IPN RETREAT 2023

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McGill | Integrated Program in Neuroscience

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Lithium responsiveness in hyperexcitable neurons derived from bipolar patient iPSC

Anouar Khayachi[1], **Malak Abuzgaya**[1], Yumin Liu[1], Kurt Dejgaard[2], Chuan Jiao[3], Anusha Kamesh[1], Lenka Schorova[1], Martin Alda[4], Boris Chaumette[3], Guy Rouleau[1], Austen Milnerwood[1]

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Abstract

Bipolar disorder (BD) is a progressive psychiatric disorder characterized by recurrent mania and depression, often comorbid with psychosis and suicide. Paralleled with other treatments, the mood stabilizer lithium (Li) is the most effective medication to prevent manic and depressive episodes. However, the pathophysiology of bipolar disorder and lithium's mode of action is not yet fully characterized and understood. Some patients react well to Li treatment for undetermined reasons, while others are entirely non-responsive. Three major questions stand out:
i) how Li is effective, ii) why for only a subset of patients, and iii) could we find a treatment for the Li non responders? Our previous studies showed that lithium dampens neuronal excitability and the activity of the glutamatergic network in mouse cortical neurons. Here, we have developed a human induced pluripotent stem cell (hiPSC) model for bipolar disorder and investigated the cellular phenotypes of glutamatergic cortical-like neurons derived from iPSCs of patients with bipolar disorder. Our results corroborate the literature discerning a hyperexcitability phenotype of young neurons, reversible by lithium treatment in neurons derived from patients who clinically responded to lithium treatment. In this study, we combined cell imaging, electrophysiology, transcriptomic, phosphoproteomic, calcium imaging and pharmacological treatments to provide a molecular signature of disease, lithium responsiveness and alternative potential therapeutic candidates.

Association of Substantia Nigra Neuromelanin with Salience Network Connectivity in First Episode Psychosis

Jessica Ahrens[1,2], Sabrina Ford[3], Betsy Schaefer[3], Philip Tibbo[4], David Reese[3], James Rioux[4], Candice Crocker[4], Kyle McKee[4], Ali Khan[3], Clifford Cassidy[5], & Lena Palaniyappan[1-3]

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Abstract

The dopamine hypothesis of schizophrenia states that hyperactive dopamine can cause the symptoms of schizophrenia. Recent work suggests neuromelanin sensitive MRI (NM-MRI) could provide a proxy measure of dopamine system function, based on the tendency of neuromelanin (NM), a breakdown product of dopamine, to accumulate in the substantia nigra (SN). NM-MRI is practical and non-invasive, providing a highly feasible and acceptable approach to study patients living with schizophrenia. Recent research shows that the NM-MRI signal correlates to psychosis severity in those with untreated schizophrenia; however, it is unknown if these results extend to those with first episode psychosis (FEP), or how NM changes over time in schizophrenia. Additionally, there is a gap in the literature on NM and cannabis use/ cannabis use disorders. We: (1) investigated if prior research results on excess SN NM in established schizophrenia extends to a first episode sample; and (2) determined the differences in SN NM in those who use cannabis versus those who do not. For baseline scans (n=62), NM was higher in the FEP group compared to HC in 226 voxels (p=0.052) and lower in 26 voxels. NM was significantly lower in cannabis users compared to non-users in 367 voxels (p=0.023) and higher in 181 voxels. These results suggest that the increased SN NM seen in those with schizophrenia may extend to those with FEP. This data will significantly add to the existing literature in the efforts to use NM as a biomarker for schizophrenia. Our results also highlight the need for more data to be conducted on cannabis use and schizophrenia to understand the relationship between NM and cannabis use.

Investigating differences in motor and visual cortex layer-5 microcircuits using 2-photon optogenetics

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Abstract

The neocortex is classically divided into six functionally distinct layers. Although primary visual cortex (V1) and primary motor cortex (M1) share many cytoarchitectural similarities, V1 mediates sensory input, and M1 provides motor output. Therefore, we were interested in V1 and M1 microcircuit differences. However, the state-of-the-art technique for probing synaptic connectivity – multiple patch clamp – is inefficient for large-scale microcircuit mapping. We therefore developed optomapping: a high-throughput connectivity mapping method. To activate M1 pyramidal cells (PCs), we injected AAV9-EF1a-DIO-STChroME-P2A-mRuby into M1 of neonatal Emx1[Cre/+] mice. In acute M1 slices from P18-P25 injected mice, we used 1040-nm two- photon spiral scans to activate candidate presynaptic PCs, while looking for responses in patched PCs. In M1 and V1, there were more intralaminar than interlaminar connections onto L5 PCs (M1: 7.9%±3% vs. 2.3%±1%, $p<0.05$; V1: 14%±2% vs. 7.1%±2%, $p<0.05$). Intralaminar connectivity was higher for L5 PCs in V1 than in M1 ($p<0.05$). In M1 and V1, we found that synaptic strengths for intralaminar inputs onto L5 PCs were indistinguishable from interlaminar inputs (M1: 0.92±0.4 mV vs. 0.22±0.08 mV, $p=0.16$; V1: 0.31±0.06 mV vs. 0.34±0.1 mV, $p=0.21$). Intralaminar input strengths onto M1 L5 PCs were also indistinguishable from intralaminar input strengths onto V1 L5 PCs ($p=0.23$). Radial connectivity did not differ between V1 and M1 L5 PCs ($p=0.87$). Synaptic strengths in V1 and M1 L5 PCs were log- normally distributed, consistent with Hebbian plasticity. In conclusion, despite their functional differences, L5 M1 and V1 microcircuits surprisingly share many properties.

Biochemical and pathological characterization of synuclein aggregates from PD and RBD patient plasma

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Abstract

Alpha synuclein aggregation is a pathological hallmark of many neurodegenerative diseases known as synucleinopathies including Parkinson Disease (PD), multiple system atrophy and dementia with Lewy bodies. Recent studies have revealed that synuclein aggregates across synucleinopathies are different in terms of their aggregation kinetics, molecular structures, and pathology. Furthermore, this difference can be seen within PD along its disease course. The aim of this study is to use seed amplification assays to detect and amplify synuclein aggregates within neuronally derived extracellular vesicles in plasma samples from PD and rapid eye movement (REM) sleep behavior disorder (RBD) patients. Since around 80% of patients diagnosed with RBD eventually develop PD within the first two decades, our approach helps us understand synuclein aggregation within PD's disease continuum. Amplified aggregates would be characterized biochemically using proteolytic digestion, circular dichroism, and electron microscopy.
Furthermore, the pathology of amplified patient aggregates will be tested using dopaminergic neurons from patient-derived induced pluripotent stem cells. Preliminary results show the successful amplification of synuclein aggregates from biological samples using the real-time quaking-induced conversion assay. Additionally, when synthetic preformed fibrils of alpha synuclein are applied to dopaminergic neurons harboring PD mutations, we detect increased presence of phosphorylated synuclein compared to control. This project will serve as an important platform for the future development of a personalized approach to the diagnosis and treatment of PD patients through non-invasive means by tailoring our approach to the patient's specific synuclein aggregation behavior

Synaptic proteins in pre-symptomatic Alzheimer's disease: biomarkers for early detection of Cognitive Decline

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Abstract

Synaptic proteins in the cerebrospinal fluid (CSF) may reveal changes in the pre- symptomatic stages of Alzheimer's disease (AD), thus may be candidate biomarkers for early detection of the disease.
Method: The PREVENT-AD cohort includes symptom-free (upon enrolment) elderly participants who are at risk of developing AD from their family history. We used enzyme-linked immunosorbent assay kits to assess CSF samples from 129 such participants for the "classical" AD biomarkers total tau, phosphorylated (181) tau and Aβ42. Neuroimaging data (MRI, PET) and neuropsychological assessments (MMSE, RBANS) were used as potential indicators disease progression. The Olink Proximity Extension Assay technology was used in the CSF samples to measure the soluble synaptic biomarkers ADAM 22 (post-synaptic), ADAM23 (pre-synaptic) whereas immunoprecipitated SYT1 (pre-synaptic) from CSF were analyzed using high- resolution selected ion monitoring analyses on a quadrupole–orbitrap mass spectrometer Q Exactive. Statistical analyses of the association of these markers with evidence of disease progression were performed using sex and *APOE* □4 status

as covariates.

Result: Among participants who remained cognitively unimpaired, we observed significant correlations between baseline CSF ADAM 22 levels and t-*tau* (R^2 = 0.22, p < 0.0001), p-tau (R^2 = 0.22, p < 0.0001), and Aβ42 (R^2 = 0.06, p = 0.01488). We also found similarly suggestive correlations also between CSF ADAM 23, CSF SYT1 and the same disease pathological markers. Covariate analyses suggested little or no variation in the associations between these synaptic proteins with t-tau and p-tau by sex, *APOE* □4 status, negative PET amyloid positivity (standardized uptake value ratio ≤ 1.37) and negative CSF total tau positivity (≤ 335pg/ul). PET amyloid positivity was significantly associated with ADAM22 and p-tau interactions whereas SYT1 was significantly associated with t-tau and p-tau in CSF tau-positive participants. In linear regression analyses, baseline CSF ADAM23 levels correlated at trend with the immediate memory performance (RBANS score) trajectory slopes estimated over the course of 5 to 8 years (spearman's rho^2 = 0.85, p = 0.0905). We found no significant interaction between other CSF synaptic protein levels and other subscales of the RBANS.

Conclusion: CSF synaptic protein levels show promising correlation with landmark AD proteins and emerging cognitive deficits.

Effects of Sustained Cannabis Abstinence on Affective Symptoms in People with Cannabis Use Disorder

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Abstract

People often report using cannabis to cope with affective symptoms, such as depression and anxiety. In contrast, longitudinal evidence supports a temporal relationship between cannabis use and the later development of affective symptoms. Employing an abstinence paradigm can help determine whether cannabis use is associated with improvements in or worsening of affective symptoms. Therefore, we investigated the effects of 28 days of cannabis abstinence on depressive and anxiety symptoms in individuals with cannabis use disorder (CB+). We hypothesize that affective symptoms will improve following 28 days of cannabis abstinence. **Methods:** CB+ participants (N=12) were randomized to an "abstinence" group (ACB+) (n=7) or to a "cannabis-as-usual" control group (UCB+) (n=5). Depression was assessed using the Hamilton-Depression Rating Scale and anxiety was assessed using the State Trait Anxiety Inventory. Affective symptoms were measured weekly over a 28-day period. Cannabis abstinence was determined using a self-report questionnaire. Given the small sample, data were interpreted graphically.
Results: Six participants (86%) successfully maintained 28 days of cannabis abstinence. In ACB+ depression symptoms increased, and anxiety symptoms remained constant over the 28-day period. In UCB+, affective symptoms remained stable. **Discussion:** Our pilot findings suggest that affective symptoms may not change with 28 days of cannabis abstinence. **Significance:** Chronic cannabis use may contribute to the onset and maintenance of affective symptoms, which may persist with one month of abstinence. Data collection is ongoing and as we increase our sample size, we hope to have more insight into the effects of cannabis abstinence on affective symptoms.

Perineuronal net labeling is associated with chondroitin sulfate disaccharide sulfation patterns

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Abstract

Perineuronal nets (PNNs) are a condensed form of extracellular matrix that form a net-like covering around certain neurons in the brain. PNNs are primarily composed of chondroitin-sulfate (CS) proteoglycans from the lectican family that consist of CS glycosaminoglycan side chains attached to a core protein. CS disaccharides (CS-d) can exist in various isoforms with different sulfation patterns. Literature suggests that CS-d sulfation patterns can influence the function of PNNs as well as their labeling. This study was conducted to characterize such patterns in different regions of the adult human and mouse brains. **Methods**: Various brain regions from adult post-mortem human and mouse brains were examined. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to quantify five different CS-d sulfation patterns. Immunolabeling for *Wisteria Floribunda Lectin* (WFL) and anti-aggrecan were performed to identify PNNs and determine if they were single- or double-labeled. **Results**: Depending on the brain region, PNNs have more affinity towards WFL or aggrecan labeling in both human and mouse. This phenomenon seems to be related to the sulfation pattern of CS-d as measured through LC-MS/MS. Of the regions examined, in both species, the hippocampus displayed the higher mono-sulfated CS-d, while the ventromedial prefrontal cortex had the highest levels of non-sulfated CS-d while being mainly labeled by WFL. **Conclusion**: This is the first cross-species comparison of PNN labeling and sulfation patterns. It illustrates the complexity of PNNs and highlights for future studies the importance of the staining protocol when examining PNNs.

Heightened response to noxious cues following development in a noxious environment

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Abstract

All nervous systems need to reliably transform sensory information into appropriate motor outputs that generate coordinated actions. Such actions do not arise de novo, but change over the course of development. The neural mechanisms underlying this adaptation, however, remain unclear. Here, we use nocifensive behaviour in Drosophila larvae as a model to study the neural mechanisms underlying developmental adaptation to a noxious environment. We see that chronic exposure to noxious cues leads to a hypersensitivity to noxious input, behavioural changes comprising a lower nociceptive threshold, an early detection of noxious cues and a delayed termination of nocifensive behaviour. This behavioural phenotype is affected by factors such as the frequency and timing of the stimulations and may be observed across all nociceptive modalities. This change in behaviour is sustained by octopamine signalling at the sensory level, with knock-down of octopamine receptors preventing sensitization but sparing optogenetically- induced nocifensive behaviour. Briefly, this research provides a better understanding of the mechanisms underlying experience-dependent changes in the nociceptive system of one of the most powerful animal models for studying genetics. This, in turn, may open new avenues of research on adaptive and maladaptive changes in nociceptive systems in general, shedding new light into the mechanisms underlying acute and chronic pain.

Ablation of Calb1+ and Calb1- nigral dopaminergic neurons reveals their distinct roles in motor function of mice

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Abstract

The cardinal motor symptoms of Parkinson's disease are due to the degeneration of dopaminergic (DA) neurons from the substantia nigra pars compacta (SNpc). However, a subset of these DA neurons, expressing calbindin (Calb1), are incredibly resilient to degeneration. Here, we wanted to investigate the roles of Calb1+ and Calb1- DA neurons in motor functions of mice. **Method**: To reveal the roles of Calb1+ and Calb1- DA neurons in motor function, we opted for a selective ablation strategy using intersectional genetic. Calb1-Ires-Cre;Dat-2A-Flpo mice, expressing Cre recombinase in Calb1 expressing neurons and Flpo recombinase in DA neurons, were injected in the SNpc with AAVs expressing a cleaved Caspase3 (taCasp3) either in Calb1+ (Cre$_{ON}$/Flpo$_{ON}$) or Calb1- (Cre$_{OFF}$/Flpo$_{ON}$) DA neurons. Three weeks post-injection, mice were subjected to a motor assessment using the rotarod, pole test and the open field. The mice were sacrificed the following week to perform histologic analysis of DA axons in the striatum and cell bodies in the SNpc. **Results**: Injection of Cre$_{OFF}$/Flpo$_{ON}$ taCasp3 in Calb1-Ires-Cre;Dat-2A-Flpo mice severely impacted the motor learning on the rotarod, whereas mice injected with Cre$_{ON}$/Flpo$_{ON}$ taCasp3 showed a similar phenotype to control mice..**Conclusion:** Our results suggest that Calb1+ and Calb1- nigral DA neurons have dual roles in motor function of mice. **Perspectives**: Further analysis will be necessary to confirm the specificity of the viral constructs. The results from the pole test and the open field might also reveal other roles from Calb1+ and Calb1- DA neurons

Uncovering the role of Podxl in photoreceptor polarity and function

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Abstract

Light detection by rod and cone photoreceptors in the mammalian retina relies on the precise compartmentalization of their apical domain into an outer and inner segment. While critical for photoreceptor function and survival, it remains unclear how this polarity is established and maintained. In this perspective, Podocalyxin-like protein (Podxl) poses as an interesting candidate. First identified in the kidney where it acts to regulate protein localization, morphology, and epithelial cell polarization, Podxl has recently been discovered to locate at the membrane of cone inner segments, and our recent results indicate that Podxl is also found in rod inner segments. To elucidate Podxl function in photoreceptors, we conditionally inactivated *Podxl* in rods and cones using the Cre-loxP system. We found that loss of *Podxl* in cones significantly impacts light-mediated response in the retina. To uncover how Podxl mediates this effect, we used IP-MS to identify potential interacting partners. The top interactor, PDZ and Plekstrin Homology domain protein 1 (Pdzph1), is hypothesized to be involved in the polarized trafficking of cargos important for vision from the inner to outer segments. Preliminary results indicate that Pdzph1 localizes to the inner segment, and interacts with Podxl. Future work is aimed at further investigating this interaction and how it affects photoreceptor biology and phototransduction. As Podxl function has never been examined in the retina, this project will lead to a better understanding of retinal diseases in which photoreceptor polarity is compromised.

Multi-Scale Sex Differences in Brain Function Using rsfMRI and Fiber Photometry: A Study in Baseline Mouse Models

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Abstract

Harnessing the knowledge that males and females can differ on several disease related outcomes is crucial since sex discrepancies exist in the prevalence and manifestation of several neurological and psychiatric disorders. However, scant attention has been paid to sex-specific effects on functional connectivity in baseline models. To understand brain function, multimodal approaches of complimentary strength are needed. The aim of this project is to investigate baseline differences in neuronal activity of the mPFC of male and female mice using resting state functional magnetic resonance imaging and fiber photometry. Typically, fMRI measures blood oxygen level dependent signal (BOLD), which is believed to be spatiotemporally linked to neuronal activity through the mechanism of neuronal coupling. Neurovascular coupling is a highly complex physiological process that involves many types of brain cells. With fiber photometry the concerted activity of cells at a specific region of interest can be examined. This cell-type specificity makes it possible to further dissect the contributions of individual neuron populations to fMRI signal in the future. Utilizing echoplanar imaging, we capture dynamic snapshots of brain activity over time, creating spatial maps of simultaneous regional activation patterns. Group ICA and dual regression are used to identify group and subject-specific spatial maps for each independent component. In a pilot study of 21 rsfMRI healthy mouse scans (10 females, 11 males), uncorrected t-values indicate higher DMN activity in females, a finding previously reported in humans. This baseline difference between sexes might be an underlying factor contributing to sex differences in depression rates.

Investigating the function of polymorphisms in APOE in chronic pain

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Abstract

Activation of microglia in the spinal cord following peripheral nerve injury is critical for the development of long-lasting pain hypersensitivity. Single-cell RNA sequencing of isolated microglia revealed that Apolipoprotein E (*Apoe*) is the top upregulated gene in spinal cord microglia at chronic time points after peripheral nerve injury in mice. APOE is a lipoprotein that is essential for the regulation of neuroimmune functions, synaptic activity, and aging. In humans, there are 3 different isoforms of APOE: APOE-ε2, APOE-ε3 and APOE-ε4. APOE-ε4 is the strongest genetic risk factor for the development of Alzheimer's disease. Previously we have shown that carriers with APOE-ε2 have significantly higher risk of developing chronic pain, whereas carriers of APOE-ε4 have lower risk.
To test the functional role of ApoE polymorphisms in chronic pain, we used humanized mice expressing APOE-ε2, APOE-ε3 and APOE-ε4, and implemented four models of chronic pain: spared nerve injury (SNI), Complete Freund's Adjuvant (CFA), hyperalgesic priming, and chronic constriction injury (CCI). To determine pain behaviors, mice were tested in von Frey, radiant paw withdrawal, mouse grimace scale, hot plate, and cold plate tests. Behavioral testing conducted at baseline revealed an increase in cold sensitivity in APOE-ε2 mice. Following behavioral testing in mice with SNI, APOE-ε4 mice showed a decrease in nerve-injury induced cold hypersensitivity. Our results support epidemiological studies in humans as they show that APOE-ε2 promotes hypersensitivity whereas APOE-ε4 is protective against developing chronic pain. Altogether, these studies might facilitate better diagnosis and treatment of individuals living with different chronic pain conditions.

Characterizing Von Economo Neurons in Schizophrenia and Major Depressive Disorder

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Abstract

Von Economo neurons (VENs) are a type of bipolar spindle-shaped neurons found in some regions of the human brain, including the anterior cingulate cortex (ACC; layer Vb) and frontal insula (FI). These neurons, absent in rodents, have been described in a few other species with large brains and complex social structures, and proposed to be involved in the regulation of negative emotions. An alteration in the number and morphology of VENs has been reported in several brain disorders including schizophrenia (SCZ) and suicide in psychosis. Recently, a transcriptomic analysis of VENs enabled the identification of differentially expressed genes in VENs vs pyramidal neurons, in particular a higher expression of genes associated with psychiatric and neurological disorders, including SCZ and depression. However, the implication of VENs in neuropsychiatric disorders remains to be largely characterized. With this project, we aim to identify specific VEN features that may be associated with major depressive disorder (MDD) and SCZ. We hypothesize that VEN densities, morphologies, and transcriptomic profiles display illness-specific alterations. Preliminary results on VEN densities in post-mortem ACC samples from male and female MDD patient's vs matched controls (n=10/group) will be presented. Together, these results should provide a better understanding of the cerebral changes that occur in MDD and SCZ and shed new light on the possible implication of VENs in mental illness.

Elucidating the impact of CSF1R variants on microglia development and function using patient- derived iPSCs

Diana T. Casas Antillon[1,2], Marie-France Dorion[1,2,3], Valerio Piscopo[3,2], Luke Healy[1,2], Thomas Durcan[3,2,1], Roberta La Piana[1,2], Jo Anne Stratton[1,2]

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Abstract

Adult leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), is a rare neurodegenerative white matter disease caused by heterozygous pathogenic variants in the colony-stimulating factor 1 receptor gene (CSF1R). Previous research has shown that specialized glial cells in the brain, called microglia, regulate neurogenesis, promote neuronal survival, and support neurodevelopmental processes. CSF1R modulates these critical functions of microglia, but in ALSP, microglial activation is driven by the dysregulation of CSF1R expression, thereby inducing a state of increased inflammation, contributing to neurodegeneration and white matter loss. Since CSF1R is an important receptor for microglia, and since iPSC-derived microglia protocols rely on CSF1R ligand binding, cells with mutations in this gene do not proliferate or differentiate well using standard culture methods, which complicates the process of generating an in vitro ALSP model. To develop a novel ALSP model, we reprogrammed peripheral blood mononuclear cells (PBMCs) from ALSP patients into iPSCs to later differentiate them into microglia by varying the culture conditions. We identified growth conditions in which microglia can be differentiated from iPSCs, but survival and differentiation state were altered in mutant cells compared with controls. In parallel, we are characterizing these cells by assessing how phagocytosis, cytokine release, migration, and adhesion vary between control and mutated lines. Understanding how variants in the CSF1R gene affect the development and function of microglia will allow us to lay the foundation for identifying potential therapeutic options for treating ALSP subjects and to generate a robust disease model that will contribute to our understanding of various common and rare microglia-mediated white matter diseases.

The control costs of human brain dynamic

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Abstract

The human brain is a complex system with high metabolic demands and extensive connectivity that requires control to balance energy consumption and functional efficiency. How this control is manifested on a whole-brain scale is largely unexplored, particularly what the associated costs are. We introduce a novel concept, average control energy (ACE), to quantify the cost of controlling idiosyncratic brain dynamics at rest. Importantly, ACE spatially correlates with oxygen metabolism, providing insight into the bioenergetic substrate preference of resting-state control. Examining the temporal dimension of control costs, we find that brain transitions within a functional hierarchical level are more efficient and frequent than expensive between-hierarchy switches. This inverse correlation between control costs and state
visits suggests a mechanism for maintaining functional diversity while minimizing energy expenditure. By dissecting spatial and temporal dimensions of control costs, we contribute to our understanding of how the brain governs its functionality while managing energy expenses.

The Influence of Prior Head Injury on Late-Life Cognition and White Matter Microstructure in Older Adults At-Risk of Alzheimer's disease

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Abstract

The long-term combined effects of mild traumatic brain injury (mTBI) and APOE ε4-allele carrier status (APOE+/-), a genetic risk factor of Alzheimer's disease (AD), on later-life cognitive outcomes and white matter structural integrity in older adults at-risk of AD is not fully understood.
Method: To investigate mTBI effects on late-life neurobehavioural outcomes, a subsample of cognitively normal adults over age 55 with a parental or multiple-sibling history of AD, from the PREVENT-AD cohort, were analyzed. Participants that self-reported at least one prior mTBI with loss of consciousness and/or memory gap (n=60, 38.3% APOE4+) were demographically matched (age, sex, education) to individuals without self-reported mTBI (n=72, 38.9% APOE4+). Cognitive outcomes were compared using Rey Auditory Verbal Learning Test measuring memory and Color-Word Interference Test (CWIT) measuring processing speed and executive functions. Further investigation of white matter tracts, bilateral superior longitudinal fasciculus (SLF), using diffusion tensor imaging to evaluate underlying structural difference between groups. Data were analyzed using 2-way ANCOVAs controlling for demographics and corrected for multiple comparisons.
Results: Significant main effect of prior head injury on cognitive outcome measures on CWIT word reading, inhibition, and switching tasks (p<0.05 corrected). Specifically, amongst APOE4- individuals, the control group performed significantly better on all sub-scores of CWIT (p<0.05 corrected). Although, no significant white matter differences between groups. Within the mTBI group, significant positive correlation between lower inhibition score and increased axial diffusivity of left SLF, controlling for age, sex, and education.
Conclusion: Our findings suggest that prior mTBI impacts cognitive aging in older adults at-risk of AD, but differentially depend on APOE4 carriership in individuals without a history of mTBI. Specifically, prior mTBI negatively impacts later-life processing speed and executive functioning skills, but not memory.
These results add to the building literature of prior mTBI as a modifiable risk factor of AD.

Developing a CRISPRa-mediated therapy to treat a novel human induced pluripotent stem cell-derived neuronal model of Smith-Magenis syndrome

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Abstract

Smith-Magenis syndrome (SMS) is an incurable neurodevelopmental disorder associated with epilepsy, obesity, and autism spectrum disorder. 23% of SMS cases are caused by point mutations in the *RAI1* gene, which encodes Retinoic Acid-Induced 1, a crucial neurodevelopmental transcription factor. Although our lab recently showed that CRISPR-activation (CRISPRa) systems targeting *Rai1* in SMS mouse models have therapeutic effects, it has not been tested in any human neuronal models.

We established a novel human neuronal model of SMS using induced pluripotent stem cells (iPSCs) derived from *RAI1*-haploinsufficient SMS patients, and developed a CRISPRa-mediated gene therapy to rescue RAI1 in our model. We are currently generating cortical glutamatergic neurons from healthy individual- and patient-derived iPSCs to characterize their cell morphology, connectivity, and synapse formation. We generated an adeno-associated virus to deliver our RAI1-targeting CRISPRa system, and confirmed that it can increase RAI1 mRNA expression by 1.7 fold in healthy iPSC-derived neurons.

We hypothesize that as a result of *RAI1* haploinsufficiency, SMS iPSC-derived neurons will have reduced soma size and dendritic spine density, dendritic morphological defects, and reduced connectivity compared to healthy neurons, which may be reversed by rescuing RAI1 via our CRISPRa therapy. The study will provide a tool to understand the human neuronal phenotypes of *RAI1* haploinsufficiency, and help uncover the therapeutic potential of CRISPRa-mediated gene therapy for SMS.

Developing a behaviour to study visual transfer learning in mice

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(Contributed Equally)

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Abstract

A human brain is able to transfer knowledge from one task to another, for example applying knowledge from lecture to the real world. This so-called transfer learning is hallmark of intelligent agents - knowledge acquired in one task can readily be applied to novel situations. The visual system must do this all the time in the form of transformation invariance. If a human sees a new object in one part of their visual field, they will have no problem recognizing the same object in another part of the visual field. We seek to further explore this process, using mouse as model system. We hypothesize if mice were to learn a task using only one side of its visual field the mouse will do just as well on the same task in the opposite visual field. If transfer occurs, what are the underlying cellular processes? If not, why and how does the mouse model differ from primates? Here we have developed a novel behaviour paradigm using an in- house built rig to unveil the process underlying visual transfer learning in mice.

Mlp60a interacts with Spire in neurons to regulate dendritic arbor development.

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Abstract

Dendrites develop highly complex arbors that are critical for the maintenance and function of neural circuits. Dendrite growth and branching are controlled through dynamic regulation of actin filaments (F-actin) by a variety of proteins. Spire is a Drosophila F-actin nucleation protein that our lab showed previously to be critical for the formation of new dendritic branches in class 4 dendritic arborization (c4da) sensory neurons. However, the presence of Spire is not sufficient to form new branches, and therefore it is important to identify additional factors that influence the ability of Spire to initiate dendritic branching. Through mass spectrometry, we identified Muscle LIM protein at position 60a (Mlp60a) as a potential Spire interacting protein. Mlp60a is known to be involved in F-actin crosslinking within z- discs of muscle cells, and is critical for myocyte development. We have found that loss of Mlp60a induced by RNAi in c4da neurons results in a significant increase in branches and total arbor length, while the area covered by the arbor is unchanged. These increases were suppressed both by a deficiency that includes *spir* and by a Spire mutant, supporting the possibility of an antagonistic interaction between Mlp60a and Spire. We are further investigating this possibility with ongoing experiments using genetic and biochemical approaches. Additionally, we are investigating their combined effects on F-actin levels, distribution, and dynamics using live confocal imaging. By characterizing a novel role for Mlp60a in dendritic development through its interaction with Spire, we provide the first evidence of Mlp60a function in the nervous system.

TNF regulates behavioural and synaptic responses to chronic morphine administration

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Abstract

The opioid crisis has demonstrated the need for new therapeutic strategies, but despite increasing research in the field, the mechanism by which opioid addiction induces neuronal plasticity is far from being understood. In the Nucleus Accumbens (NAc), a key structure of the reward system, glial cells are activated by drugs of abuse such as cocaine or morphine and contribute to the development of addictive behaviors.
We have previously shown that repeated cocaine administration activates striatal microglia and induces the production of the inflammatory cytokine Tumor Necrosis Factor (TNF). TNF signalling then depresses glutamatergic synaptic strength and mitigates cocaine-induced locomotor sensitization. Whether this phenomenon is specific to cocaine or can be generalized to other drugs is not known. As opioids also activate microglia, we investigated the potential role of microglial TNF in regulating opioid sensitization. We quantified the TNF response of microglia to morphine treatment and measured the impact of TNF on morphine-induced NAc synaptic plasticity and behavioral sensitization.
Our findings demonstrate that chronic morphine treatment causes synaptic and behavioral changes that are likely different to those induced by cocaine. This gives us new insight on the plasticity mechanisms involved in opioid addiction and underlines the role of TNF in regulating it. Importantly, the fact that TLR4 activation is capable of mitigating morphine-induced locomotor sensitization demonstrate that this receptor is a potential therapeutic target in the treatment of opioid addiction.

Functional Neurobiology of Neurokinin B Expressing D1 Neurons in the Lateral Stripe of the Striatum

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Abstract

The striatum is made up of medium spiny neurons (MSNs) which are divided into two groups: dopamine 1 receptor (D1) neurons, which directly project to other brain regions; or dopamine 2 receptor (D2) neurons, which indirectly project. [1,2,3,4] This division, called the conventional dichotomy model (CDM), is used to sort the functional roles of MSNs.[2,4] However, recent research suggests D1 and D2-MSNs have overlapping functions/projections.[5,6] Additionally, molecularly heterogeneous MSN subpopulations have been discovered that complicate the binary D1 or D2 characterization.[2] A D1-MSN subpopulation (NKB-D1-MSN), distinct in its location (lateral stripe of the striatum (LSS)), contributes to this molecular heterogeneity through its co-expression of neurokinin B.[2,7] Our study will use mice to clarify the CDM's molecular and organizational oversimplification by functionally exploring this unaccounted for MSN. NKB-D1-MSNs will be locationally confirmed using *in situ* hybridization. Projection targets will be evaluated through anterograde tracing using Tac2-IRES-Cre transgenic mice. For evaluating functionality, NKB-D1-MSNs will be depleted in the LSS of Tac2-IRES-Cre mice using intracranial injections of a Cre- activated caspase 3-expressing virus; control mice of the same strain will get a sham injection.[9,10] For the role of D1, D1 will be knocked out in all NKB-D1-MSNs by crossing Tac2-IRES-Cre mice with D1 floxed mice; Tac2-IRES-Cre mice will serve as controls.[9] All groups will be subjected to locomotion, reward, cognition, and emotion-related behavioural testing; which MSNs are hypothesized to regulate.[2,6]Our results will clarify the current model of striatal functioning and advance research in diseases affecting the striatum such as addiction, Parkinson's, Huntington's, etc.

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Restless legs syndrome drug screen in *C. elegans* model.

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Abstract

Restless legs syndrome (RLS) is a chronic sleep-related sensorimotor disorder characterized by a strong impulse to move the legs and relieve uncomfortable sensations. In 2007, a genome-wide association study identified significant associations between RLS and three genomic regions, of which comprises a highly significant intronic variant in the homeobox gene *MEIS1*. Carriers of this particular *MEIS1* variant have a 50% increased risk of developing RLS. Using a simple and strong genetic model organism *Caenorhabditis elegans*, our team previously reported reduced expression of *UNC-62* (C. elegans ortholog of *MEIS1*) to be associated with iron homeostasis via an increased expression of ferritin ortholog (FTN-1). The *unc-62* orthologue is expressed in different issues (hypodermis, intestine, and nervous system), and its downregulation led to a strong movement phenotype. Different *unc-62* alleles showed defects in *cat-2/tyrosine hydroxylase* (involved in dopamine synthesis). In our work, we took advantage of the mobility difference between the *unc-62(e644)* strain and the control strain (*N2*) and performed an unbiased drug screen. We identified 21 compounds (from a library of ~4,000 compounds) showing promise in their ability to rescue the mobility of *unc-62(e644)*. The benefits and impact of these compounds are under validation. To correlate the dopaminergic system and iron expression, we generated *unc-62* strains expressing GFP::DAT-1 and GFP::FTN-1 to monitor their expression. Our work highlights the advantages of using the unc-62 model to evaluate other genes and pathways involved in RLS.

Developmental axonal swellings depend on action potential propagation signalling

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Abstract

The development of axons and the establishment of contacts between neurons is an important step during brain development and subsequent formation of functional brain circuits. Recently we demonstrated that axonal swellings appear transiently on cerebellar Purkinje cell axons during postnatal development where they propagate action potentials with higher fidelity and are associated with enhanced cerebellar function. An understanding of how axonal swellings form is thus important. We aimed to further investigate the role of firing in the formation of axonal swellings. We performed 2-photon time-lapse imaging in acute cerebellar slices from juvenile mice (P10 - P14) and added sub-saturating levels of tetrodotoxin (TTX; 1, 2.5, 5 and 10 nM) to parametrically block different concentrations of Na^+ channels and as a result, impair action potential propagation in the axon to different degrees. Paradoxically, we found that low concentrations of TTX that block fewer somatic action potentials resulted in more axonal swellings that formed faster. Higher sub-saturating concentrations of TTX blocked more somatic action potentials but resulted in fewer and slower-forming axonal swellings. Our results support a model in which action potential propagation failure is required for axonal swelling formation, but a balance between successful action potentials and failures exists. These data suggest that mild impairment of action potential propagation may be the optimal trigger to activate signalling cascades to form swellings and boost action potential fidelity.

What the Gut Microbiome Can Tell us About Mental Health: A Prospective Longitudinal Study of Patients Newly Diagnosed With Cancer

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Abstract

Detecting and managing cancer-related distress is pivotal within cancer care. Unaddressed distress results in impairments, social seclusion, and compromised treatment adherence, impacting recovery and survival. This research investigates bio-psycho-social determinants of cancer-related distress, notably the interplay of the gut microbiome and psycho- social dimensions. Preclinical and clinical evidence underline gut-brain axis dysbiosis in depressive pathologies. This study extends this paradigm to oncology, aspiring to identify gut- microbiota as biomarkers for mental health sequela in individuals recently diagnosed with cancer. We aim to enroll 150 people recently diagnosed with breast, lung, or head and neck cancer. Over the course of the study, participants are requested to complete a battery of validated questionnaires such as the Hospital Anxiety and Depression Scale, Functional Assessment of Cancer Therapy-General, and the Impact of Events Scale. Structured Clinical Interview assessing DSM-V criteria for various disorders occur at baseline and 3 months, along with stool sample collection for 16S sequencing. Preliminary analysis of 30 microbiome samples highlights v5v6 primer superiority for taxonomic resolution. We observed significant differences in alpha and beta diversity between healthy controls and cancer patients. Lastly, patients with baseline anxiety/depression exhibit distinctive microbiome profiles. This study innovatively probes quality of life via novel biomarkers, including the gut microbiome. While we acknowledge the preliminary nature of the evidence, these nascent findings hold promise in informing subsequent research endeavors. By potentially informing novel screening protocols, our study may facilitate early resource allocation to mitigate distress trajectories among individuals deemed to be at elevated risk.

Characterizing patterns of neural activity in midbrain organoids as a model for studying Parkinson's disease

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Abstract

Human derived midbrain organoids (hMOs) are a promising tool that can be used to study Parkinson's disease (PD) on a patient specific level. Yet, much is unknown about how accurately hMOs recapitulate the human brain. In human models of PD, the progression of the disease leads to changes in neural activity. In this study, we aim to determine whether hMOs can capture these changes in neural activity associated with PD. We have generated hMOs using induced pluripotent stem cells derived from PD patients and their CRISPR corrected controls and recorded their network activity over the course of 9 months using a Micro-Electrode Array.

Using custom Python scripts, we then compared these patterns of activity between mutant and control (CTL) hMOs. In organoids derived from patients carrying a synuclein triplication mutation, we see a decrease in overall activity across the organoid compared to their CTLs.

However, mutant hMOs showed an increase in the strength of single neuron and population wide bursts, as measured by the number of bursts, the firing rate within a burst, and the duration of the burst. This suggests that although mutant hMO activity is decreased, the organization of neural activity is shifted towards strong bursting activity. These findings are complementary to neural activity described in mouse models of PD and may reflect compensatory mechanisms as a response to cell death. To test if this change in activity was due to a decrease in dopamine (DA) transmission, we treated hMOs with exogenous L-Dopa and recorded their activity before and after treatment. Here, we saw a decrease in both the number of bursts and population bursts in mutant hMOs but not CTLs, suggesting that the altered network activity in mutant hMOs may be due to decreased DA transmission.

Neurons exhibit an accelerated aging phenotype in EAE and MS

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Abstract

Multiple sclerosis (MS) is a complex neuroimmune disease. Loss of brain volume, particularly of the grey matter, is one of the best clinical correlates to sustained disability for MS patients, suggesting that neurodegeneration in MS may be a relevant area of study to identify novel therapeutics. To this end, it is essential to understand how neurons are altered by injurious inflammation.

Methods: RNA-sequencing, miRNA-sequencing, and ATAC-sequencing was performed on retinal ganglion cells from EAE mice at different timepoints and underwent differential gene and pathway analysis. Previously published single-nucleus sequencing datasets from neurons from MS patients were analyzed to validate findings from EAE neurons. Immunohistochemistry (IHC) was conducted to validate dysregulation of pathways of interest at the protein level. Intravitreal AAV injection was conducted to target senescence in RGCs.

Results: Pathway analysis of RNA-sequencing from EAE mice suggested a preponderance of senescence-associated pathways in neurons and correlated with transcriptomic changes seen in naïve aged mice. Equally, single-nucleus sequencing of cortical neurons from grey matter of MS patients similarly confirmed the presence of a senescence like signature, characterized by alterations to chromatin modification pathways and accumulation of DNA damage. IHC confirmed that retinal ganglion cells in EAE mice accumulate yH2AX in their nuclei, and exhibit changes to histone methylation and nuclear envelope integrity. Lastly, AAV-mediated gene therapy to rejuvenate RGCs protected from cell death in EAE mice.

Conclusions: Inflamed and injured neurons undergo changes that are reminiscent of a senescence- signature, predominantly with alterations to chromatin marks, nuclear integrity, and DNA damage. Targeting aging lead to preservation of neurons in EAE. Identifying drugs targeting neuronal senescence may be a strategy to preserve neurons in MS.

Development of a novel dichoptic reading application to treat amblyopia

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Abstract

The neurodevelopmental disorder amblyopia, or lazy eye, occurs when the brain can only process visual information from one eye. Current amblyopia treatment research is focused on binocular tasks instead of the typical patching treatment which is not effective across age groups and has low compliance rates. The goal of this study was to assess reading as a binocular treatment for amblyopia. Here, a dichoptic e-book application was developed as a platform to study the feasibility of this task for amblyopes. An application prototype was developed and uploaded onto tablets for participant assessments. Using anaglyph red/green/black presentation
to allow for independent adjustments of monocular and binocular contrast participants read e- books. Controls and amblyopes were questioned on application use comfortability and their reading speed was measured. We discovered that amblyopes read significantly slower than controls in all the dichoptic presentations and amblyopic participants read slower in all dichoptic presentations than in control presentations. This indicates that their visual systems were forced to integrate information from both eyes. Furthermore, when the contrast of text seen by the fellow eye was reduced, reading speed increased in accordance with current research on binocular
training approaches. In conclusion, this research showed that amblyopes can read binocularly using the e-book application platform suggesting that it may be an effective treatment for
amblyopia. Future steps in this research are aimed towards training amblyopes on reading in this application to improve their binocular vision.

Uncovering the role of the WAVE regulatory complex during neuronal migration

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Abstract

Impaired neuronal migration can lead to improper circuit formation, neuronal cell death, and functional and/or cognitive defects. During neuronal migration, reorganization of the actin cytoarchitecture is critical for directed cell motility. One evolutionarily conserved molecular machine responsible for actin remodelling is the hetero-pentameric WAVE Regulatory Complex (WRC). The WRC promotes branched actin polymerization and subsequent formation of cell surface extensions known as lamellipodia. Recently, siRNA knockdown of the WRC component Nckap1, showed cortical layering defects *in vivo*, suggesting these neurons require the WRC for their migration, however, how WRC activation is instructed remains poorly understood. One brain region containing highly migratory neurons is the cerebellum. Therefore, we knocked out Nckap1 from a subset of cerebellar neurons (Nckap1 cKO) to investigate WRC- mediated neuronal migration. Because the cerebellum is a coordination centre, we screened for potential locomotion phenotypes and identified Nckap1 cKOs have severe ataxia, fine motor deficits, and produce abnormal walking patterns. Histological characterization revealed that adult Nckap1 cKOs have anterior cerebellar hypoplasia with a 75% reduction in total cerebellar size. Next, we will investigate whether the reduction in cerebellar area is linked to developmental migration defects of Nckap1 cKO neurons *in vivo* by using the EdU-pulse chase assay, in combination with novel *in-vitro* migration assays that are currently being developed. Ultimately, understanding the molecular mechanisms that regulate neuronal migration will provide insight into how neurons localize their soma for the formation of complex brain structures, which can be utilized for therapeutic and regenerative strategies for patients with neuronal migration defects.

Molecular Biomimicry and the Synthetic Synapse: Engineering a Stable Synaptogenic Extracellular Matrix

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Abstract

Synapses are highly specialized sites of asymmetric cell – cell contact that mediate information transfer between neurons. Many proteins have been identified that contribute to the complex processes that underlie the formation, organization and maintenance of synapses, and the
molecular biology of synapse formation is increasingly well understood. Surprisingly, synaptic differentiation does not require a cellular target. Hemi-synaptic specializations form quickly at sites of neurite adhesion to microspheres coated with a synaptogenic protein or a synthetic
cationic polypeptide like poly-lysine. This raises the possibility that functional hemi-synaptic connections could be directed to form onto engineered surfaces; however, studies examining the stability of synaptic specializations formed in brain onto poly-lysine coated beads found they were unstable and degraded within a few weeks after implantation. Here, we demonstrate that microbeads coated with nanoparticles of dendritic polyglycerol amine (dPGA), a non-protein
macromolecular biomimetic of poly-lysine, promote enhanced synaptogenesis and synapse stability compared to conventional poly-lysine. We propose that synthetic synaptogenic extracellular matrices that are resistant to proteolysis could be used to engineer electrodes with enhanced neural-biocompatibility and support bi-directional communication with neurons by directing the formation of stable of synaptic specializations.

The role of radial astrocytes in plasticity of the developing visual system.

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Abstract

During late stages of brain development, efficient circuit wiring relies on instructive cues from sensory experience and neural activity to drive synaptic plasticity and achieve mature functional connectivity. Initially thought to only implicate neurons, more recently astrocytes have been shown to be directly involved in the neural plasticity mechanisms that mediate structural and functional circuit refinement. Given that astrocytes invade brain regions, providing guidance and structural support, do they play a role in tuning their functional properties as well? Using the visual system of Xenopus *laevis* we conducted live calcium imaging while presenting visual stimuli to study the role of radial glia in neural plasticity. To selectively control the activity state of radial astrocytes of the tectum they were preferentially transfected with chemogenetic calcium channels.
We observed only a small number of cells responding to the visual stimuli, which is consistent with previous findings of sparse information encoding. Glial activation increased the strength and duration of network wide short- and long-term depression after plasticity inducing stimuli. On the other hand, the activity of the neuropil, where retinal ganglion axons synapse onto tectal neurons, saw a significant increase in responsiveness to the stimuli after induction and glial activation, in contrast to the control group which had no changes in responsiveness after training.
Our results indicate that glia are acting between the synapses and the cell body to modulate signal transduction and plasticity.

Biological processes underlying a cognitive-anatomical signature of intervention strategies in mice

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Abstract

Evidence suggests that vascular risk factors such as obesity and hypertension are associated with a higher risk of Alzheimer's Disease (AD). Due to the lack of treatments, there is considerable interest in investigating intervention strategies on modifiable risk factors in order to delay the onset of dementia. As obesity is one such modifiable factor, we studied two intervention strategies: a low-fat diet and exercise, and their effects on the brain anatomy of the triple-transgenic mouse model of AD (3xTgAD) and in their wild-type counterpart (WT). Mice were fed a high-fat diet to promote obesity before intervention. We derived a cognitive-anatomical signature of these interventions with partial least squares analysis (PLS). We further applied a spatial gene enrichment analysis (SGEA) to examine the underlying biological processes of this signature.
All 3xTgAD and WT mice were fed with a control diet (12% fat) for the first 2 months and then put on either a low-fat diet (LFD) (10% fat) or a high-fat diet (HFD) (60% fat) until 4 months. From 4-6 months, 3xTgAD and WT mice were randomly assigned to a low-fat diet intervention, exercise, or no intervention. MRI images were acquired at 2, 4, and 6 months (TR=20 ms, TE=4.5 ms, voxel dimensions = 100 µm isotropic, 7T). PLS revealed a brain pattern that correlates with better cognitive performance and exercise. SGEA showed gene modules related to carbohydrate homeostasis, suggesting that intervention strategies studied here could be executing their beneficial effects by the modulation of genes related to energy homeos

Insulin metabolism in the interaction of ELA and impulsive behaviors.

Ameyalli Gomez-Ilescas[1,2], Marcio Bonesso Alves[2], Patricia M. Miguel[1,2], Anne-Marie Arel-Dubeau[1,2], Gisele Sanda[1,2], Bonnie Alberry[1,2], Patricia Pelufo Silveira[1,2].

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Abstract

Recent studies have shown the potential role of insulin in mediating the effects of early life adversity (ELA) on the brain. For instance, rodent intrauterine growth restriction (FR) is linked to dopamine release impairment in areas of the mesolimbic pathway, but dopamine release can be restored with insulin administration. However, prior research suggests that sex differences may exist in the impact of ELA exposure on humans and animal models. To study the sex-specific modulation of insulin on the interaction between ELA and impulsivity, we used a FR model in Sprague Dawley rats by applying 50% food restriction during pregnancy (day 10 onwards) and cross-fostering all animals to Ad libitum dams at birth. Impulsive behavior was evaluated as adults using a delayed gratification task after i.p. injection with either saline or insulin (5IU/Kg.). To study the insulin activation cascade, PI3- kinase activity was measured on the ventral tegmental area (where insulin receptors are found on dopaminergic neurons) by ELISA. Our results show that females but not males are more intolerant to delayed rewards specifically after FR. The tolerance to reward in males seems to be influenced by their catch-up weight from birth (P0) to weaning (P21). Furthermore, insulin injection increases the tolerance to delay in FR females but has no effects in FR males. Our results indicate a neuroendocrine sex-dependent modulation of impulsivity through the insulin pathway, possibly acting on the dopaminergic system involved in impulsivity control.

The real-time top-down (attentional) effects on sensory eye dominance

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Abstract

Purpose. To investigate the role of top-down attention on ocular dominance in real-time using dichoptic phase-scrambled movie. **Methods.** 18 adults with normal vision participated in our study. Fourier phase spectrum scrambled movie images were displayed on one eye (unattended eye), and natural movie images were presented to the other eye (attended eye) in dichoptic conditions. Same mixed movie images (phase-scrambled image mixed with natural image) were presented to both eyes as control conditions (binocular conditions). Movies were displayed under binocular with sound (Bino Sound(+)), binocular without sound (Bino Sound(-)), dichoptic with sound (Dic Sound(+)) and dichoptic without sound (Dic Sound(-)) conditions. The perceptions (more natural or more phase- scrambled image) of participants were measured during the movie watching. **Results.** The proportion of more-scrambled perception was significantly larger than more-natural perception in Bino Sound(+), Bino Sound(-) and Dic Sound(-) conditions, but not in Dic Sound(+) condition. The perceptions were not different between Dic Sound(+) and Dic Sound(-) conditions after the data were normalized to the corresponding binocular conditions. The proportion of more-scrambled perception gradually increased across the 10-minute of movie watching under both Dic Sound(+) and Dic Sound(-) conditions. This indicate that the eye with scrambled image was more getting more dominant over time. **Conclusion.** We demonstrate that the eye-specific attention affects ocular dominance progressively over time. The visual attention enhancement by audiovisual interaction might not have eye selective effects. Our study provides a better understanding of the role of top-down control in ocular dominance plasticity.

Investigating the temporal dynamics of dichoptic masking

Daniel Gurman, Alexandre Reynaud

Abstract

In the standard model of binocular combination, inputs from the two eyes not only sum together but also suppress each other. Interocular suppression is often characterized through dichoptic masking, a phenomenon in which the detection of a target presented to one eye is reduced by a noise mask presented to the other eye. However, the temporal dynamics of interocular suppression are not well understood. In particular, the relationships between simultaneous masking, backward masking, and forward masking are not known for dichoptic stimuli. Our objective was to better understand these relationships.

We employed a dichoptic suppression paradigm using a two-alternative-force-choice task. Stimuli were displayed on a passive 3D screen. Participants indicated the orientation of a target grating presented to one eye while a pink noise mask was presented to the other eye at the same spatial location but at a different time. The contrast of the target was adjusted using a 2- up 1-down staircase. Thirteen interstimulus intervals between the mask and the target were used to individually investigate the three masking types.

Our results revealed the presence of a masking effect for all three masking types. Surprisingly, the strongest masking effect was found in the backward masking condition.

These findings provide novel insight into the temporal dynamics of dichoptic masking, particularly in revealing the strong effect of backward masking, and may have implications in the general understanding of amblyopic suppression and in the development of suppression- related treatments for amblyopia.

Rai1 modulates dominance behaviour in mice by regulating interneuron signaling

Minza Haque, Wei-Hsiang Huang

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Abstract

RAI1 is a transcription factor that regulates the expression of many genes involved in circuit assembly, neurotransmission, synaptic plasticity, and circadian rhythm in the mammalian brain. Loss of Rai1 function is strongly implicated in the pathophysiology of ASD, namely a syndromic ASD called Smith-Magenis Syndrome (SMS). In our work, we study models of SMS to understand the neurobiology of ASD, because SMS is a single-gene disorder that recapitulates some of the core phenotypes of ASD. Preclinical mouse models of SMS exhibit a strong social deficit in a paradigm that assesses dominance, which is observed in both pan-excitatory and pan- inhibitory neuron conditional knockout (cKO) mice. Although we know that loss of Rai1 from pan-inhibitory neurons leads to a 'less dominant' mouse compared to its wild-type counterpart, we do not know the underlying neurobiology for this phenotype. Therefore, our project is designed to tease out the role of different interneuron subtypes in regulating dominance behavior in both male and female mice. Thus far, we report novel findings that reveal Rai1's role in regulating social dominance bidirectionally via VIP, SST and PV interneurons.

Targeting the Integrated Stress Response Pathway in Depression

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Abstract

Major Depressive Disorder (MDD) is one of the most common psychiatric diseases in the world, with an average lifetime prevalence of 14.6%. Approximately two thirds of patients with MDD do not respond to typical antidepressants. Stimulation of protein synthesis with ketamine or mTORC1 activator, NV-5138, produces antidepressant effects. Protein synthesis is also regulated via the integrated stress response (ISR) pathway. The ISR inhibits protein synthesis during cellular stress through the phosphorylation of the eukaryotic initiation factor alpha subunit (p-eIF2α). Hence, an inhibitor of the ISR (called ISR inhibitor, or ISRIB) stimulates protein synthesis and improves cognitive functions in animal models. ISRIB is presently in clinical trials for the treatment of Amyotrophic Lateral Sclerosis. Here, we tested the hypothesis that the ISR pathway is dysregulated in depression and activation of protein synthesis via the ISR might have antidepressant effects. Our preliminary results show that mice with excitatory or inhibitory neuron- specific reduction of p-eIF2α exhibit reduced depression-like behaviors, as measured in the forced swim, tail-suspension, and novel suppression feeding tests. We also show that ISRIB partially alleviates depression-like behaviors. Finally, quantification of p-eIF2α via immunohistochemistry in mice exposed to chronic social defeat show increase and decrease in p-eIF2α respectively in the ventral and dorsal hippocampus. In conclusion, our results suggest a potential role of the ISR pathway in the regulation of depressive behaviors.

Targeting 14-3-3 adaptor proteins to promote CNS axon regeneration

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Abstract

In the central nervous system (CNS), axons do not regenerate spontaneously, so disrupting them can lead to neurodegenerative diseases, traumatic injury, and disability. To contribute to the development of therapeutics for treating spinal cord injury and other CNS diseases, our lab explores various avenues for promoting axon regeneration, including finding new molecular
targets and small molecules that have a regenerative effect both *in vitro* and *in vivo*. 14-3-3 adaptor proteins regulate intracellular signalling pathways, both in normal and disease states. 14- 3-3 proteins, categorized by isoform and tissue specificity, interact with their target protein to
modify its activity and intracellular location. 14-3-3 proteins can also be found in a lesser extend in the extracellular environment, in exosomes or following cell death. Protein-protein
interactions (PPIs) are an important focus for drug discovery since they allow pathways to be targeted rather than specific targets. Fusicoccin is a small molecule as well as a 14-3-3-targeted drug. Our lab has shown that the addition of Fusicoccin A (FC-A) stimulates axon growth *in vitro* and axon regeneration *in vivo* by stabilizing 14-3-3 PPIs. In combination with a microtubule stabilizer, the most potent FC-A analogue, FC-NCPC, promotes even greater outgrowth. We are currently exploring the effects of this combination therapy *in vitro* in retinal neurons and *in vivo*
in our rodent optic nerve crush model. This research can potentially contribute to the development of a therapy for the long-distance axon regeneration important for functional recovery in the CNS.

IgLONs modulate synapse formation

Luyang (Simon) Hua[1], Alyson Fournier[1]

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Abstract

The synapse provides the basis for signal transmission between neurons. Various cell adhesion molecules regulate the formation of synapses by promoting the interaction between presynaptic and postsynaptic neurons. Proteins of the IgLON subfamily of the immunoglobulin superfamily have been described as regulators of neuronal outgrowth, cell adhesion, and hippocampal synapse formation. IgLONs contain three immunoglobulin domains and a glycosylphosphatidylinositol anchor. The expression of IgLONs in the cortex and hippocampus colocalizes with synaptic markers. Additionally, the homo- and heterodimers of IgLONs have been shown to be compatible with a model of interaction across the synaptic cleft. In this study, we identify IgLONs as modulators of cortical synapse formation. In vitro overexpression of IgLONs in neurons increases the number of excitatory synapses while the overexpression has no effect on the number of inhibitory synapses or dendritic spines. In vitro expression of IgLONs in non-neuronal cells induces the clustering of excitatory, but not inhibitory, synaptic markers. Furthermore, IgLONs have been shown to undergo cell surface proteolysis through ectodomain shedding mediated by adamalysins and matrix metalloproteinases. In vitro expression of IgLONs in non-neuronal cells treated with adamalysin or matrix metalloproteinase inhibitor induces even greater clustering of excitatory, but not inhibitory, synaptic markers. In this study, we identify IgLONs as inducers of cortical excitatory synapse formation and their functions are regulated by ectodomain shedding.

Brain Functional Flexibility and It's Link to Alzheimer's Disease Pathology at the Preclinical Stage

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Abstract

Alzheimer's disease (AD) is the most common form of dementia which is characterized by amyloid-beta (Aβ) and hyperphosphorylated tau measured by PET (Positron Emission Tomography). Abnormal accumulation of Aβ and tau in brain starts years prior to the onset of its clinical symptoms, defining the preclinical stage of AD. Investigating the link between Aβ and tau with brain's function at the preclinical stage of AD is an important step for better characterizing early AD-related brain functional features. Thus far, most studies focusing on brain's functional connectivity as a major functional feature of brain, have not considered the dynamics of these connections that are relevant to human's behavior and cognition. In our study, we used a subset of 218 individuals from the PREVENT-AD cohort (cognitively unimpaired individuals at high risk of developing AD) with both Aβ and tau PET along with resting state functional Magnetic Resonance Imaging (fMRI) scans. First, we defined a quantitative measure that is a representative of the brain functional connections variability (functional flexibility) in time, using the edge centric method. We then investigated the relationship of our proposed measure with Aβ and tau at the whole brain level and in the DMN and limbic functional networks, two networks that showed higher Aβ and tau deposition in the preclinical AD. While we found no significant association between pathology and brain's functional flexibility, there was a marginally significant difference in the functional flexibility between high- and low-level Aβ-PET individuals. Our results also revealed no relationship between conventional static functional connectivity and Aβ and tau PET.

Role of leptin receptor-expressing pericytes in obesity-associated neuroinflammation

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Abstract

The anorexigenic hormone leptin is released into circulation by adipocytes in the proportion to the size of fat deposits and is then sensed by leptin receptor (LepR) expressing neurons in the brain to maintain energy homeostasis. Our lab recently discovered that about 40% of vessel-enwrapping hypothalamic pericytes express the LepR and that selective ablation of pericytic LepR leads to overeating and a loss of leptin responsiveness in hypothalamic LepR neurons. Importantly, intravenously injected fluorescently tagged leptin was specifically retained at LepR pericytes and this retention was attenuated in mice that were deficient in pericytic LepR suggesting that LepR pericytes regulate blood brain barrier (BBB) permeability in a leptin dependent manner. My project aims to delineate the precise mechanism of how LepR pericytes are engaged in creating these locally restricted leaks in the BBB and explore the consequences of hyperleptinemia on LepR pericyte function. I hypothesize that the LepR-pericytes mediate leptin brain entry by local weakening of the inter- endothelial junctions they associate with leading to an increase in BBB permeability that facilitates entry not only of leptin but likely other circulating factors as well, including proinflammatory cytokines. My preliminary results indicate that diet-induced obesity leads to an increase in neuroinflammatory markers in wild-type but not in pericyte-specific LepR deficient mice, suggesting that LepR-pericytes mediate obesity-associated neuroinflammation. This research may provide a rationale for the strong link between obesity and neuroinflammation: that obesity induced hyperleptinemia causes chronic leakage at brain vessel sites enwrapped with LepR pericytes which promotes entry of pro-inflammatory factors.

Assessing myelination to study repair in the injured neonatal brain

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Abstract

Hypoxic-ischemic encephalopathy (HIE) is a major cause of significant mortality and long-term morbidity. Currently, therapeutic hypothermia (TH) is the only treatment for these neonates; however, it is often not efficient and does not promote repair. Thus, alternate treatments must be developed, and one such candidate treatment is sildenafil (Viagra®). **Objective**: To assess the myelination pattern in the context of HIE, TH and sildenafil therapies. **Methods**: Brain MRIs were performed around days 2, 10 and 30 of life in near-term/term healthy and neonates with HIE treated with TH+/-sildenafil. We measured the T2* values in different regions of interest (ROIs) using a T2* mapping sequence and compared them between experimental groups. **Results**: On day 2 of life, T2* values were significantly increased in all ROIs in the neonates with injury compared to those without injury. By days 10 and 30, T2* values remained significantly increased only in the HIE neonates with injury treated only with TH. The HIE neonates with brain injury treated with TH and sildenafil displayed T2* values not anymore significantly different from those without injury by days 10 (all ROIs, except PCC, OR and PWM) and 30 (all ROIs). Besides, by day 30, the HIE neonates with brain injury treated with TH and sildenafil displayed T2* values significantly decreased compared to neonates treated only with TH (all ROIs, except lentiform). **Conclusion**: Myelination was impaired after HIE and despite TH. Sildenafil promoted myelination in this context and may thus contribute to brain injury recovery.

Genetic Modulators of α-Synuclein Aggregate Propagation in Parkinson's Disease: a Genome-Wide Approach

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Abstract

One of the major hallmarks of Parkinson's Disease (PD) is the presence of Lewy bodies, which are comprised of protein aggregates including α-synuclein (αSyn). Aggregates of αSyn derived from Lewy bodies have been shown to spread PD pathology in the brain, contributing to disease progression. Lab- generated preformed fibrils (PFF) of αSyn have also been shown to propagate transcellularly between neurons, which is thought to augment their toxic effect in mouse models. While many pathways have been suggested to play a role in the internalization and propagation of αSyn aggregates, our understanding of the various mechanisms remains limited. Our lab previously conducted a CRISPR knockout (KO) screen to identify genes required for PFF uptake; whereas, in this work, we utilize an opposite and complementary approach to activate genes with CRISPR activation (CRISPRa). We
identified putative genetic modulators of αSyn fibril uptake by performing a FACS-based genome-wide CRISPRa screen on the accumulation of fluorescently labelled PFF in immortalized cells. This approach yielded distinct genetic targets which are suggested to play a role in inflammation, endo-lysosomal trafficking, and protein glycosylation. Select genes will be further validated using iPSC-derived neurons as a physiologically relevant model to provide further insight into the mechanisms of αSyn accumulation. This research will shed light on the function of key genes and proteins that are important in the neuronal uptake of αSyn fibrils. Identifying novel genetic targets will then allow for potential development of therapeutics, combating PD symptoms and/or halting its progression.

Photoreceptor reprogramming to prevent neurodegeneration

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Abstract

Retinitis Pigmentosa (RP) is a neurodegenerative disease where rod photoreceptor cells degenerate, which leads to the secondary loss of cone photoreceptors and irreversible blindness. Previous work has shown that knocking down Nrl, a rod-determining transcription factor, is sufficient to reprogram degenerating rods into cone-like cells, thereby slowing down rod degeneration and preventing vision loss by preserving endogenous cone photoreceptor cells (Montana et al. 2013, Yu et al. 2017). While these results are exciting and open a new therapeutic avenue for RP, gene knockdown approaches are less amenable to clinical applications due to potential side effects and could not produce a fully differentiated cone photoreceptor. Our lab has recently, identified the transcription factor Pou2f2 as a negative regulator of Nrl (Javed et al. 2020). Additionally, we showed that the transcription factors Ikzf1 and Ikzf4 can reprogram adult mouse fibroblasts and glial cells into neuronal cells (Boudreau- Pinsonneault et al. 2021), offering novel opportunities to develop reprogramming paradigm to convert rods into cone-like cells and potentially preventing neurodegeneration. Based on our work and the published literature, we hypothesize that overexpression of Nrl repressor, Pou2f2, in combination with Ikzf1 and/or Ikzf4 to rearrange chromatin in rods, will reduce the expression of Nrl and reprogram them into cone-like cells, preventing total blindness in mouse models of R

High salt intake increases RhoA-mDia1 signaling and triggers cytoskeleton reorganization in magnocellular vasopressin neurons

Banruo Li, Simona Kobrinsky, Suleima Jacob-Tomas, Masha Prager-Khotoursky

Abstract

High dietary salt (HDS) is a major factor contributing to the pathogenesis of salt-sensitive hypertension. Recent studies suggest that central sodium detection mechanisms contribute to increases in the blood pressure following HDS. Changes in plasma sodium are detected by specialized osmosensory neurons located in the hypothalamic supraoptic and paraventricular nuclei (SON and PVN). Under normal physiological conditions, increased plasma sodium activates SON and PVN magnocellular neurons releasing vasopressin (VP), antidiuretic hormone causing renal water retention and vasoconstriction, to achieve fluid homeostasis. Chronic exposure to HDS is associated with excessive osmotic activation of VP neurons, leading to a VP- mediated increase in blood pressure. Magnocellular VP neurons harbor unique cytoskeletal networks comprised of a subcortical actin layer, an array of actin comet-like structures, and an interweaved microtubule scaffold, regulating the sensitivity of neuronal activation. Chronic exposure to HDS increases the actin and microtubule density in VP neurons. mDia1 is the major direct RhoA effector, mediating actin and microtubule polymerization and stability. Our data suggest that RhoA and mDia1 are elevated under the plasma membrane of VP neurons following HDS. Besides, icv administration of mDia1 inhibitor SMIFH2 decreases actin density in VP neurons. We hypothesize that chronic exposure to HDS causes an activation of the RhoA-mDia1 pathway to increase the cytoskeletal density and osmosensitivity of VP neurons, leading to excessive VP secretion, volume expansion, elevated blood pressure, and hypertension.

Delayed Rectifier Regulation of Cerebellar Molecular Layer Interneuron Dendrosomatic Signalling and Filtering

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Abstract

Fragile X syndrome is the most common single gene cause of inherited intellectual disability and is associated with CNS hyperexcitability. Here, we demonstrate that the loss of the protein encoded by the Fmr1 gene, Fragile X messenger ribonucleoprotein (FMRP), in mice alters dendritic signalling and excitability in cerebellar stellate cells (SC). In Fmr1-/- knockout
(Fmr1-/-) mice, SC have larger excitatory postsynaptic potentials (EPSP) following parallel fiber stimulation and found diminished levels of A-type and TEA sensitive delayed rectifier potassium channel (Kdr) currents. Using an established one-compartment Hodgkin-Huxley type model we find that attenuation in A-type, Kdr and calcium dependent potassium currents was unable to reproduce the experimentally observed increase in EPSP amplitude. In an expanded two- compartment Hodgkin-Huxley type model we assess whether decreases of potassium channels in different compartments of SCs contributes to increased EPSP amplitude in Fmr1-/- SCs. From this 2-compartment model, we predict that the reduction of dendritic Kdr is the key determinant of EPSP amplitude. To assess the impact of diminished dendritic Kdr currents on dendritic physiology a model with a somatic compartment and a dendritic cable was developed. This model takes the basic morphological proximal/distal aspect of dendrites into account and enables investigation into dendritic filtering. Using an Ornstein–Uhlenbeck noise process and an linear chirp stimulus, both dendritic Kdr and A-type potassium currents were found to contribute to dendritic filtering in SCs. Taken together, the disruption of FMRP dendritic delayed rectifier modulation is a key determinant in the dendrosomatic signalling and filtering incerebellar SCs.

Identifying patient-derived variants that impact the function of human Excitatory amino acid transporter 1 (hEAAT1) in vivo.

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Abstract

Glial cells in the brain control the bioavailability of glutamate, a neurotransmitter critical for nearly every aspect of brain function. Excitatory amino acid transporters (EAATs) play an important role as glutamate transporters, but they also serve a dual function as chloride (Cl^-) channels. However, the importance of EAAT-mediated Cl^- flux for normal brain function is not well understood. This study examines how patient-derived variants of human EAAT1 (hEAAT1) affect these dual functions, using Drosophila as a model system. Mutations of hEAAT1 have been identified in patients with episodic ataxia type 6 (EA6). Furthermore, we have shown previously that EA6-related mutations in hEAAT1 primarily affect the Cl^- channel, upending the conventional view that this disease involved reduced glutamate uptake. For this study, we selected 16 patient-derived missense variants at conserved residues to determine which of these variants disrupt hEAAT1 function in vivo. Transgenic fly lines have been created for each of these mutations to allow for their selective expression in glial cells of dEaat1- null animals. Using a custom tracking system established in our lab, we are analyzing key features of larval crawling behavior. We are also characterizing how these mutations affect hEAAT1 expression and cellular morphology using immunohistochemistry and static confocal imaging. In combination with electrophysiological characterization of the variant proteins in Xenopus oocytes, these results will provide insight on the mechanisms of glutamate transport and ion conductance through EAAT proteins and could one day influence improved treatment options for patients with EA6 and related disorders.

Molecular and Neural Mechanisms Underlying Dysfunction of Postnatal Hippocampal Neurogenesis in Tuberous Sclerosis Complex

Max Kowalczyk, Wei-Hsiang Huang

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Abstract

The hippocampus is a brain structure critical for cognition, learning, and memory, and is unique because it is one of the sites of adult neurogenesis. The adult-born dentate cells (dGCs) are a group of neurons that continuously integrate into the existing hippocampal network and are integral to hippocampal brain functioning. mTOR hyperactivation in adult-born dGCs has been hypothesized to elicit morphological deficits that cause network disruption, resulting in cognitive impairments, learning/memory deficits, and epilepsy. Tuberous Sclerosis Complex (TSC) is a neurodevelopmental disorder caused by a mutation in the *TSC1* or *TSC2* genes, although *TSC2* will be the gene of focus as it is more commonly mutated and elicits more severe neurodevelopmental effects. Tsc2 functions as a negative regulator of mTOR signalling by inhibiting the mTORC1 and 2 complexes and human TSC patients present with many of the same phenotypes as those seen in patients with mTOR pathway mutations. However, whether Tsc2-mediated mTOR hyperactivity within adult-born dGCs is sufficient to elicit hippocampal dysfunction is not known. To determine this, the study generates Tsc2 loss in a subset of adult-born dGCs in mice to allows us to better understand how Tsc2 controls neuronal wiring, morphology, and behaviour. To further pinpoint how Tsc2 elicits these effects, I will delete two mTOR complex components, Rictor and Raptor proteins, to test if mTORC1 or mTORC2 activity is required for specific aspects of neural development. Together, this study will uncover the neurobiology of Tsc2 in adult-born dGCs along with cognitive features and the contribution of each mTOR complex.

Unveiling Movement Pa/erns as Cogni3ve Nodes: Exploration and Exploitation Embodied Decision-Making in Macaques

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Abstract

Exploring the intricate rela0onship between cogni0on, movement, and social dynamics is fundamental in understanding decision-making processes. In this study, we designed an embodied 2-armed bandit task to unravel movement patterns associated with internal states of explora0on and exploita0on. The experiment uncovered dis0nc0ve movement signatures corresponding to op0mal and subop0mal explora0on as well as op0mal and subop0mal exploita0on. This highlights the often-overlooked role of movement as a central node in cogni0ve processes. The iden0fica0on of dis0nct movement patterns corresponding to different cogni0ve states enriches our understanding of decision processes.
The experiment also explored social factors. The findings shed light on the interplay between movement and social dynamics. Intriguingly, both choice behaviour and movement patterns were profoundly influenced by hierarchical status within a social context. This underscores the profound impact of social factors on decision-making and iden0ty. These results provide intriguing clues about the mechanisms underpinning theory of mind. The impact of social context on choice behaviour and movement underscores the role of social factors in shaping cogni0ve processes and iden00es. This research serves as a steppingstone toward unravelling the intricate interplay between movement, cogni0on, and social dynamics, providing valuable insights into both individual and collec0ve decision-making processes.

The Estrus Phase Increases Neuronal Network Excitability And Favors *In Vitro* Ictogenesis

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Abstract

The menstrual cycle is associated with changes in estrogen and progesterone blood concentrations, which have profound physiological effects on brain excitability and thus on behavior. These hormonal changes also play a role in neurological disorders such as epilepsy. Thus, women presenting with focal epilepsy can report increased seizure occurrence/severity during their menstrual cycle; such condition is termed catamenial epilepsy. Firm evidence on the fundamental mechanisms leading to catamenial seizures (and thus the identification of effective treatments) remain elusive. Therefore, we used here an in vitro model of epileptiform synchronization, which is induced by the K+ channel blocker, 4-aminopyridine (4AP), to study with field potential recordings the changes in spontaneous seizure-like events (SLEs) occurring during the estrous cycle in the entorhinal cortex of parvalbumin (PV)-ChR2 female mice. Although shorter in duration than in women (4-5 days vs 28 days), the rodent estrous cycle is characterized by four phases identified as proestrus, estrus, metestrus and diestrus. We found that the duration of SLEs was significantly longer during estrus (96.75s ± 9.45s; n= 69 SLEs) than during diestrus (47.10s ± 3.03s; n= 124 SLEs) (p<0.001). Rates of ictal discharges were however not different between these phases. 8Hz optogenetic stimulation of PV-positive interneurons triggered field responses had higher power during estrus (-38dB) (n= 255 runs of optogenetic stimulation) compared to diestrus (-42dB) (n= 255 runs of optogenetic stimulation) (p<0.001). Together, our findings indicate that SLEs are modulated during the estrous cycle. They also suggest that the estrus phase, which is presumably associated with increased interneuron excitability, favors seizure generation and maintenance.

Following topographic map formation in the developing Xenopus retinotectal system

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Abstract

The retinotectal projection in the Xenopus visual tectum is topographically organized. Neurons in the retinotectal system undergo extensive activity-dependent plasticity during early
development, which is believed to refine the retinotopic map to form a more precise
representation of the visual world. We have previously observed marked changes in the three- dimensional layout of the retinotopic map within the tectal volume over a span of several days in development. To examine this change in the context of single tectal neurons, we performed
calcium imaging in the optic tectum of GCaMP6-expressing *Xenopus laevis* tadpoles where tectal cells were sparsely labelled with Alexa594-dextran dye. Animals were imaged at stage 45 and again at stage 48, a period during which extensive tectal growth and robust activity-dependent plasticity occurs. We recorded the morphology of the dextran-labelled cell and performed visual receptive field mapping to extract the functional retinotopic map in the same tectal volume. By observing the position of the dextran-labelled cell in relation to the topographic map, as well as the response of the labelled cell to positioned visual stimuli, we expect to gain insight on whether changes in retinotopic map layout are a result of cell addition and migration, or shift in receptive field representations at the level of individual cells.

Characterization of myelin deficits in rats with Alzheimer's-like tauopathy

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Abstract

Alzheimer's disease (AD) is the most common form of dementia conceptualized as progressive pathological changes in grey matter: extracellular plaques composed of aggregated amyloid-beta (Aβ) and intracellular neurofibrillary tangles (NFTs) composed of phosphorylated tau. However, in addition to the grey matter in AD brains, there are significant abnormalities in white matter which are accompanied by glial pathological alterations. We postulate that the AD tauopathy is the main driver of the white matter pathology. However, there is no direct evidence on the relationship between tau pathology and demyelination. Therefore, our overarching goal is to evaluate whether and how a progressive tauopathy leads to myelin defects and relate to cognitive capabilities. To explore the effects of a progressive tauopathy on myelin health, we will apply our newly generated McGill-R955-hTau transgenic rats, which expresses the longest form of human tau with the P301S mutation. We will first characterize the cognitive function of transgenic rats at 12 months and 20 months in comparison to wild-type rats. Then we will examine region-specific alterations in myelination patterns and oligodendrocyte marker expression profiles as well as the main features of human tauopathies and neurodegeneration.

Transgenic rats display age-dependent increases in human-specific tau, Phospho-Tau and conformation-Tau. The transgenic rats present cognitive impairments, brain atrophy, white matter loss and degraded myelin basic protein at 20 months of age. At 12 months of age, transgenic rats display cognitive impairments only in the social interaction test. Overall, McGill- R955-hTau transgenic rats display tau pathology-driven defects in the white matter.

Investigating a role for netrin-1 in long-lasting synaptic potentiation

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Abstract

Long-term potentiation (LTP) is an activity dependent form of plasticity that strengthens glutamatergic synapses and serves as a cellular model of learning and memory formation. We have demonstrated that netrin-1, a secreted chemotropic cue that regulates cell migration, axon guidance and synaptogenesis during neural development, is required and sufficient for the initial phases of LTP at Schaffer collateral synapses through rapid recruitment of GluA1 AMPA receptors in adult mouse. Previous findings indicate that netrin-1 can rapidly initiate protein synthesis through local translation in neurons, suggesting that netrin-1 may regulate long-term changes in synapse strength through translation of synaptic proteins. Here, we provide evidence that transient bath application of netrin-1 results in a persistent potentiation of synaptic responses for >4 hours in adult hippocampal brain slices, indicating that netrin-1 induced synaptic strengthening is long-lasting. Using genetic manipulations, electrophysiology and classical molecular biology technics with different LTP induction paradigms we investigate the subtility of netrin-1 role in LTP. We aim in particular to determine if the late phase of netrin-1 induced synaptic potentiation requires protein synthesis, and if neuronal expression of netrin-1 is required for the late protein synthesis dependent phase of LTP.

Hyperpolarization-Activated Currents Drive Sequential Neuronal Activation in Sleep

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Abstract

Sequential neuronal patterns are believed to support information processing in the cortex, yet their origin is still a matter of debate. We report that neuronal activity in the mouse head-direction cortex (HDC, i.e. the post-subiculum) was sequentially activated along the dorso-ventral axis during sleep at the transition from hyperpolarized "DOWN" to activated "UP" states, while representing a stable direction. Computational models suggested that these dynamics could be attributed to a spatial gradient of hyperpolarization-activated currents (Ih), which we confirmed in *ex vivo* slice experiments and corroborated in other cortical structures. These findings open up the possibility that varying amounts of Ih across cortical neurons could result in sequential neuronal patterns, and that travelling activity upstream to the entorhinal-hippocampal formation organises large-scale neuronal activity supporting learning and memory during sleep.

Objective criteria for characterizing participants in the PREVENT-AD cohort into cognitively unimpaired vs. Mild Cognitive Impairment (MCI) progressors

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Abstract

Mild Cognitive Impairment (MCI) is the transitional state between healthy aging and Alzheimer's Disease (AD). Individuals with MCI are at an increased risk of developing AD and thus provide a unique opportunity to study and potentially prevent dementia. Diagnosis is performed on a single-case basis by clinicians, making the classification subject to interrater variability and diagnosticians' bias, and thereby leading to heterogeneity within MCI groups. This warrants the need for objective criteria to identify individuals progressing to MCI. Participants in this study were part of the PREVENT-AD cohort, comprising a group of clinically unimpaired older adults with family history of AD. We used combinations of several cognitive tests, including RBANS neuropsychological battery, RAVLT, Trail Making Test, and Stroop Test, to identify objective evidence of cognitive decline which was defined as performance of 1.5SD below the standardized mean in at least two variables within a cognitive domain. Subjective cognitive complaint was determined on the basis of interviews with the participants or an informant.

Using objective, cross-sectional criteria, we classified less participants in the cohort as MCI progressors as compared to subjective clinician-based criteria. Overall, there was little overlap between the groups of MCI progressors identified by objective versus subjective criteria as measured by Cohen's kappa. Defining objective criteria for a diagnosis of MCI will enhance uniformity of outcomes and reduce bias. More work is needed to specify adequate cross-sectional and longitudinal measures.

Quantifying Protein Synthesis in Oligodendrocytes in Cell Culture

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Abstract

Oligodendrocytes are central nervous system glial cells that produce myelin, which is a vital insulating layer that facilitates axonal action potential propagation. Oligodendrocyte morphology and bioenergetics are dynamically modulated by extracellular signals like the secreted protein *netrin-1* and its receptors. Myelin formation and myelin plasticity are hypothesized to be influenced by the regulation of local protein translation in oligodendrocytes. The objective of this study is to develop a technique to study the mechanisms that regulate translation in oligodendrocytes and to determine the influence of netrin-1. Oligodendrocyte precursor cells were isolated from the neocortices of newborn rat pups and then differentiated and maintained in cell culture. Protein translation was assayed using the level of incorporation of puromycin into newly synthesized proteins. Puromycin is a tyrosyl-tRNA analog that is incorporated into actively transcribing proteins and can then be detected using a puromycin-specific antibody and fluorescence microscopy. Cells were briefly starved, followed by treatment with netrin-1 or buffer, and newly synthesized proteins then labelled with puromycin. Signal intensity associated with myelin basic protein (MBP) positive regions of interest was then quantified. The specificity of the puromycin antibody was validated against non-puromycin treated controls, and its incorporation was inhibited with cycloheximide, an inhibitor of translation elongation. Insulin increases protein synthesis and is being investigated as a positive control. Our ongoing studies aim to quantify the impact of netrin-1 on local protein synthesis in oligodendrocytes, in particular targeting the signalling pathways involved and the translation of key myelin proteins.

Maternal gastrointestinal nematode infection positively influences aspects of neurodevelopment in the uninfected mouse pup

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Abstract

Infection of pregnant and lactating mice with the gastrointestinal (GI) nematode, *Heligmosomoides bakeri*, has been shown to up-regulate expression of genes critical for long- term potentiation (LTP) in the brain of 1 week old uninfected pups. Furthermore, 3-4 week old offspring of *H. bakeri* infected mothers were able to remember the location of an escape hole in the Barnes Maze Test after 7-days, while offspring of uninfected mothers could not, indicating enhanced long-term memory retention in response to maternal infection. The aim of the present study was to test the consequences of this maternal nematode infection on hippocampal LTP in the uninfected juvenile offspring. Outbred CD-1 mice were infected repeatedly or sham infected during pregnancy and lactation. When offspring were 3 weeks old, we explored high-frequency induced LTP in the hippocampal CA1 area using extracellular field recordings. LTP was observed in a higher proportion of pups of infected mothers (71%) compared to those of uninfected mothers (14%), indicating earlier onset of LTP in response to maternal infection. Additionally, the slope of the fEPSP recorded 60 minutes after high- frequency stimulation was greater in response to maternal infection. Finally, we explored the neuroimmune system in the hippocampus of offspring and found a greater number of astrocyte and microglia cells in response to maternal *H. bakeri* infection. Taken together, these findings suggest that maternal GI nematode infection may increase fitness of the next generation by positively influencing neurodevelopment via regulation of the neuroimmune system.

Spatial mapping of mouse midbrain dopamine neurons using multiplexed error-robust fluorescent in- situ hybridization (MERFISH)

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Abstract

The midbrain dopamine (DA) system contains a relatively small number of neurons yet acts broadly as a neuromodulator in the striatum and cortex. Despite their small number, DA neurons contain
considerable heterogeneity in their transcriptomic identity and projection targets. However, the
distribution of these subtypes in the midbrain has not been accurately mapped. We utilized Multiplexed Error-Robust Fluorescent In-Situ Hybridization (MERFISH) to spatially map molecularly-defined DA
neuron subtypes in the mouse midbrain. A gene panel was created of 500 genes including known DA subtype markers and genes associated with
neurotransmitter/neuropeptide synthesis, transport, and receptors. We identified 10 major DA neuron clusters and mapped their location within the substantia nigra pars compacta, ventral tegmental area, caudal linear nucleus, and dorsal raphe regions. Three
clusters appeared which showed expression of glutamatergic and/or GABAergic genes including a Slc17a6/Calb2 population (Glutamatergic), Slc17a6/Gad2 (Glutamatergic/GABAergic) and
Gad2/Gad1/Slc32a1 (GABAergic). We then sought to integrate our data with single-nuclei RNA-seq data generated by DA enriched preparations. Using the RNA-seq dataset cluster identities as a reference, we were able to query and annotate the spatial transcriptomic dataset. Our work highlights the power of MERFISH to add spatial information to existing single-nuclei RNA-seq datasets and further characterize the heterogeneity of complex neuronal populations.

Neuropathogenic mechanisms of human mutations in the gene encoding the receptor tyrosine kinase EPHB2

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Abstract

The corpus callosum (CC) is the most prominent connection in the brain, linking the left and right cerebral hemispheres, with its size correlated with the degree of brain evolution. Agenesis of the corpus callosum (ACC) is a common human brain malformation resulting in higher-order cognitive deficits, reflecting the importance of interhemispheric communication in highly evolved brains. Yet, the aetiology of ACC is unclear. In the nervous system, the EPH family receptor tyrosine kinases propagate contact-mediated cell-cell signalling between neurons, promoting cell repulsion/adhesion, which underlies neural circuit wiring. One of the genes previously shown as required for normal development of the mouse CC is *EphB2*. However, the possibility that EPHB2 is required for callosal development in humans has not been assessed. Moreover, the precise function of EPHB2 in CC formation remains elusive. We identified 9 *EPHB2* gene mutations in 8 human patients showing mild to severe ACC, intellectual disability, and various behavioural abnormalities. Using biochemical and cellular approaches, we demonstrate that the patient mutations perturb multiple EPHB2 receptor functions: ephrin binding, clustering, and endocytosis, cumulatively modifying EPHB2 signalling. Notably, altered EPHB2 signalling level correlates with the severity of ACC in patients. Furthermore, modulation of EPHB2 expression in callosal neurons via *in-utero* electroporation in mice perturbs callosal development: EphB2 loss of function blocks initial outgrowth and targeting of axons to the contralateral hemisphere, while overexpression of EphB2 inhibits cortical migration of callosal neuron cell bodies. Together, our experiments argue that *EPHB2* is required for CC development in humans.

The AMPA receptor-GSG1L signaling complex is uniquely identified by its spatiotemporal expression, native interactome and a privileged allosteric site

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Abstract

Transmembrane AMPA receptor regulatory proteins (TARPs) and germ cell-specific gene 1-like protein (GSG1L) are claudin-type AMPA receptor (AMPAR) auxiliary subunits that profoundly regulate glutamatergic synapse strength and plasticity. While AMPAR-TARP complexes have been extensively studied, less is known about GSG1L-containing AMPARs. Here, we show that GSG1L's spatiotemporal expression, native interactome and allosteric sites are distinct. GSG1L generally expresses late during brain development in a region-specific manner, constituting about 5% of all AMPAR complexes in adulthood. While GSG1L can co-assemble with TARPs or cornichons (CNIHs), it also assembles as the sole auxiliary subunit. Unexpectedly, GSG1L acts through two discrete evolutionarily-conserved sites on the agonist-binding domain with a weak allosteric interaction at the TARP/KGK site to slow desensitization, and a stronger interaction at a novel site that slows recovery from desensitization. Together, these distinctions help explain GSG1L's evolutionary past and how it fulfills a unique signaling role within glutamatergic synapses.

Spatial transcriptomics of the human prefrontal cortex in major depressive disorder

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Abstract

Major depressive disorder (MDD) is a debilitating, heterogeneous disease characterized by depressed mood, diminished interests and impaired cognitive function. Roughly 380 million people are currently suffering with MDD, worldwide. Women are 2–3 times more likely to develop MDD than men, while exhibiting greater functional impairment and symptom severity. Although some genetic associations have been detected between MDD and underlying risk factors, it remains a challenge to delineate causal disease mechanisms from these findings. Using snRNAseq, our lab recently reported that the greatest dysregulation attributable to MDD occurred in deep-layer excitatory neurons and immature oligodendrocyte precursor cells (OPCs): contributing roughly half of all changes in observed gene expression. Though, questions still remain to understand the complex interplay of different cell-types and how their localization may contribute to MDD in both males and females. Using 10X Genomics's Visium spatial gene expression assay, we aim to assess spatial patterns of differential gene expression between individuals with a history of MDD and healthy controls in the BA9 region of the prefrontal cortex (n=10). We have integrated canonical immunofluorescent markers (NeuN, GFAP) into our Visium assays to provide a further cell-type annotation. This study aims to be the first, to our knowledge, to evaluate spatial patterns of differential gene expression in the context of MDD and the first to study the co-localization of different cell types in the brains of depressed individuals who died by suicide.

Comparing motor and visual cortex layer-2/3 microcircuits using 2-photon optogenetics

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Abstract

Microcircuit structure determines information processing in different neocortical areas. However, state-of-the-art methods like multiple patch clamp are impracticable for large-scale microcircuit mapping. We therefore created optomapping, a high-throughput 2-photon optogenetics technique that tests hundreds of connections across all cortical layers. Here, we compare V1—a key neocortical input area—to primary motor cortex (M1)—a key neocortical output area. We injected AAV9-EF1a-DIO-STChroME-P2A-mRuby into V1 and M1 of postnatal day (P)1-2 Emx1[Cre/+] mice to activate PCs. In P20-P27 acute slices, we used two- photon spiral scans at 1040nm to activate candidate presynaptic PCs in a cortical column, while looking for responses in patched PCs. We found higher and stronger L5→L2/3 PC connectivity in V1 than M1 (7.9%±2% vs. 0.54%±0.4%, $p < 0.001$; 0.34±0.007mV vs. 0.011±0.001mV, $p < 0.0005$). However, V1 had no laminar differences in synaptic strength ($p = 0.23$). L2/3 of M1 had more intralaminar than interlaminar connections (7.5%±1% vs. 0.54%±0.4%, $p < 0.001$), whereas L2/3 of V1 had higher interlaminar connectivity from L4 than intralaminar from L2/3 (24%±5% vs. 7%±1%, $p < 0.001$) consistent with the canonical V1 circuit. Similarly, V1 exhibited higher connectivity farther from the patched cell (exponential decay constant λ: 200±60μm vs. 81±30μm, $p = 0.11$), likely illustrative of the V1 L4 to L2/3 pathway. Additionally, synaptic strengths in L2/3 of both M1 and V1 were log-normally distributed. Although we find some distinct differences, our findings primarily highlight how L2/3 microcircuits of M1 and V1 are similar despite functional differences.

Genetic restriction of mGluR5 to intracellular membranes delays recovery from

Persistent inflammatory pain in mice.

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Abstract

Previous pharmacological studies have implicated intracellular metabotropic glutamate receptor 5 (mGluR5) in persistent pain. Cell permeable but not impermeable antagonists effectively reduce neuropathic and inflammatory injury-induced pain hypersensitivity. To overcome limitations of pharmacological manipulation, we used mice in which mGluR5 was genetically targeted to intracellular membranes (mGluR5^{IM} mice) to determine changes in several measures of pain behaviour. mGluR5^{IM} and mGluR5$^{wild-type (WT)}$ mice of both sexes were injected with formalin and the time spent licking, biting or flinching the injected paw was recorded. Separate groups of mice of both genotypes and sexes were injected with Complete Freund's Adjuvant (CFA) and were then measured for mechanical allodynia, thermal hyperalgesia and motor performance for 4 months post-injection. mGluR5^{IM} mice spent significantly longer exhibiting pain behaviour during the late phase of the formalin response compared to mGluR5^{WT} mice. In the mGluR5^{IM} group only, females demonstrated significantly more late phase pain behaviour than males. Following CFA injections, mGluR5^{IM} mice had significantly lower mechanical paw withdrawal thresholds (PWTs) in the injected paw at 2 weeks (males only) and 1 - 4 months (males and females) post-injection compared to mGluR5^{WT} mice. Additionally, mGluR5^{IM} mice had significantly lower PWTs in the non- injured paw from 1 - 3-months post-injection, compared to mGluR5^{WT} mice. Conversely, there were no significant differences in thermal hypersensitivity between genotypes. No signs of motor deficits were found in any group following CFA injection. These findings support the importance of the intracellular localisation of mGluR5 in persistent pain modulation. This work also highlights a yet unreported sex difference in mGluR5 nociceptive signalling and implicates intracellular mGluR5 as a potential contributor to mirror image pain.

Testing the effect of dichoptic surround masking in amblyopic vision

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Abstract

Amblyopia, a developmental vision disorder, is characterized by persistent spatial deficits in the amblyopic eye due to strong interocular suppression from the good fellow eye. This study aimed to determine if presenting a dichoptic surround mask to the amblyopic eye can selectively eliminate the abnormal suppression from the fellow eye to the amblyopic eye, improving contrast sensitivity, or if it only suppresses the stimulus in the fellow eye. By using a dichoptic center- surround masking paradigm, both amblyopes and controls performed a psychophysical task of detecting a central target in a two-interval forced-choice procedure. Stimuli were horizontally oriented 0.5 cycles per degree (cpd) gratings, with the central test stimulus measuring 2 degrees and the surround mask measuring 6.5 degrees in diameter. The experimental setup consisted of a pair of interleaved test conditions, where the target was presented either to the amblyopic eye or to the fellow eye, along with three distinct surround mask conditions i.e., absence of a mask, a fellow eye mask, and an amblyopic eye mask. The results indicated that contrast thresholds in the fellow eye were more elevated when the mask was also in the fellow eye, indicating monocular suppression. In contrast, amblyopic eye thresholds were raised in both fellow and amblyopic eye masking conditions, but to a greater extent in the fellow eye masking condition, indicating dichoptic suppression. Overall, the findings suggest that amblyopes exhibit greater dichoptic suppression in the amblyopic eye from fellow eye masks compared to suppression in the fellow eye from amblyopic eye masks. Furthermore, individuals with amblyopia are vulnerable to suppression, regardless of whether the suppression arises from the amblyopic eye or from the fellow eye.

Factors contributing to spasticity development in people with acute stroke

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Abstract

Background & Aims: Stroke is a leading cause of disability in Canadian adults. Up to 60% of individuals with stroke develop spasticity, which is a velocity- and muscle length–dependent
increase in resistance to externally imposed muscle stretch. Early detection of spasticity is vital to better tailor treatments and administer them earlier to lessen the impact of spasticity on recovery. Our goal is to determine the relationship between stroke lesion location, descending
motor tract integrity, and changes in spinal motoneuronal excitability using a novel measure, the Tonic Stretch Reflex Threshold (TSRT), in individuals with acute stroke. *Methods*: Individuals are recruited into the study within one week of their stroke and assessed weekly for 12wks to evaluate sensorimotor deficits and spasticity in elbow flexors and/or ankle plantarflexors (TSRT; Modified Ashworth Scale; etc.). Brain and spinal cord scans are done 6wks after stroke using anatomical and diffusion Magnetic Resonance Imaging (MRI). Manual lesion delineation of MRI scans is performed with the FSL program, and diffusion data analysis of the reticulospinal and corticospinal tracts is done using the Spinal Cord Toolbox. To date, preliminary data has been acquired from 10 individuals with acute stroke in an ongoing study. *Results & Significance*: Results will more accurately predict who will develop spasticity after a stroke, allowing for earlier detection and more individualized treatment. By improving our accuracy in predicting which individuals will develop spasticity, treatments may be tailored to minimize the impact of spasticity on recovery and increase functional independence in people living with stroke.

The mGlu2 positive allosteric modulator AZD8529 alleviates L-DOPA-induced dyskinesia and psychosis-like behaviours in the parkinsonian marmoset

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Abstract

AZD8529 is a selective metabotropic glutamate 2 (mGlu2) receptor positive allosteric modulator (PAM) that has undergone clinical trials for schizophrenia and smoking cessation. Previously, we demonstrated that the selective mGlu2 PAMs LY-487,379 and CBiPES alleviated L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia and psychosis-like behaviours (PLBs) in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset model of Parkinson's disease (PD). However, neither drug has clinically relevant pharmacological properties, contrary to AZD8529, which could be repurposed if efficacious. To assess the effect of AZD8529 on L-DOPA-induced dyskinesia and PLBs in the MPTP-lesioned marmoset, parkinsonism was induced by MPTP injections followed by oral administration of L- DOPA/benserazide to elicit dyskinesia and PLBs. On experimental days, marmosets were injected with L-DOPA (15/3.75 mg/kg s.c.) along with vehicle or AZD8529 (0.1, 0.3, 1, and 10 mg/kg s.c.). After treatment, marmosets were recorded for 6h and this footage was analysed for dyskinesia, PLBs, and parkinsonism. The results showed a reduction in global dyskinesia severity (up to 70%, P<0.001), and on-time with disabling dyskinesia (up to 97%, P<0.001) when compared to L-DOPA/vehicle. Similarly, there was a reduction in global PLB severity (up to 64%, P<0.001), and on-time with disabling PLBs (up to 94%, P<0.001) when compared to L- DOPA/vehicle. Additionally, AZD8529 increased the duration of the anti-parkinsonian action of L-DOPA at doses of 0.3 mg/kg and above (up to 29%, P<0.05). Our results demonstrate the potential of AZD8529 and mGlu2 positive allosteric modulation for alleviating L-DOPA- induced dyskinesia and PLBs and amplifying L-DOPA anti-parkinsonian effects.

Expanding the spectrum of white matter abnormalities in Wolfram syndrome: a retrospective review of six cases

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Abstract

Wolfram syndrome (WFS) is a rare genetic disorder clinically characterized by optic atrophy (OA), diabetes mellitus, sensorineural deafness, and diabetes insipidus. It typically manifests before age 20 and progresses into adulthood, often with important neuropsychiatric complications. Pathogenic variants in *WFS1* (monoallelic/biallelic) or *CISD2* (biallelic) genes cause WFS. The neuroradiological features of WFS include cerebellar and/or brainstem atrophy with visual pathway and white matter abnormalities (WMA), ranging from small ovoid lesions to diffuse, symmetrical changes. Following the identification of multifocal, progressive WMA in a molecularly confirmed WFS individual, which prompted the consideration of multiple sclerosis (MS), we sought to verify whether MS-like lesions constitute a novel WFS-associated MRI pattern. Therefore, we retrospectively analyzed the clinical, genetic, and radiological data from six unrelated, genetically-confirmed WFS subjects. Three of six subjects (50%) showed multifocal WMA that disseminated in space and time, suggesting an inflammatory process. The observed locations of MS-like lesions were: callosal/pericallosal (2/3 subjects), juxtacortical/U-fiber (2/3), subcortical (all), periventricular (all), cerebellar white matter/peduncles (1/3), and in the C-spine (2/3). Two subjects had at least one gadolinium-enhancing lesion. All six subjects had at least one of the following known WFS MRI features: symmetrical, diffuse involvement of the peritrigonal areas/optic tracts, cerebellar atrophy, or pons signal changes. In summary, our report expands the WFS spectrum of white matter involvement to include progressive, seemingly inflammatory lesions. Although we cannot exclude the possibility of a WFS-MS dual diagnosis, the roles of *WFS1* and *CISD2* in myelination suggest a selective white matter vulnerability in WFS.

MRI-based classifier to identify close-to-onset cases in C9orf72 genetic frontotemporal dementia

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Abstract

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative condition with an imprecise age-of-onset prediction. Despite the identification of genetic mutations associated with FTD, accurately predicting the onset of symptoms remains a challenge. The existence of brain atrophy before clinical symptoms in genetically-inherited FTD suggests the promising use of neuroimaging biomarkers for identifying individuals at high risk of the disease. In this study, we developed an MRI- based classifier to differentiate symptomatic FTD cases with the C9orf72 mutation from healthy
individuals. We applied this classifier to asymptomatic mutation carriers to detect those who are at a potential risk of developing the disorder. The research utilized the Genetic Frontotemporal Dementia Initiative (GENFI) cohort, comprising symptomatic carriers, presymptomatic carriers, and controls (aged > 40). The classifier achieved 87.6% accuracy in distinguishing symptomatic FTD cases from controls. Testing on presymptomatic carriers revealed 25.6% exhibiting brain scans akin to symptomatic subjects. Neuropsychological assessments demonstrated significantly poorer performance in presymptomatic cases identified by the classifier in Boston Naming Test, Trail Making Test, Verbal Fluency Task, and Digit Symbol Substitution Test. Our MRI-based classifier, leveraging
neuroimaging biomarkers, shows potential in identifying high-risk asymptomatic individuals for FTD. Early detection could revolutionize disease management. However, longitudinal follow-up is vital for validation. This study underscores neuroimaging's role in predicting FTD onset and enhancing clinical strategies for this intricate neurodegenerative disorder.

Characterization of a novel medulloblastoma tumor suppressor

Sukumaran S, Schlienger S, Wu CL, Charron F

Abstract

Medulloblastoma is an aggressive pediatric brain tumor. The Sonic hedgehog (Shh) pathway plays an important role in medulloblastoma tumorigenesis through its ability to induce granule cell pre- cursor (GCP) proliferation. Ptch1 is a Shh receptor and *Ptch1* mutant mice are a clinically-relevant model of medulloblastoma. We identified *Psmd2* (a proteasome subunit) as a novel gene that is mutated in medulloblastoma. We showed that inactivation of *Psmd2* in the *Ptch1* mouse model dramatically increases medulloblastoma incidence. The Shh pathway requires the primary cilium and the proteasome for its signal transduction. Thus, I hypothesize that Psmd2 acts as a tumor suppressor by controlling proteasomal activity linked to the primary cilium and thus negatively regulating the Shh pathway.

First, I will investigate the role of Psmd2 in ciliogenesis. I will assess whether *Psmd2* inactivation affects ciliogenesis in GCPs by quantification of cilia length and number of ciliated cells.

Second, I will determine the effect of *Psmd2* inactivation on the proteasome and Shh pathway components. I will examine the downstream effects of *Psmd2* inactivation by measuring the deg- radation of Gli proteins, RNA levels of Gli-target genes and proliferation rate of GCPs.

Third, I will investigate the consequences of proteasome inactivation on tumor formation. I will determine the effect of loss of proteasomal components on medulloblastoma aggressiveness.

This project will provide insights into the role of specific proteasomal components in medulloblas- toma and thus might help develop novel and more targeted therapies.

Role of LRRK2-G2019S mutation on neuronal immune signaling

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Abstract

We are interested in the interaction between genetic risk and inflammatory environmental triggers in the development and progression of Parkinson Disease (PD). LRRK2 gene variation and mutations confer the highest genetic risk for familial PD, and LRRK2 mutations cause typical, late-onset PD, which is clinically indistinguishable from the idiopathic disease. LRRK2 has been widely associated with inflammation and immune cell function, while it is still unclear the effects of LRRK2 mutation on inflammatory response outside of immune cells, particularly in neurons. Neurons require a robust intracellular trafficking machinery and quality control mechanisms to support their long-term viability and functionally. LRRK2 has been demonstrated to have a regulatory role in the endo-lysosomal system, which is responsible for intracellular protein trafficking, secretion, and degradation. This work explores the effects of the most common LRRK2 mutation (G2019S) in the regulation of immune signaling onto neurons. We describe experiments in LRRK2-G2019S knock-in (GKI) mouse neuronal primary cultures treated with a proinflammatory trigger, interferon-gamma (IFNy). Our initial results show an increase in LRRK2 protein levels upon IFNy stimulation in both WT and GKI neurons. While only GKI neurons show increased lysosomal density upon immune stimulation, which might be related to mitochondrial DNA release and inflammasome activation. The data establish a framework to interrogate the impact of LRRK2-G2019S mutation in balancing an immune response with neuronal function and survival through the complex mitochondria/lysosome axis.

IMPACT's role as a translational regulator in memory, social behavior, and neural plasticity

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Abstract

Translational control is an important regulatory mechanism in neural plasticity, particularly during neurodevelopment. Dysregulation of this critical step is implicated in several pathologies, including Autism Spectrum Disorder (ASD). The IMPrinted and AnCienT gene (IMPACT) is a protein coding gene for the translational regulator protein IMPACT, via a negative regulation of General Control Nonderepressible 2 (GCN2) kinase activity. GCN2 phosphorylates the alpha subunit of Eukaryotic Initiation Factor 2 (eIF2α) as a cellular stress response. GCN2's phosphorylation of eIF2α serves as an inhibitor of eIF2, which causes a repression of general translation of mRNAs and decreased global protein synthesis. This translational regulatory mechanism also plays a critical role in the nervous system. However, the impact of chronic phosphorylation of eIF2α throughout neurodevelopment has not been explored. In this *in vivo* study, we investigated the neurological effects due to loss of IMPACT, using a transgenic mouse model which removed the expression of IMPACT (IMP$^{-/-}$). This in turn led to increased GCN2 expression and increased phosphorylation of eIF2α. We found that loss of the IMPACT protein causes deficits in social novelty preference, elicits repetitive behavior, and impairs long term memory. Many of these phenotypes are present in patients with neurodevelopmental disorders, particularly ASD. We also identified specific mRNAs translationally regulated by IMPACT in the hippocampus and in the prefrontal cortex. Taken together, our research supports the hypothesis that IMPACT is an important translational regulator in neurodevelopment, and mutations that impair its function may have implications in neurodevelopmental disorders such as ASD

Interrogating single-cell connectivity in sensorimotor circuitry using high-throughput mapping techniques

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Abstract

Understanding how humans and non-human animals communicate acoustically with each other continues to be a central question in neuroscience. Songbirds serve as powerful animal models for this endeavor because their vocalizations (birdsongs) are regulated by activity within a discrete and specialized sensorimotor circuitry ("song system") analogous to brain areas implicated in speech production and acquisition in humans. The nucleus HVC (acronym used as a proper name) in the song system of songbirds is functionally analogous to the premotor cortex in mammals and is critical for the acquisition and performance of birdsong. Here, we take advantage of a multiplexed, high-throughput, single- neuron mapping technique called MAPseq (Multiplexed Analysis of Projections by Sequencing), to interrogate single-neuron projections in HVC and to construct a fine-grained map of connectivity in the song system. This technique can reveal the projection patterns of thousands of individual neurons in single animals by cellular barcoding and thus define connectomic cell types. To adapt MAPseq for use in songbirds, we tested a range of viral pseudotypes and injection regimes to efficiently infect neurons in sensorimotor nuclei of the song system. We found that different pseudotypes differentially infect neurons in different areas of the songbird brain and successfully identified an injection regime for HVC. We are tracing HVC projections using MAPseq, having confirmed established patterns of connectivity using bulk projection assays and are currently sequencing RNA barcodes in target areas to reveal fine microcircuitry in the song system.

Investigating the mechanisms underlying crossed and uncrossed disparity sensitivity in Stereoscopic Vision

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Abstract

Human stereo vision has always been a topic of great concern in the field of neuroscience. With the assistance of psychophysics and developed techniques, it becomes much easier to discover the fundamental mechanisms behind them. It is still unclear whether the ability to judge depth polarity relies on a single mechanism or whether there are separate mechanisms (channels) encoding crossed ("popping in") and uncrossed ("popping out") disparities. To tackle this question, I would conduct psychophysical experiments with a "2-by-2 forced-choice paradigm". This paradigm is developed based on the perfect discrimination model from Watson and Robson (Watson & Robson, 1981). It allows us to tell how different depth polarities are processed from a subject's performance in detection (noticing an in-depth stimulus) and discrimination (recognizing the polarity of the stimulus). This paradigm helps us to determine when the subject hits a certain level of detection or discrimination performance in a trial. We expect that if a discrimination can be perfectly accomplished at detection threshold, we can then believe that there are separate channels that are involved in both disparities. The goal is to better understand how crossed and uncrossed disparities are processed in individuals by investigating individual cases. This study would contribute to the clinical treatment of patients with stereo blindness. It is also expected to expand to the field of computer simulation vision in the foreseeable future.

AMPA receptor gating unveils a hidden Ca^{2+} pocket critical to ion transport

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Abstract

a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA) subtype ionotropic glutamate receptors (iGluRs) are critical to synaptic transmission, plasticity, and learning. Canonically, divalent cation permeability of AMPARs is known to be determined by RNA-editing at the Q/R site in the pore region. However, understanding of the mechanism and structural basis remains unresolved. Here, we investigated the open-pore architecture of the Ca^{2+}-permeable AMPAR (CP-AMPAR) in complex with auxiliary protein TARP □2 under various ionic conditions at high resolution (2.3-2.6Å). Our results show that, different from dehydrated cations through potassium channels, numerous putative ion and water densities are observed in the pore of AMPARs. Moreover, the conserved SYTANLAAF motif at the gate in iGluRs converts to a Ca^{2+} binding site (site-G) in the open state. Functionally, the novel site-G is shown to be crucial for external Ca^{2+} mediated channel block and Ca^{2+} permeability. The seizure related N619K mutation adjacent to site-G promotes channel opening, but attenuates Ca^{2+} binding, and therefore reduces external Ca^{2+} block and Ca^{2+} permeability. Identification of site-G extends the prevailing view on the mechanism of Ca^{2+} permeability in AMPARs built upon the Q/R-site in the selectivity filter. Importantly, its conservation amongst iGluRs suggests a broader role in regulating monovalent versus divalent ion permeability.

Characterizing the behavioral signatures of the marmoset model through DeepLabCut, a deep learning program

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Abstract

As a small primate, the common marmoset has been proposed as an ideal preclinical model for human diseases, such as Parkinson's, to bridge the gap between rodent research and clinical trials. As changes in the behavior can reflect early biomarkers of disease onset and progression, our goal is to assess and quantify the behavior in healthy animals first. We are using DeepLabCut, a deep learning program for noninvasive animal behavior tracking in laboratory uses. In our lab setting, we use cameras to record the animals' daily activity and movements in their cages, then we use DeepLabCut to build a skeleton with spatially labeled body parts to detect the typical behavioral components of marmosets. This project represents the first step of marmoset behavioral analysis to develop diagnostic and prognostic biomarkers for Parkinson's Disease, which can be eventually translated into use in human diagnosis and future clinical care. In the context of Parkinson's disease, one specific relevant priority is to use computational tools that aid in the identification of motor and cognitive deficits. Using the marmoset model, my project will contribute to this priority by providing more accessible and efficient measurements for behavioral dynamics within animal infrastructures. Therefore, the proposed project will promote the use of computational models in animal models for behavioral analysis and further applications of relevant research projects in our lab.

Investigating the Cannabis Withdrawal Trajectory in Individuals with Cannabis and Tobacco Co- use

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Abstract

Cannabis and tobacco co-use is prevalent, and individuals who co-use have elevated relapse rates compared to those using cannabis alone. Our group has previously shown that individuals who co- use experience greater cannabis withdrawal severity, a strong predictor of cannabis relapse, compared to individuals who use cannabis alone. In this secondary analysis, we compared the trajectory of cannabis withdrawal severity during 28-days of cannabis abstinence in individuals with cannabis use disorder parsed according to tobacco co-use status.
Methods: We recruited men with cannabis use disorder (N=20) who were parsed according to heavy tobacco co-use (CT+, ≥10 cigarettes/day, n=11) and light tobacco co-use (CT-, ≤5 cigarettes/day, n=9). Participants completed 28 days of cannabis abstinence encouraged by contingency management and supportive therapy. Cannabis withdrawal symptoms were assessed weekly using the Marijuana Withdrawal Checklist (MWC). Abstinence was determined biochemically using gas chromatography mass spectrometry and self-reported cannabis use.
Results: Fourteen participants achieved 28 days of biochemically-verified cannabis abstinence and four participants significantly reduced their cannabis use (>70%); two participants relapsed and were excluded from the analyses. The final sample included nine participants in the CT+ group and nine participants in the CT- group. A repeated measures analysis of variance revealed a significant interaction (group x time) effect for MWC severity (p=0.03), such that in the CT+ group, cannabis withdrawal symptoms remained elevated in severity during 28 days of cannabis abstinence compared to CT-. The specific withdrawal symptoms that drove the interaction were irritability and anger.
Conclusions: Cannabis withdrawal severity remained uniquely elevated in CT+ across multiple time- points during 28 days of cannabis abstinence compared to CT-. This information is key to effectively treating cannabis use, since withdrawal symptoms that remain elevated in severity for an extended duration would prolong the risk of relapse, impeding long-term recovery. Personalized approaches that address heavy tobacco co-use in CT+ may augment success for cannabis cessation attempts.

Precise measurement of motor learning in a mouse model of Fragile X Syndrome

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Abstract

The ability to learn motor skills is essential for survival and is a fundamental aspect of human behavior. How different parameters of learning change during skill acquisition and the underlying neural circuit mechanisms remain incompletely understood. In order to understand this problem, we trained C57BL/6 wild-type (WT) mice to perform a skilled forelimb reaching task and tracked their movements using DeepLabCut to measure paw trajectory and kinematics. Furthermore, to examine the neurological substrates of motor learning dysfunction, we also utilize a mouse model (*Fmr1* KO) of Fragile X Syndrome (FXS), a severe intellectual disability that causes an array of deficits including impaired motor learning. Our results revealed that *Fmr1* KO mice have lower success rates at the end of learning, compared to WT mice, aligning with prior FXS studies. Given that FXS is known to cause impairments in gross motor skill acquisition and coordination, we predict differing reach trajectories and kinematics in *Fmr1* KO mice compared to WT mice. Precise characterization of this deficit will enable us to link neural activity to specific behavioral differences with our planned in vivo calcium imaging experiments. Exploring the neural correlates of learning will provide valuable insight into how the refinement of coordinated movements is accomplished by cerebellar substrates, advancing our understanding of motor learning disorders. Our findings can aid in developing targeted treatments for FXS and similar conditions, in addition to the insight consistent parameters of learning can offer for optimizing rehabilitation strategies following neurologic injury.

Altered microRNA expression in extracellular vesicles from degenerating human neurons

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Abstract

The development of neurodegenerative diseases often begins long before symptom onset, highlighting the importance of early disease detection and diagnosis. Extracellular vesicles (EVs) are promising sources of peripheral biomarkers given their diverse molecular cargo, including microRNAs (miRNAs), which may reflect early pathological processes occurring in their parent cell. EVs produced by cells of the central nervous system can cross the blood-brain barrier and be collected from peripheral blood. Here, we use a reductionist *in vitro* approach to profile miRNA expression in EVs secreted by degenerating neurons. Human induced pluripotent stem cells (iPSCs) were differentiated into mature cortical neurons and challenged with toxic stimuli to induce degeneration. EVs were isolated from the cell culture media of degenerating neurons and subjected to miRNA sequencing. We identify a panel of dysregulated miRNAs in EVs from neurons experiencing oxidative damage, excitotoxicity, and hypoxic stress. To evaluate the biomarker potential of these miRNAs in patients, we explore mechanisms of purifying neuronal EVs from human blood samples for comparative miRNA analysis. We aim to identify a conserved miRNA signature that correlates with neuronal damage and may be used to establish blood-based biomarkers for neurodegenerative diseases.

Ionotropic glutamate receptor involvement in neocortical epileptiform synchronization *in vitro*

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Abstract

4-aminopyridine (4AP) is a voltage-gated potassium channel blocker that induces epileptiform activity in *in vivo* and *in vitro* preparations by increasing excitatory and inhibitory signaling.

Previous studies have reported that spontaneous interictal- and ictal-like epileptiform activities occur during 4AP application in neocortical brain slices obtained from "wild" guinea pigs or rats. Moreover, during application of 4AP, ictal discharges can be elicited by optogenetic stimulation of principal cells or interneurons in the entorhinal cortex, as well as of neocortical interneurons in transgenic mice. We have also reported that stimulating CamKII- positive, glutamatergic principal cells triggers ictal discharges; however, the specific contribution of different ionotropic glutamatergic receptor subtypes to these events remains to be addressed. As previously identified in the CamKII-ChR2 mouse entorhinal cortex, we found here that optogenetic stimulation of principal glutamatergic neurons during 4AP application (150 µM) induces in neocortical slices obtained from these transgenic mice ictal-like discharges that are characterized by an initial field potential shift followed by a series of after-discharges. The duration and the amplitude of the field potential shift associated to these ictal-like discharges were significantly reduced by application of an NMDA receptor antagonist (CPP, 5 µM), while a non-NMDA receptor antagonist (NBQX, 5 µM) eliminated the afterdischarges while preserving the field potential shift. Finally, ictal-like discharges were fully abolished by concomitant application of CPP and NBQX. Our findings demonstrate the involvement of both NMDA and non-NMDA receptors in the epileptiform synchronization leading to 4AP-induced ictal-like discharges in the neocortex of CamKII-ChR2 mice in an *in vitro* brain slice preparation.

Indirect Regulation of AMPA-mediated EPSP in the Cerebellum Interneuron in Fragile X Syndrome

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Abstract

Fragile X syndrome (FXS) is the most common single-gene cause of inherited intellectual disability and autism. Affected individuals and preclinical mouse models show brain hyperexcitability, although the underlying mechanism is poorly understood. Here we show that loss of Fragile X Messenger Ribonucleoprotein (FMRP) alters dendritic signaling and excitability in cerebellar molecular layer interneurons (MLIs - stellate cells). We observed a large but briefer excitatory postsynaptic potential (EPSP) in $Fmr1^{-/-}$ stellate cells (SC) following excitatory parallel fiber (PF) stimulation. We demonstrate that the change in EPSP halfwidth is caused by an increased GABAergic transmission. The enlarged peak amplitude is due to the decreased surface expression of TEA-sensitive delayed rectifier potassium channel (Kdr) currents and a delay in the activation properties in $Fmr1^{-/-}$ SCs. Computational H-H modeling revealed that the dendritic Kdr are critical for EPSP amplitude and hyperexcitability. Pharmacological block by TEA converted the profile of EPSP in WT SCs to that of $Fmr1^{-/-}$ mice further validating the importance of Kdr channel. Interesting, introduction of an N-terminal fragment of FMRP into $Fmr1^{-/-}$ mice restore the EPSP amplitude and associated hyperexcitability to that of WT mice. Contrary to conventional understanding , our study demonstrates that neuronal signaling deficits in FXS can also include translational independent mechanisms that can be corrected acutely by using a fragment of FMRP.