronic binge-like alcohol drinking upregulates GPR55 receptors in the frontal cortex and a voluntary consumption of edible dough containing phytocannabinoid, cannabidiol (CBD) resulted in a modest suppression of binge-like alcohol drinking. Preliminary findings using fiber photometry indicate that GPR55 activation increases the activity of VTA dopaminergic neurons. Taken together, our findings reveal a recruitment of GPR55-

mediated signaling in binge alcohol drinking and suggest that GPR55 could be a novel therapeutic target for the treatment of AUD.

34. Devaluation of response-produced safety signals reveals circuits for goal-directed versus habitual avoidance in dorsal striatum

Erika C. Andrade*, Robert M. Sears, Shanna B. Samels, Lindsay C. Laughlin, Danielle M. Moloney, Donald A. Wilson, Matthew R. Alwood, Justin M. Moscarello, Christopher K. Cain

Active avoidance responses (ARs) are instrumental behaviors that prevent harm. Adaptive ARs may contribute to active coping, whereas maladaptive avoidance habits are implicated in anxiety and obsessive-compulsive disorders. The AR learning mechanism has remained elusive, as successful avoidance trials produce no obvious reinforcer. We used a novel outcome-devaluation procedure in rats to show that ARs are positively reinforced by response-produced feedback (FB) cues that develop into safety signals during training. Males were sensitive to FB-devaluation after moderate training, but not overtraining, consistent with a transition from goal-directed to habitual avoidance. Using chemogenetics and FB-devaluation, we also show that goal-directed vs. habitual ARs depend on dorsomedial vs. dorsolateral striatum, suggesting a significant overlap between the mechanisms of avoidance and rewarded instrumental behavior. Females were insensitive to FB-devaluation due to a remarkable context-dependence of counterconditioning. However, degrading the AR-FB contingency suggests that both sexes rely on safety signals to perform goal-directed ARs.

35. Circuit-specific, chemogenetic neuromodulation of the basal ganglia of nonhuman primates

Arnaud Yves Falchier*, Brian Russ, Kurt Masiello, Brent Butler, Charles Shroeder

Deep Brain Stimulation (DBS), applied to areas like the subthalamic nucleus (STN), is a standard treatment for Parkinson Disease (PD), however, DBS has inherent surgical risks as well as potential for infections and adverse side effects. Our overarching goal is to establish novel chemogenetic neuromodulation strategies in nonhuman primates (NHPs) that utilize and build upon the strengths of DBS but resolve many DBS limitations, and ultimately to translate these to clinical therapies in humans. We focus on Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), which work via specialized excitatory or inhibitory receptors genetically inserted into neurons. The main objective of the project is to develop more effective and specific DREADD induction in NHPs and to use a circuit-specific retro-infection method to selectively infect the neurons comprising STN→ GPi pathway, believed to be key to motor symptoms in PD, and b) use focused ultrasound prior to surgical delivery of viral constructs to augment DREAD expression in the STN→GP circuit. We are using positron emission tomography (PET) and behavioral assessments to gauge the strength of viable DREADD receptor expression, and post-mortem histology to screen for neuropathology and to assess the density and anatomical distribution of transduced neurons. If this project succeeds, we will start the second phase of the program funded under a UG3/UH3 mechanism. The main objective of the second phase (UH3) is to determine if activation of DREADDs in STN neurons projecting to GPi, using the oral DREADD agonist deschloroclozapine (DCZ), reduces motor abnormalities in NHPs treated with a neurotoxin to induce a PD-like condition. Success in this work and its human translation may be game-changing for the treatment of PD and other neurological/psychiatric disorders.

36. Development and open-sharing of tools to process digital audio: Preliminary pipelines for transcription and editing of verbal recall in NKI-RSII

Daniel Garcia-Barnett*, Anna MacKay-Brandt, Stan Colcombe

The Rey Auditory Verbal Learning Test (RAVLT) is a classic word-learning paradigm that is widely-used in experimental and clinical research. It is known to robustly capture variance in episodic memory performance across healthy and memory-impaired lifespan populations. Furthermore, the RAVLT can leverage digital tools for the capture of high precision behavior to, both, serve as a rich resource for individual difference analyses and serve as a bridge for laboratory-based assessments with the potential to inform everyday functional outcomes. With this in mind, the RAVLT was included in the NKI-RSII Mobile Brain Body Imaging (MoBI) procedure. The goal of MoBI is to extract high-precision coordinated behavioral and physiological signals to inform the next generation of cognitive neuroscience insights. While tools for processing and analyzing eye tracking data are plentiful, tools for processing audio of word recall are not only few, but poorly suited for the needs of the research. Namely, the three main needs for processing RAVLT audio are reliable and cost/time efficient 1) transcription of digital audio signal, 2) quality assurance of the transcription, and 3) HIPAA-compliant standards for data security protections. Manual transcriptions are infeasible due to the throughput: not only considering the number of participants' data but also its density with each participant recalling across 7 distinct trials. Additionally, while there are many easily accessible, cost-effective tools for audio transcription, participant anonymity was a key priority, and so any web-enabled or otherwise public tools that could not adhere to data security standards were ruled out. Therefore, we developed an efficient and accessible protocol to address these challenges. To address the challenges of data security and transcribing audio signal, we leveraged Picovoice: a fast, flexible, and accessible tool to process all data offline that is intrinsically private and HIPAA-compliant. To address the challenge of quality assurance, we developed an in-house tool to quickly and efficiently check a transcription's quality. Both tools are easily accessible through GitHub and accessible through most operating systems. The in-house GUI imports a transcription file and its associated audio, and allows one to quickly work through the transcription dataset to verify correct transcriptions, or edit the dataset if inaccurate timestamps, words, or other utterances are included. This is all done through a visual interface to facilitate navigation of the dataset directly using an audio waveform visualization. Full integration of transcription and quality checking protocols into one workspace is a future development goal. Further, integrating audio processing pipelines with the eye tracking analysis (e.g. visualize fixations or gaze patterns during or between recalls) is another direction of continued development. The in-house GUI was developed as a specific solution for processing NKI-RSII data, however, we anticipate sharing this resource with the research community for ongoing development, extensions, and improvements.

37. Stress effects on central and peripheral exosome levels and simultaneous transcriptomic profiles

Hope Kronman*, Amarjyot Singh, Shofiul Azam, Danielle Zelli, Timothy Lau, Josh Dobbin, Betty Bigio, Carla Nasca

Background: An excess of exosomes, nano-vesicles released from all cells and key regulators of brain plasticity, is emerging as a mechanism associated with depression and other mental illnesses. Remarkably, the effects of chronic stress - a risk factor for mental illnesses - on central and peripheral exosome levels remain poorly understood; even less is known about the relationship between exosomes and gene expression in mood-regulatory brain areas.
Methods: Using two separate surface markers, we isolated a population of neuronal exosomes from blood and key brain areas and ascertained the levels of these specific exosomes in the response to chronic restraint stress (CRS) in mice. We also used RNA sequencing and

bioinformatic analyses for a simultaneous transcriptomic characterization of the effects of CRS on two key brain areas.
Results: We found increased levels of neuronal exosomes in the ventral dentate gyrus (vDG) after CRS, and that these changes map those observed in neuronal exosomes isolated from plasma. We also found an reverse pattern of regulation in basolateral amygdala (BLA), where levels of neuronal exosomes decreased following CRS. These opposite changes in neuronal exosomes are mirrored by a CRS-induced differential regulation of gene expression profiles in the two brain areas, with β-estradiol gene acting as a potential upstream regulator of these processes.
Conclusions: This study provides a novel conceptual template for future studies of new forms of local and distant intercellular communication in stress neurobiology by showing specific relationships between peripheral and central exosome levels and the corresponding transcriptional changes in stress response. Future work may also include analyses of exosome cargo for a further correspondence of neuronal transcription to neuronal and peripheral exosome levels to what those exosomes are carrying.

38. Pupil response tracks global and anterior insula activation in the human brain

Maximilian Nentwich*, Christine Chesebrough, Noah Markowitz, Elisabeth Freund, Ashesh Mehta, Stephan Bickel

The brain continuously switches between states of internally and externally directed attentional states. A possible mechanism in coordinating switches between attentional states is the anterior insula acting as a switch. Activity in the anterior insula is further related to changes in pupil diameter. This suggests that arousal, and correlated changes in global signal variations, could be related to attentional states. To investigate the relationship between activity in the anterior insula, pupil diameter, and the global signal we analyze simultaneous intracranial EEG and pupil tracking data recorded during passive movie watching in 4 patients. We focus on slow fluctuations (<0.25Hz) of the broadband high-frequency amplitude (BHA, 70-150Hz) in channels in the anterior insula, and the global signal, the average BHA across all gray matter channels. In 3 out of 4 patients, we find a significant peak in the cross-correlation of the pupil diameter and BHA in the anterior insula, as well as the global signal. Changes in pupil diameter are delayed towards BHA by 1-2 seconds. In 3 out of 4 patients, we also find a significant peak in the cross correlation between the BHA in the anterior insula and the global signal at a near-zero delay. In addition, pupil diameter increases after BHA peaks in the anterior insula and the global signal. However, in this preliminary analysis, the timing of individual peaks in both signals does not appear to be related. We show that, while slow fluctuations of BHA in the anterior insula are related to fluctuations in the global signal, local peaks in either signal are distinct. Our results provide the basis for further analysis of local peaks in BHA in the anterior insula and the global signal as potential markers of attentional states.

39. Enigma of pyramidal neurons: Chirality-centric view on biological evolution. Congruence to molecular, cellular, physiological, cognitive, and psychological functions

Victor Dyakin*

The mechanism of brain information processing unfolds within spatial and temporal domains inherently linked to the concept of space–time symmetry. Biological evolution, beginning with the prevalent molecular chirality, results in the handedness of human cognitive and psycho-logical functions (the phenomena known as biochirality). The key element in the chain of chirality transfer from the downstream to upstream processes is the pyramidal neuron (PyrN) morphology–function paradigm (archetype). The most apparent landmark of PyrNs is the geometry of the cell soma. However, “why/how PyrN’s soma gains the shape of quasi-tetrahedral symmetry” has never been explicitly articulated. Resolving the above inquiry is only possible based on the broad-view assumption that encoding 3D space requires specific 3D geometry of the neuronal detector and corresponding network. Accordingly, our hypothesis states that if the primary function of PyrNs, at

the organism level, is sensory space symmetry perception, then the pyramidal shape of soma is the best evolutionary-selected geometry to support sensory-motor coupling. The biological system's non-equilibrium (NE) state is fundamentally linked to an asymmetric, non-racemic, steady state of molecular constituents. The chiral theory of pyramidal soma shape conceptually agrees that living systems have evolved as non-equilibrium systems that exchange energy with the environment. The molecular mechanism involved in developing PyrN's soma is studied in detail. However, the crucial missing element—the reference to the fundamental link between molecular chirality and the func-tion of spatial navigation—is the main obstacle to resolving the question in demand: why did PyrNs' soma gain the shape of quasi-tetrahedral symmetry?