ONWAR
Graduate School
Neurosciences
Amsterdam Rotterdam

ONWAR / CEN

Annual PhD Meeting 2026

Book of Abstracts

DATE
26–27 November 2026

VENUE
Woudschoten Hotel & Conferentiecentrum

ADDRESS
Woudenbergseweg 54, Zeist

166	37	8
Abstracts	Topics	Themes

WELCOME

Welcome to the ONWAR/CEN Annual PhD Meeting 2026

Dear participants,

It is a great pleasure to welcome you to Woudschoten in Zeist for two days of neuroscience. Every year, this meeting brings together the PhD candidates of ONWAR, the joint graduate school for neuroscience PhD students across Amsterdam and Rotterdam, to share their work, meet each other and build the network that will carry them through their careers.

This book collects the abstracts of all posters presented at the meeting. They span the full breadth of our field: from synapses, glia and ion channels to cognition and behaviour, and from new methods and computational models to neurodegenerative, developmental and psychiatric disorders.

Whether you are presenting for the first time or in the final year of your PhD, we hope you will use these two days to ask questions, give feedback and find unexpected connections between your work and that of others.

We wish you an inspiring meeting!

The ONWAR organising committee

At a glance

DATE
26–27 November 2026

TIME
All day

VENUE
Woudschoten Hotel & Conferentiecentrum

ADDRESS
Woudenbergseweg 54, Zeist

Reading this book

The abstracts are grouped by **theme** and **topic**, as chosen at registration. Every abstract shows the poster number and room, or the session of the talk, at the top. The programme, poster rooms and poster list follow the Contents; click any entry there to jump to it.

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03 **Development** 6 abstracts p. 70

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PROGRAMME

Programme

Thursday 26 November

08:10 / 08:40	**Buses leave from Driebergen-Zeist station**	
08:45–09:15	**Registration and coffee**	Information desk
09:15–09:30	**Welcome**	Zaal 30
09:30–10:30	**Swammerdam lecture**	Zaal 30
10:30–10:45	**Coffee break**	
10:45–11:45	**Oral sessions 1 (short)** **1A** New approaches in psychiatric disorders · Woudzicht (108) **1B** iPSC-Derived Network Models · Zaal 30	
11:45–12:30	**Blitz 1**	Zaal 30
12:30–13:30	**Lunch**	Restaurant
13:30–14:15	**Blitz 2**	Zaal 30
14:15–15:45	**Poster session I** Day 1 posters (see the room maps)	
15:45–16:00	**Coffee break**	
16:00–17:30	**Oral sessions 2** **2A** Synapses and Plasticity · Woudzicht (108) **2B** Cognition and Behavior · Zaal 30	
18:00–20:00	**Dinner**	Restaurant
20:00–00:30	**Evening programme**	

Friday 27 November

07:00–09:00	**Breakfast**	Restaurant
09:00–09:15	**Announcements**	Zaal 30
09:15–09:45	**Blitz 3**	Zaal 30

09:45–11:00 **Poster session II and coffee**
Day 2 posters (see the room maps)

11:00–12:30 **Oral sessions 3**
3A Translational Neuroscience · Zaal 30
3B Novel Insights in MS · Woudzicht
3C Development · Zaal 15

12:30–13:50 **Lunch and walk outside** Restaurant

13:50–15:20 **Oral sessions 4**
4A Alzheimer's and Aging · Zaal 30
4B Novel In Silico Methods · Woudzicht
4C Imaging the Live Human Brain · Zaal 15 (45 places)

15:20–15:30 **Coffee break**

15:30–16:45 **Workshops**
AI for research (Zaal 24), From Lab to Industry (Zaal 25), How to Write a Rubicon Grant (Zaal 15), Take off Your Culture Glasses? (Woudzicht), Make Your Own Research Comic (Zaal 22/23)

15:30–16:45 **Round table: How to keep the post-PhD path in academia?** Zaal 30

17:00–17:30 **Closing ceremony** Zaal 30
Awards and closing remarks

17:40 **Buses leave from Woudschoten**

TALKS

Oral Sessions

SESSION 1A

New approaches in psychiatric disorders

Thursday 26 November · 10:45–11:45 · Woudzicht (108) · Chair: Hein van Maarle

Natalia Schilder p. 162
The Effects of Oral Tributyrin Supplementation in a Murine, Double-Hit Model of Depression

Sofie van Koppen p. 147
Age-Related Effects of Alcohol and Cannabis Exposure in Rats: An Overview of My PhD Trajectory

Zeli Chen p. 176
Submitted Explore SNP Effects on the Longitudinal Features of Substance Use

Thije Willems p. 61
A Role for the AMPAR Subunit GluA3 in Sleep and Memory

SESSION 1B

iPSC-Derived Network Models

Thursday 26 November · 10:45–11:45 · Zaal 30 · Chair: Ronald van Kesteren

Juliette Chevalier p. 121
Peroxisomes: The Forgotten Organelle

Tasha Ibrahim p. 112
Using Patient-Derived PSEN1-Mutant iPSCs to Study Excitation/Inhibition Imbalance in Alzheimer's Disease

Iris Kruijff p. 110
The Role of Exercise in Brain Lipid Metabolism in Alzheimers Disease

Ambika Mahajan p. 46
Cell-Type-Specific Responses to Oxidative Stress

SESSION 2A

Synapses and Plasticity

Thursday 26 November · 16:00–17:30 · Woudzicht (108) · Chair: Harold MacGillavry

Kim Verdaasdonk p. 31
Beyond Protein Abundance: Synaptic Phosphoproteomic Signatures of Contextual Fear Memory

Thomas Blok p. 53
Proteomic Analysis of Learning-Induced Changes in Perisynaptic Astrocytic Processes

Renee Pullen p. 35
From Synapse Structure to Molecular Identity: Spatiomolecular Mapping of mGluR5 in CA1 Engram Cell Spines

Dimitris Samouil p. 28
Mechanisms of Subtype-Specific Regulation of Metabotropic Glutamate Receptor Surface Mobility

Bastian Meth p. 24
CCDC186 Is a Specific Regulator of Dense Core Vesicle Biogenesis.

SESSION 2B

Cognition and Behavior

Thursday 26 November · 16:00–17:30 · Zaal 30 · Chair: Jan Willem de Gee

Sandra Parisi p. 69
Temporal Dynamics of ATF3-Expressing Neuronal Ensembles Induced by Fear Conditioning

Amber van Mierlo p. 192
Causal Relevance of Areas of the Dorsal Mouse Cortex in Audiovisual Representations: An Optogenetic Scanning Study

Puk Nuijten p. 196
From Thalamic Stimulation to Perception: Cortical and Perceptual Detection Responses to Electrical Activation of the LGN

Iris van den Heuvel p. 204
Touch Responses in Barrel Cortex Layer 5 Pyramidal Cell Types Are Differentially Shaped by Visuotactile Experience

SESSION 3A

Translational Neuroscience

Friday 27 November · 11:00–12:30 · Zaal 30 · Chair: Frank Meye

Tom Coopmans p. 41
EPSP Propagation in Human Layer 2 and 3 Cortical Pyramidal Neurons

Natia Shamugia p. 42
High Prevalence of Resonance in Human Cortical Interneurons

Miranda Moore p. 43
Less IS More: Reduced Cortical Excitability Enables Efficient Neural Coding and Higher Cognitive Ability

Eline Vansina p. 116
Developing a Reliable Rodent phMRI Protocol for Studying Methylphenidate Tolerance

Blom Kraakman p. 203
Tactile Processing in the Mouse Inferior Colliculus

SESSION 3B

Novel Insights in MS

Friday 27 November · 11:00–12:30 · Woudzicht · Chair: Geert Schenk

Lisanne van de Bovekamp p. 135
Targeting the CXCL12/ACKR3 Axis Drives Remyelination in Human MS Lesions ex vivo

Nine Kok p. 160
Uncovering the Molecular Drivers of BBB Impairment in Multiple Sclerosis

Lukas Lütje p. 128
Cerebrospinal Fluid Proteomics Links Compartmentalized Adaptive Immunity to Broad-Rim Lesion Pathology in Progressive Multiple Sclerosis

SESSION 3C

Development

Friday 27 November · 11:00–12:30 · Zaal 15 · Chair: Marten Smit

Jaime Borregon Jimenez p. 122
The Neurodevelopmental Disorder-Associated CAMK2A-p.Thr286Pro Variant Causes Severe Learning Deficits Due to Molecular and Synaptic Hyperactivity

Nadine Maas p. 117
Development of an N-of-1 Therapeutic Antisense Oligonucleotide for a Unique UNC13A Variant Causing a Neurodevelopmental Disorder

Vivienne Bauer p. 74
The Neuronal ER Proximity Proteome and Its Role in Local Translation

Emmy Hoeksema p. 150
Early Life Nutritional Programming of Neuroinflammation: The Impact of Dietary ω6/ω3 Fatty Acids Ratios on Microglia

Falk Brönnle p. 200
Hearing More than Sound: Characterizing Multisensory Neurons in the Inferior Colliculus

SESSION 4A

Alzheimer's and Aging

Friday 27 November · 13:50–15:20 · Zaal 30 · Chair: Aniko Korosi

Niek Renckens p. 51
Microglial Morphological Changes Near Engram Dendrites Accompany Memory Impairment in Alzheimer's Disease

Thijmen Ligthart p. 98
Neuronal Resilience to Tau Pathology: Sequestration of Active CK1δ Drives the Formation of Granulovacuolar Degeneration Bodies

Liyueyue Liu p. 81
Altered Age-Dependent Somatic Mutational Trajectories in ALS Motor Cortex Neurons

Marina Shiryaeva p. 85
Cell-Type-Specific Effects of γ-Secretase Inhibition on Cholesterol Metabolism in Neural Cells

SESSION 4B

Novel In Silico Methods

Friday 27 November · 13:50–15:20 · Woudzicht · Chair: Sophie van der Sluis

Femke Waleboer p. 113
Divergent Transcriptomic and Functional Aging of Molecularly Defined Neuron Types in Human Brain

Marijke Stokkel p. 173
Development and Validation of Proximity Extension Assay-Based Classification Models for Alzheimer's Disease Molecular Subtypes

Roberta Giannelli p. 95
Multi-Omics Approach for Defining the Disease Trajectory of FrontoTemporal Dementia

Maureen van der Grinten p. 198
The Neural Dynamics of Prosthetic Vision: From Simulations to Perception

SESSION 4C

Imaging the Live Human Brain

Friday 27 November · 13:50–15:20 · Zaal 15 (45 places) · Chair: Simon van Gaal

Eva van Heese p. 167
Sleep Stage-Dependent BOLD-CSF Coupling in Central Disorders of Hypersomnolence: An fMRI-EEG Study

Merel Koster p. 140
Clearing the Air: Smoking and Neurobiological Changes Across the Early Stages of Psychosis

Judit Campdepadrós Barrios p. 59
How External Goals Shape Learning Under Moral Conflict

Margot Steijger p. 56
Arousal Modulates Performance but Not Decodable Visual Representations in EEG

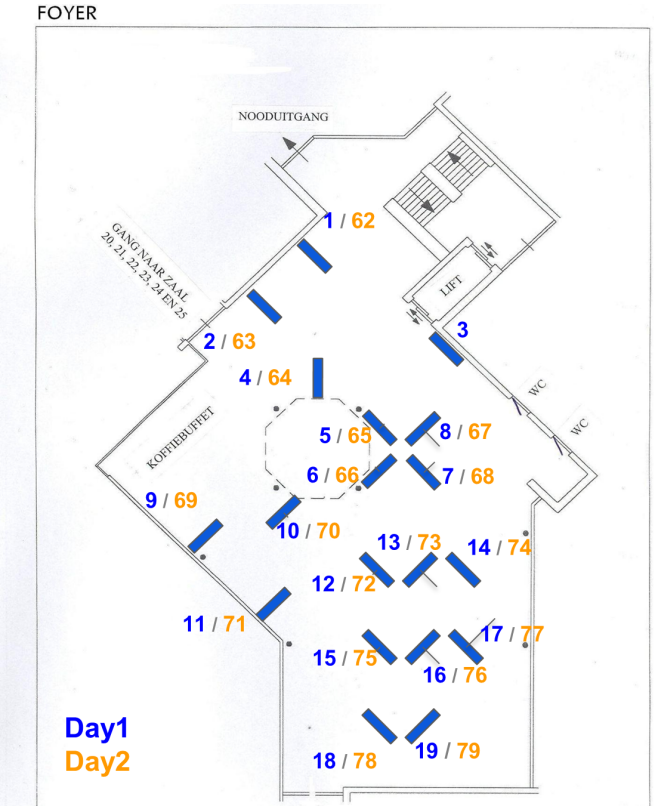
Sabine Gnodde p. 197
Testing the Neural Mechanisms of Visual Consciousness

Poster Rooms

Every board carries two posters: the number in **blue** is presented on day 1 (poster session I), the number in **orange** on day 2 (poster session II).

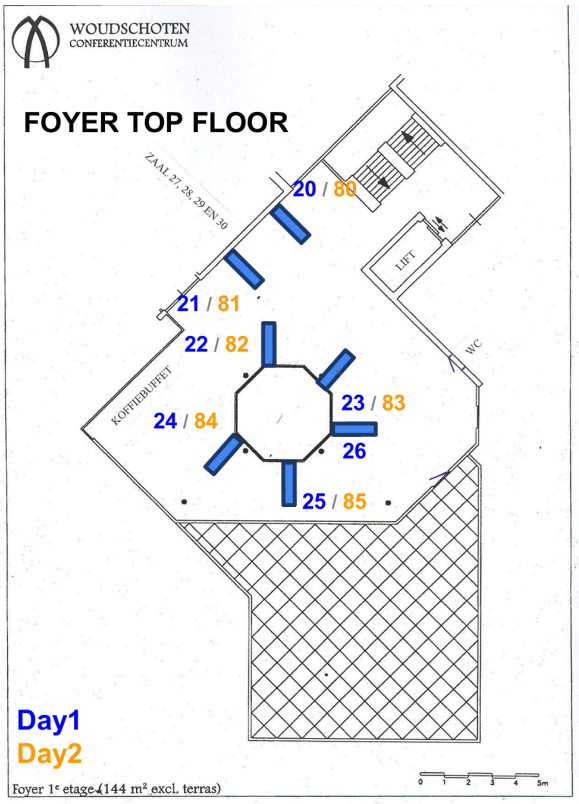
Foyer ground floor

Posters **Thu** 1–122 **Fri** 62–79



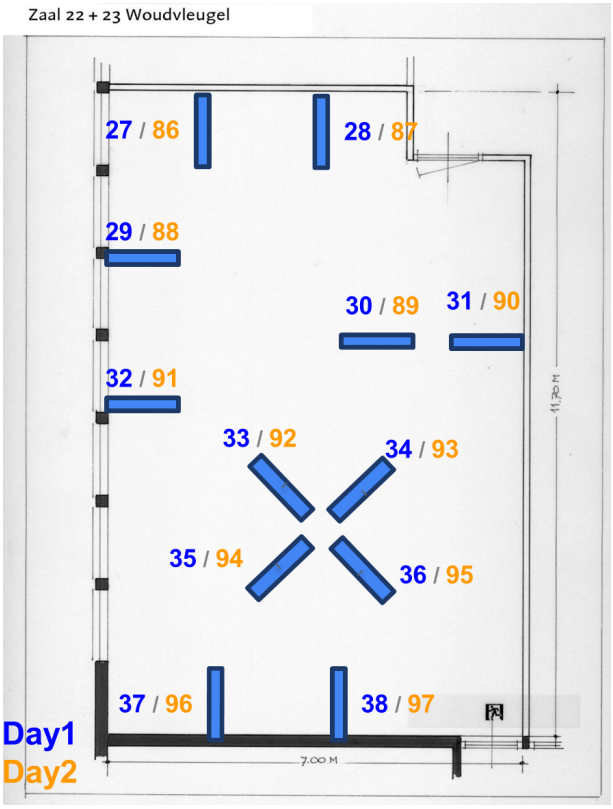
Foyer top floor

Posters **Thu** 20–26 **Fri** 80–120



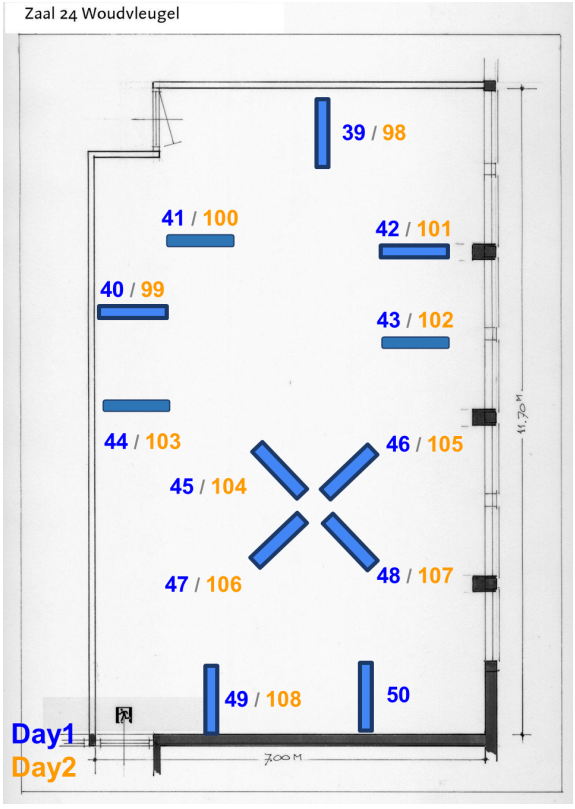
Zaal 22 + 23 Woudvleugel

Posters **Thu** 27–38 **Fri** 86–97



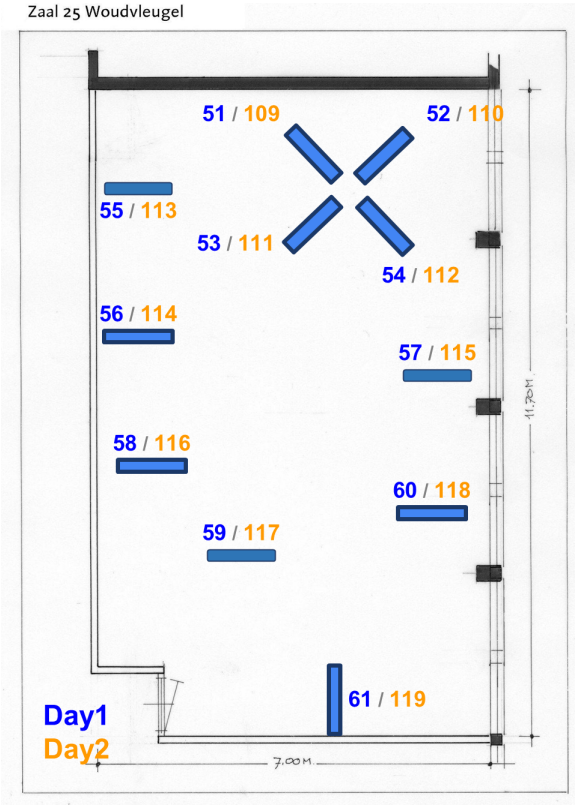
Zaal 24 Woudvleugel

Posters **Thu** 39–50 **Fri** 98–108



Zaal 25 Woudvleugel

Posters **Thu** 51–61 **Fri** 109–119



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CCDC186 Is a Specific Regulator of Dense Core Vesicle Biogenesis.

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PHD YEAR: Year 4
TALK: Session 2A
WHEN · WHERE: Thu 16:00–17:30 · Woudzicht (108)
KEYWORDS: Dense Core Vesicles, Neuropeptide Release, iPSCs

BACKGROUND

Dense core vesicles (DCV) are specialized vesicles for the regulated secretion of neuropeptide transmitters, peptide hormones and neurotropic factors. However, the biogenesis and maturation of these vesicles remains poorly understood, with only a few proteins, like CCDC186, shown to be involved.

METHODS

We assessed DCV as well as synaptic vesicle (SV) release in a human iPSC derived CCDC186 KO neurons using a single vesicle resolution imaging assay and examined morphological features using confocal imaging. We further visualized DCV cargo trafficking through the secretory pathway using a retention-using-selective-hooks (RUSH) assay.

RESULTS

KO of CCDC186 resulted in a drastic decrease of DCV, but not SV, release, that is explained by a severe lack of DCVs in the cell. Although general cell and organelle morphology was normal, RUSH experiments revealed a severe defect in Golgi exit of DCV cargo in line with the reduction of DCVs.

CONCLUSIONS

This study identifies CCDC186 as a key regulator of DCV biogenesis that seems to be specific for the regulated secretion pathway. Future experiments will focus on gaining mechanistic insights in CCDC186 function as well as identifying the protein machinery working with CCDC186 in this process.

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Differential Expression of ATF3 During Integrated Stress Response and Chemical LTP

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PHD YEAR
Year 3

POSTER NO.
50

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Integrated Stress Response | cLTP | Proteostasis

BACKGROUND

Molecular mechanisms involved in memory are not fully understood, however, the regulation of protein synthesis is recognized as essential. It has been demonstrated that protein synthesis is regulated by the Integrated Stress Response (ISR), with strong evidence linking ISR dysregulation to neurodegenerative disease. Activating transcription factor 3 (ATF3), a member of the ATF/CREB family, plays a key role in both memory formation and the ISR. Previous studies demonstrated that ATF3 is upregulated in hippocampal neurons during memory. Moreover, this transcription factor is known to be upregulated during ISR activation. In both contexts, the exact molecular mechanisms regulating ATF3 expression remain unclear. Our aim is to investigate these regulatory mechanisms during memory and ISR activation.

METHODS

Cross-comparison of RNA-seq data demonstrated specific regulation of ATF3 under ISR activation. To study the molecular mechanisms involved in memory processing, we established a primary mouse neuron model using chemical LTP (cLTP) to induce robust neuronal activity. We used high content microscopy to investigate the consequences of activating specific ISR kinases and acute protein synthesis on ATF3 expression.

RESULTS

Upon ISR activation, we observed ATF3 upregulation. This upregulation is not completely due to the ISR kinases. Furthermore, we demonstrated that ATF3 upregulation during cLTP was not due to the ISR. During the ISR and cLTP, ATF3 was not regulated at the translational level.

CONCLUSIONS

Our results provide evidence that the ATF3 expression is regulated by a non-canonical pathway of the ISR. Upregulation of ATF3 during cLTP is not due to ISR activation. Moreover, our results suggest that during the ISR and cLTP, ATF3 is regulated at the transcriptional level but this remains to be confirmed.

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Using the RAB3A-Dependent Secretome to Find New Cargoes of the Neuronal Regulated Secretory Pathway

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PHD YEAR: Year 2
POSTER NO.: 61
LOCATION: Zaal 25 Woudvleugel · Thu
KEYWORDS: Dense-Core Vesicles, RAB3A, Secretome

BACKGROUND

In neurons, dense-core vesicles (DCVs) carry neuropeptides and other signal molecules, which are secreted in a regulated manner. However, the composition of the DCV secretome has not yet been characterized. RAB3A, small a GTPase, is required for DCV, but not synaptic vesicle exocytosis in most neuronal cell types, which allows for specifically studying the DCV-dependent secretion.

METHODS

To study the cargoes of DCVs, a RAB3a KO mouse was used. Brain slices were stimulated and the secretome before and after stimulation was analyzed using mass spectrometry based proteomics. DCV proteins were further characterized by functional imaging.

RESULTS

From the detected proteins in the secretome, 72 were secreted in a RAB3a and stimulation dependent manner of which 17 were established DCV protein and 55 were unknown cargoes. Of the unknown cargo, the main categories identified were related to RNA/ribosomal proteins or proteolytic enzymes. The localization and exocytosis patterns of these cargoes were validated in mouse neuronal cultures using microscopy.

CONCLUSIONS

In the study a novel method was established for studying DCV exocytosis, which revealed previously unknown DCV cargo.

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Visualizing Noradrenergic and Dopaminergic Modulation of Insular Cortex Neurons with an A-Kinase Activity Reporter (tAKARα) in Acute Mouse Brain Slices

Iris Berden

PHD YEAR
Year 2

POSTER NO.
64

LOCATION
Foyer ground floor · Fri

KEYWORDS
Insular Cortex · Neuromodulation · Dopamine · Noradrenaline · PKA-Dependent Signaling · Fluorescent Lifetime Imaging

The insular cortex (IC) is an associative cortical region that integrates internal and external sensory information and plays a role in learning, motivation, and emotional awareness. The IC is functionally heterogeneous, with the anterior insula primarily involved in higher-order cognitive functions, whereas the posterior insula is more strongly associated with the integration of internal and external sensory information. Neuromodulators, such as noradrenaline and dopamine, can modify circuit activity and shape behavioral outcomes by differentially regulating distinct neuronal cell types. Such cell-type specific effects may arise from differences in receptor expression, connectivity, and neuroanatomical organization. Recently, pyramidal neurons within the IC have been characterized by their electrical properties, morphology, anatomical location, and local and long-range connectivity, providing a framework for investigating cell-type-specific neuromodulation. This study aims to determine how dopamine and noradrenaline modulate the function of distinct pyramidal neuron populations in the IC. The variety of functional effects and expression levels of G-protein coupled receptors (GPCRs) have historically complicated the study of neuromodulator signaling within cell populations. Yet, most GPCRs converge onto a limited set of second messenger signaling molecules, including cAMP/PKA. Here, we leverage the ability to visualize and quantify PKA activity as an important hallmark of neuromodulator-induced signaling at the (sub)cellular level in cell populations. To quantify PKA-dependent neuromodulator signaling, we use the microtubule-targeted A-kinase activity reporter alpha (tAKARα), a Förster resonance energy transfer (FRET)-based sensor, in combination with one-photon fluorescence lifetime imaging (1pFLIM). This approach enables quantitative measurements of PKA activity in insular neurons in response to agonists for the dopaminergic and noradrenergic receptors within acute mouse brain slices. By identifying which insular neuron populations are selectively modulated by dopamine and noradrenaline, we aim to provide new insights into the neuromodulatory mechanisms that shape the operation of the insular cortex circuits.

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Mechanisms of Subtype-Specific Regulation of Metabotropic Glutamate Receptor Surface Mobility

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PHD YEAR
Year 4

TALK
Session 2A

WHEN · WHERE
Thu 16:00–17:30 · Woudzicht (108)

KEYWORDS
mGluR SMLM Nanoorganization

BACKGROUND

Metabotropic glutamate receptors are dimeric G protein-coupled receptors (GPCRs) that critically regulate synaptic transmission and plasticity through diverse signaling pathways, The precise organization of GPCRs at the cell membrane determines the magnitude of receptor activation and the ability to spatiotemporally confine downstream signaling. Yet, how the lateral diffusion and membrane organization of distinct mGluRs is regulated remains poorly understood.

METHODS

Here, using super-resolution microscopy and single-molecule tracking in heterologous cells and neurons, we observed remarkably distinct surface mobility profiles across the different mGluR subtypes.

RESULTS

More specifically, group I mGluRs, mGluR1 and 5, have comparable diffusion properties in heterologous cells, but show distinct mobility properties in neurons, and differentially respond to agonist treatment. Additionally, mutating crucial sites for receptor activation increases mGluR5 surface mobility, while the antagonist MPEP has no effect. Similarly, the group II mGluRs mGluR2 and 3, show opposite responses to receptor activation, in both surface mobility and nanoclustering.

CONCLUSIONS

Together, our findings demonstrate that distinct mechanisms regulate mGluR surface mobility across receptor subtypes and cellular membranes. Complementing this, we will further resolve endogenous neuronal mGluR distribution and signaling partners, deepening our understanding of how spatiotemporal membrane organization of mGluRs relates to function providing new insight into synaptic transmission and plasticity in health and disease.

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Activity-Driven Axonal Plasticity in Parvalbumin Interneurons

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LOCATION: Foyer ground floor · Thu
KEYWORDS: Axon Initial Segment, Parvalbumin Neurons, Sodium Channels

Optimal network activity requires a delicate excitatory-inhibitory balance maintained by diverse neuronal types in the brain. Neurons adjust their action potential output through activity-driven remodeling of their axon initial segments (AISs), and our ongoing work reveals that this process is highly cell type-specific. Chronic silencing of dissociated primary rat cultures induced an increased sodium channel Nav1.6 expression and heightened excitability in glutamatergic neurons while GABAergic neurons retained a stable firing activity. This absence of change in excitability could be due to the diversity in GABAergic neurons. For instance, parvalbumin (PV) interneurons are characterized by high-frequency firing that provides precise inhibition and network synchronization. However, how they particularly adjust their output in response to perturbations in network activity remains to be elucidated. Here we use the Nav channel blocker tetrodotoxin (TTX) to show that chronic silencing induces activity-dependent plasticity throughout the axon of PV neurons. First, TTX application resulted in the diffusion of ankyrin-G (AnkG) towards the distal AIS, coupled with an upregulation of Nav1.1 and Nav1.6 expression. Notably, the proximo-distal arrangement of Nav1.1 and Nav1.6 was abolished, making these two Nav1 isoforms colocalize at the AIS. Second, we also observed that PV neurons uniquely form node-like structures marked by AnkG and Navs along the axon in the absence of myelin. TTX treatment prompted an increase in AnkG and Nav1.6 expression in these node-like structures, while Nav1.1 remained unaffected. We are now investigating the activity-regulated trafficking mechanisms controlling AnkG and Nav1.6 distribution and assessing the functional implications of this axonal plasticity. Deciphering how PV neurons calibrate their excitability by reorganizing their axonal architecture could reveal how they coordinate with other neurons to maintain network homeostasis.

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From SNAREs to Signals: Deciphering the Exocytic Machinery Controlling Ion Channels at the Axon Initial Segment

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PHD YEAR: Year 2
POSTER NO.: 70
LOCATION: Foyer ground floor · Fri
KEYWORDS: Exocytosis, Kv2.1, SNARE Complex, Axon Initial Segment, Plasticity

Maintaining a balanced network activity in the brain is vital for proper functioning. Neuronal firing rate is controlled through homeostatic mechanisms: besides synaptic plasticity, this also includes intrinsic excitability modulation. Intrinsic excitability is determined at the axon initial segment (AIS), where action potentials are generated. The AIS undergoes structural plasticity in response to changes in network activity. Through its lengthening and shortening, the AIS is able to regulate action potential firing probability. During this plasticity response, ion channels responsible for generation of the action potentials are inserted and removed, depending on subtype and network activity. Recent work has shown removal of some of these ion channels to be dependent on endocytosis. This points to the presence of ion channel recycling machinery within the tightly regulated proteome of the AIS. While the presence and functionality of the endocytic machinery have already been defined, the presence, composition, and functional relevance of exocytic machinery at the AIS has yet to be described. Here, using knock-ins and immunocytochemistry in dissociated rat hippocampal neurons, we show various proteins of the exocytic SNARE-machinery to be present at the AIS. Additionally, we describe the Kv2.1 ion channel to form clusters which could function as a structural platform to couple exocytosis and endocytosis. Lastly, we show these Kv2.1 channel clusters to respond to changes in activity. Deciphering the composition and regulation of recycling machinery at the AIS will be critical in understanding AIS plasticity and what role this plays in homeostatic regulation of network activity.

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Beyond Protein Abundance: Synaptic Phosphoproteomic Signatures of Contextual Fear Memory

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PHD YEAR
Year 4

TALK
Session 2A

WHEN · WHERE
Thu 16:00–17:30 · Woudzicht (108)

KEYWORDS
Phosphoproteomics Synapse Contextual Fear Conditioning

BACKGROUND

The synapse is a protein-dense unit central to neural communication. Dynamic adaptation of synapse strength and structure is essential for cognitive processes such as learning and memory. Protein phosphorylation, a ubiquitous post-translational modification (PTM), can rapidly mediate protein function, localization and interactions, thereby enabling real-time control over synapse function. While phosphorylation dynamics of some synaptic proteins have been studied within the first hours after learning, it remains largely unknown whether the phosphoproteome is reconfigured days later during recent memory maintenance. Here we aim to identify how aversive contextual memory maintenance alters the phosphoproteome and proteome of hippocampal synapses.

METHODS

We subjected mice to contextual fear conditioning (CFC) and sacrificed them 30 minutes or 72 hours after learning to capture the corresponding phosphorylation states. Home-caged naïve animals served as a baseline. Hippocampi were collected, synaptosomes isolated, and a low-input mass spectrometry-based phosphoproteomics workflow established. For each sample, paired total and phospho-enriched peptides were generated and analyzed by LC–MS using diaPASEF acquisition and DIA-NN processing. A custom MS-DAP–based pipeline enabled synapse-wide quantitative proteomic and phosphoproteomic analysis.

RESULTS

We detected 18035 unique phosphopeptides with site localization probability >0.9 across 3854 proteins. Differential expression analysis revealed learning- and time-dependent phosphorylation signatures related to specific synaptic sub-compartments and function. Moderate correlations between phosphopeptide effect sizes and their corresponding proteins indicate that phosphorylation dynamics are largely decoupled from protein abundance.

CONCLUSIONS

Our results delineate how the synaptic phosphoproteome reconfigures over time after learning, suggesting a role for phosphoregulation in sustaining contextual fear memory at hippocampal synapses.

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Cellular Mechanisms Setting Local Rules of Spike-Timing Dependent Plasticity

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PHD YEAR
Year 3

POSTER NO.
36

LOCATION
Zaal 22 + 23 Woudvleugel · Thu

KEYWORDS
Synaptic Plasticity
Cortical Layer-5 Pyramidal Neurons
Computational Modeling

BACKGROUND

Synaptic plasticity is commonly regarded as the cellular and molecular substrate of memory. Spike-timing dependent plasticity (STDP) based on temporally correlated pre- and post-synaptic activity is widely present in the brain, but rules of how correlated activity translates into synaptic weight changes varies between cell types, brain regions, and species. In cortical layer 5 pyramidal neurons (L5PTs), STDP rules were shown to be robust but dependent on synapse location along the apical dendrite. Proximal synapses follow the classical (Hebbian) STDP rule, while distal synapses obey an inverse rule. It has been hypothesized that underlying mechanisms could relate to dendrite morphology or biophysics, cellular physiology or to synapse-specific properties, but this was never tested.

METHODS

Using biophysically detailed computational models of rat L5PTs, combined with a synaptic plasticity model based on thresholding synaptic calcium currents, we aimed to disentangle the influence of cell morphology, biophysics, cellular physiology, and synapses on synaptic plasticity rules.

RESULTS

We found that synaptic NMDAR-mediated calcium currents are predictive of many STDP-based rules observed empirically, allowing to explain, for example, how dendritic location of synapses leads to frequency-dependent STDP rules at proximal synapses while distal synapses follow dendritic spike-based plasticity rules. Importantly, we show that these rules are conditional on cell electrophysiology and how they are robust despite biophysical and morphological diversity.

CONCLUSIONS

Our work thus sets the stage to reveal how synaptic, cellular, and network properties interact with one another to establish the different variants of STDP rules that are observed across cell types and species.

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Cerebellar Subpopulation-Specific Differences in Intrinsic Excitability and Plasticity Related to Distinct Movement Kinematics

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PHD YEAR: Year 3
POSTER NO.: 15
LOCATION: Foyer ground floor · Thu
KEYWORDS: Cerebellum, Purkinje Cells, Plasticity, Synaptic Activity, Eye Movements

The cerebellum plays a key role in sensorymotor integration, movement, coordination and balance. Purkinje cells (PCs) are the only output neurons of the cerebellar cortex. The cerebellum is not homogeneous; AldolaseC (AldoC) expression forms alternating longitudinal bands of positive and negative PCs across the cerebellar cortex that differ in physiology and connectivity. The flocculus is a key cerebellar hub for the control and adaptation of compensatory eye movements, in which AldoC expression creates two bands: 9+ and 9−. Here, we aim to test our working hypothesis that the 9+ and 9− subpopulations of PCs in the flocculus contribute different aspects to floccular functioning and thereby eye movements. To this end, we first performed ex vivo electrophysiological slice recordings and tested the synaptic input, intrinsic and synaptic plasticity between 9+ and 9− PCs in the flocculus− identified using Kcng4-cre/Ai14 mice. We found that 9- PCs show a higher frequency of spontaneous excitatory and inhibitory post synaptic currents compared to 9+ PCs. Then, we examined synaptic plasticity of the parallel fiber to Purkinje cell synapse and found a difference in long term potentiation (PF-PC LTP) between 9+ and 9- PCs. Next, based on observed differences in intrinsic activities, we did see a significant difference in intrinsic plasticity of 9+ and 9− PCs. So far, our results suggest that 9− floccular PCs are more strongly linked to aspects of movement and have more dynamic synaptic and non-synaptic features, compared to 9+ PCs.

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ER Cisternae and Tubules Cooperatively Support Dendritic Spine Growth During Synaptic Activity

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PHD YEAR: Year 2
POSTER NO.: 113
LOCATION: Zaal 25 Woudvleugel · Fri
KEYWORDS: ER, Synaptic Plasticity, Local Translation

BACKGROUND

Dynamic regulation of synaptic strength is essential for proper neuronal communication. One form of synaptic plasticity is long-term potentiation (LTP) of a dendritic spine, which requires proteomic changes and results in spine enlargement. The molecular mechanisms regulating synaptic plasticity and spine enlargement remain incompletely understood. Previous work has implicated the endoplasmic reticulum (ER) in facilitating spine enlargement during LTP. The ER is compartmentalized into two distinct structures, where cisternae are the predominant site for protein synthesis, and tubules are responsible for lipid exchange and ER calcium homeostasis. However, it remains unclear which ER structure and function(s) contribute to synaptic plasticity. Therefore, we here aimed to investigate the potential differential roles of ER cisternae and tubules during induced LTP.

METHODS

We expressed or knocked down fluorescently tagged ER-shaping proteins CLIMP63 and RTN4, marking ER cisternae and tubules respectively. We used fixed and live-cell imaging to study the localization of these markers to dendritic spines upon induction of chemical LTP (cLTP).

RESULTS

We show that ER cisternae localize to the base of spines and ER tubules occasionally enter spines dynamically. We find that spines containing either ER structure enlarge during cLTP stimulation. Further, ER associated spine enlargement appears to be codependent on both ER structures as knockdown of ER cisternae- or ER tubule-shaping proteins abolished enlargement during cLTP. Lastly, we examine the requirement of ER-based localized translation for spine enlargement upon LTP. Together, our data suggests that ER cisternae and tubules have differential functional roles in spines that cooperatively contribute to spine enlargement during LTP.

CONCLUSIONS

Together, our data suggests that ER cisternae and tubules have differential functional roles in spines that cooperatively contribute to spine enlargement during LTP.

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From Synapse Structure to Molecular Identity: Spatiomolecular Mapping of mGluR5 in CA1 Engram Cell Spines

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PHD YEAR
Year 4

TALK
Session 2A

WHEN · WHERE
Thu 16:00–17:30 · Woudzicht (108)

KEYWORDS
Synapse Memory mGluR5

Memory formation is associated with coordinated structural and molecular remodeling of hippocampal engram cell synapses. Previous work has revealed learning-induced alterations in synaptic connectivity, dendritic spine morphology, and synaptic protein composition within these neurons. However, it remains unclear how specific molecular changes at engram cell synapses relate to spine morphometry and how these features contribute to the spatial organization of spines along the dendritic arbor. Here, we present a high-resolution microscopy pipeline to investigate protein localization at CA1 engram cell synapses following contextual fear conditioning (CFC). By combining virus-dependent engram labeling, immunohistochemistry, high-resolution confocal microscopy, and 3D image reconstruction, we map and quantitate protein distribution across defined synaptic subtypes with single-synapse resolution. This approach enables the integration of molecular, structural, and connectivity-related features within hippocampal circuits. Using this workflow, we examine the spatial organization of metabotropic glutamate receptor 5 (mGluR5), a target previously identified by proteomics as enriched in CA1 engram cell synapses 72 h after contextual fear learning. We find mGluR5 preferentially localized at engram-to-engram synapses and associated with distinct morphological features. These results suggest a coordinated molecular and structural program at engram synapses, in which mGluR5 may be involved. Future studies dissecting the engram-specific function of mGluR5 will further clarify its contribution and relationship to structural plasticity and memory formation.

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Human E/I Networks Tune Presynaptic Connectivity Through Development and GABAergic Activity

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PHD YEAR
Year 3

POSTER NO.
6

LOCATION
Foyer ground floor · Thu

KEYWORDS
Excitation-Inhibition Balance · hiPSC Neurons · Synaptic Plasticity

BACKGROUND

Maintaining a balanced ratio of excitatory and inhibitory (E/I) synaptic input is essential for stable neuronal network function, yet the mechanisms by which human neuronal networks compensate for altered cellular E/I composition remain poorly understood. We investigated whether various E-I ratios of human induced pluripotent stem cell (iPSC)-derived neuronal cultures regulate presynaptic connectivity to preserve synaptic E/I balance during development and after disruption of inhibitory neurotransmission.

METHODS

Human NGN2-induced glutamatergic and ASCL1/DLX2-induced GABAergic neurons were co-cultured at defined E/I ratios and analysed after 4 or 10 weeks of maturation. Presynaptic inhibitory and excitatory puncta were quantified using confocal microscopy. To investigate the role of inhibitory signalling, GABAergic neurons lacking STXBP1-mediated vesicle release were compared with wild-type cultures.

RESULTS

Mature (10-week) networks exhibited stable total synapse density across diverse cellular E/I ratios through adaptive scaling of inhibitory and excitatory presynaptic densities, indicating homeostatic regulation of synaptic connectivity. In contrast, immature cultures showed incomplete presynaptic compensation. Loss of GABAergic neurotransmission disrupted inhibitory presynaptic scaling, altered synaptic E/I balance, and abolished subtype-specific connectivity patterns observed in wild-type cultures. Excitatory neurons preferentially formed excitatory-to-excitatory connections in mature wild-type networks, whereas this organization was lost in networks with STXBP1 inhibitory neurons.

CONCLUSIONS

Human neuronal networks dynamically adjust presynaptic connectivity to compensate for changes in cellular E/I composition during maturation. GABAergic neurotransmission is required for proper inhibitory presynaptic tuning and subtype-specific circuit organization, highlighting inhibitory activity-dependent synaptic remodelling as a mechanism underlying network homeostasis and a potential contributor to neurodevelopmental disorders associated with E/I imbalance.

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Resolving How Interactions Between the Post-Synaptic Density and the Actin Cytoskeleton Drive Activity-Dependent Reorganization of the Synapse at the Nanoscale

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PHD YEAR: Year 2
POSTER NO.: 103
LOCATION: Zaal 24 Woudvleugel · Fri
KEYWORDS: Plasticity, Post-Synapse, Nanoscale

BACKGROUND

Long-term potentiation (LTP) of synaptic strength is mediated by series of molecular events that result in persistent modification of synaptic structure, composition and function. It has long been held that an increase of AMPA-type glutamate receptors (AMPARs) in the postsynaptic density (PSD) is the principal mechanism by which synaptic strength is augmented. However, research from the last decade demonstrated that the nanoscale organization of molecular assemblies within post-synaptic compartments is equally critical. Specifically, the reorganization of receptor and scaffolding molecule nanoclusters relative to presynaptic release sites is pivotal for LTP expression. Yet, the underlying molecular mechanisms that drive reorganization of nanoclusters in the PSD during LTP remain elusive.

METHODS

To address this, we resolved the activity-dependent nanocluster reorganization of endogenous post-synaptic proteins using CRISPR/Cas9-mediated protein tagging and super-resolution microscopy.

RESULTS

We found an LTP-induced increase in nanocluster number and density of GluA1-containing AMPARs, PSD95, GKAP and SHANK3, although at different temporal scales. Moreover, we show that the LTP-dependent reorganization of PSD95 nanoclusters relies on the interaction between SHANK3 and the actin cytoskeleton.

CONCLUSIONS

In sum, our results indicate that the interaction between the PSD and the actin cytoskeleton is essential for the LTP-driven nanoscale reorganization of the post-synapse.

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SPReADing It Thin: Resolving Single AMPA Receptor Complex Stoichiometry Through Membrane Fusion-Mediated Dilution

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Year 2

POSTER NO.
90

LOCATION
Zaal 22 + 23 Woudvleugel · Fri

KEYWORDS
AMPARs Stoichiometry Microscopy

BACKGROUND

AMPA receptors (AMPARs) mediate fast excitatory synaptic transmission. Their properties are regulated by auxiliary subunits, including TARPγ8 and CNIH2, as well as the less-studied proteins Shisa6 and Shisa7, which are highly expressed in hippocampal neurons. In particular, it remains unclear how these auxiliary subunits are organized within native AMPAR complexes and whether they coexist within the same receptor assemblies. Determining their stoichiometry is essential for understanding how they collectively regulate synaptic function.

METHODS

Despite advances in super-resolution microscopy, it remains challenging to determine the stoichiometry of single protein complexes in an intact biological system. To determine the stoichiometry of AMPAR complexes, we employ SPReAD (Single Protein Recovery After Dilution), enabling single-complex analysis while minimizing disruption of native assembly. A U2OS cell line stably expressing VSV-G was generated to induce cell fusion, allowing membrane proteins to dilute to densities suitable for single-molecule imaging. Subsequently, photobleaching step analysis and qPAINT will be used to quantify the number of AMPAR subunits and auxiliary proteins within individual complexes.

RESULTS

We have established a stable U2OS cell line that forms syncytia within an hour following low-pH exposure. We are currently optimizing culture conditions for single-complex imaging. Subsequently, we will use this technique to determine the stoichiometry of AMPARs and their major hippocampal auxiliary subunits.

CONCLUSIONS

This approach will enable direct analysis of the composition of AMPAR complexes and provide insight into how multiple auxiliary subunits are combined within individual receptors. Understanding this organization will help reveal how auxiliary subunits collectively shape synaptic transmission.

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The AIS at the Nanoscale: How Does the MPS Remodeling Participate in Local Control of Voltage-Gated Ion Channels During AIS Plasticity?

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PHD YEAR
Year 3

POSTER NO.
39

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
AIS Plasticity | Super-Resolution Microscopy | Voltage-Gated Sodium Channel

BACKGROUND

The axon initial segment (AIS) is a highly specialized subcellular domain localized between the somatodendritic and axonal compartments where action potentials are initiated. Action potential generation and modulation highly depend on the distribution of voltage-gated ion channels which are anchored by the scaffold protein AnkyrinG at the AIS membrane. AnkyrinG (AnkG) further interacts with a submembrane network of periodically organised actin rings and spectrins called the membrane-periodic skeleton (MPS). In response to changes in network activity, the AIS undergoes rapid structural remodeling either by relocating along the axon or altering its length, with significant impact on neuronal excitability. Increasing evidence shows that AIS plasticity involves changes in actin dynamics and actin-associated proteins (formins, myosin). However, the link between cytoskeleton dynamics and acute re-organization of AIS membrane proteins during AIS plasticity remains elusive.

METHODS

We used a previously established chemical Long Term Depression (cLTD) plasticity paradigm that triggers sodium channel Nav1,2 shortening in vitro in dissociated rat hippocampal neurons via Clathrin-mediated endocytosis at the distal AIS. We first aimed at assessing whether actin dynamics are required for cLTD-induced AIS shortening using immunocytochemistry and SIM microscopy in fixed and live samples. Then, we aim to decipher the mechanisms regulating acute re-distribution of voltage-gated ion channels during AIS plasticity by measuring their diffusion behaviour with single particle tracking. Using super-resolution microscopy, we first aim at resolving the nanoscale re-organization of the MPS

RESULTS

We found that blocking actin polymerization prevents Nav1.2 shortening.

CONCLUSIONS

Resolving the precise mechanisms by which these channels are re-arranged during AIS plasticity will provide important insights into how neurons regulate their excitability, relevant in health and disease.

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Electrophysiological and Morphometric Properties of Chandelier Cells in the Primary Visual Cortex

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PHD YEAR
Year 3

POSTER NO.
27

LOCATION
Zaal 22 + 23 Woudvleugel · Thu

KEYWORDS
Chandelier Cells · Axon Initial Segment · Electrophysiology

BACKGROUND

Encoding of sensory information in the neocortex is critically modulated by inhibitory interneurons, notably the parvalbumin expressing basket cells (BCs) and chandelier cells (ChCs). Although the membrane properties and integrative features of BCs have been thoroughly characterized, a detailed account of the ChCs is still lacking, including the origin of action potentials in the axon initial segment (AIS). Here, using the Vipr2-Cre mouse line we used genetic targeting of ChCs to investigate their electrophysiological and morphological properties.

METHODS

We injected Vipr2-Cre mice with Cre-dependent fluorophores (PHP.eB_AAV_dlox_mcyRFP1 or AAV1_dlox_hM3dq_EGFP) to label ChCs. To compare the results with BCs, WT mice were injected retro-orbitally with a new promoter, BIPV4e and a fluorescent reporter (PHP.eB _AAV_BIPV4e_dTomato_nlsdTomato). Whole-cell recordings were performed from fluorescently labelled cells in layer 2, and biocytin-filled cells were morphological reconstruction (3D Neurolucida) to extract anatomical dimensions and reconstruct complete dendritic and axonal arborizations.

RESULTS

We found that, compared to BCs, the ChCs had a significantly higher input resistance and lower rheobase current together with a higher dendritic complexity but a similar somatodendritic surface area. The AISs of ChCs were characterized by a similar length and location while their APs were significantly broader. Interestingly, the majority of ChCs (81% of recorded cells, 17/21) were myelinated around the proximal axonal branches.

CONCLUSIONS

Our data show that the structural and functional characteristics of ChCs show overlap with parvalbumin-positive BCs as well as several unique properties, which facilitate powerful dendritic integration and rapid highly synchronized firing during arousal.

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EPSP Propagation in Human Layer 2 and 3 Cortical Pyramidal Neurons

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PHD YEAR
Year 4

TALK
Session 3A

WHEN · WHERE
Fri 11:00–12:30 · Zaal 30

KEYWORDS
Human Neurons | Electrophysiology | Imaging

BACKGROUND

The human cortical column has expanded over the course of evolution compared to other species, especially in cortical layers 2 and 3. While the neurons themselves as well as the inter-cell distances have increased, previous studies found that soma to soma latencies have not. To further study the signal propagation of human and mammalian cortical pyramidal neurons, we investigated the propagation speed of subthreshold signaling within the dendritical part of pyramidal neurons, in acute slices of both murine and human brains.

METHODS

Acute cortical brain slices were whole-cell patched, while stimulating individual spines using 2-photon glutamate uncaging. The high precision of this method allows for investigation of previously observed differences in soma to soma signaling delays between human and mouse pyramidal neurons. Recorded cells were stained and 3D-reconstructed to investigate the influence of morphology on subthreshold signal propagation.

RESULTS

EPSP propagation delays and speed were found to be significantly affected by the synapse location on the dendrite, as well as raw latency. When correcting for morphological confounders such as dendritic diameter and electrotonic distance, these relations still hold.

CONCLUSIONS

EPSP propagation speed differs depending on the location of the synapse, the cell type and species.

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High Prevalence of Resonance in Human Cortical Interneurons

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PHD YEAR
Year 4

TALK
Session 3A

WHEN · WHERE
Fri 11:00–12:30 · Zaal 30

KEYWORDS
Human Cortex | Cortical Interneurons | Subthreshold Resonance | HCN | PVALB | VIP | SST | LAMP5

Neurons in cortical circuits respond selectively to network oscillations of specific frequencies—a phenomenon called membrane potential resonance. While resonance is well studied in human pyramidal neurons, it is largely unexplored in human interneurons. We leveraged electrophysiological and transcriptomic (Patch-seq) data, along with novel recordings, to ask which genetic, physiological, and morphological mechanisms underlie the resonant properties of human cortical LAMP5, VIP, PVALB, and SST interneurons. We find that resonance is substantially more prevalent among human interneurons compared to mouse interneurons, with human parvalbumin (PV) interneurons exhibiting the highest prevalence of resonance. In contrast to human pyramidal neurons, the resonance properties of human interneurons were not dependent on cortical depth. Instead, human interneuron resonance frequency and strength were strongly correlated with intrinsic electrophysiological properties such as low input resistance and high membrane voltage sag. This was supported by increased expression of genes encoding resonance-associated voltage-dependent HCN, which differentiated resonant from non-resonant human interneurons. HCN blockade eliminated resonance in acutely recorded human interneurons, and an HCN-mediated voltage sag increase in cultured adult human brain tissue was associated with an increase in resonance prevalence and strength. Using conductance-based computational models with idealized human and mouse morphologies, we mechanistically disentangle the roles of human morphology and active conductances in resonance generation. We demonstrate that these morphological features afford human interneurons sharper frequency tuning which translates in the suprathreshold domain under noisy, in vivo-like conditions. Our findings provide new insights into human interneuron input-output function and species differences, guiding more informed interpretations of human cortical dynamics and translation from mouse models.

Less IS More: Reduced Cortical Excitability Enables Efficient Neural Coding and Higher Cognitive Ability

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PHD YEAR
Year 4

TALK
Session 3A

WHEN · WHERE
Fri 11:00–12:30 · Zaal 30

KEYWORDS
Neural Efficiency · Cortical Excitability · Human Intelligence

BACKGROUND

What makes some brains smarter than others? The neural basis of individual differences in cognitive ability remains poorly understood, particularly how mechanisms at different scales relate to one another and to intelligence.

METHODS

We examined how network dynamics in the human temporal cortex relate to the intrinsic excitability of its pyramidal neurons, and how both scales bear on cognitive ability. Using a multi-scale dataset spanning single-neuron electrophysiology and local network dynamics, we assessed these relationships across individuals. To address the underlying mechanism, we then constructed biophysically detailed models of high-IQ and low-IQ neurons and tested their computational abilities.

RESULTS

Higher IQ was associated with reduced excitability at both the cellular and network levels. Biophysical modelling showed that reduced cellular excitability confers a computational advantage: neurons from higher-IQ individuals encoded information more efficiently, transmitting more bits per spike.

CONCLUSIONS

Reduced neuronal excitability, rather than being a deficit, supports more efficient information encoding. This provides a candidate multi-scale mechanism linking cellular biophysics, network dynamics, and cognitive ability.

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Sex-Specific Developmental Alterations in Purkinje Cell Spiking and Action Potential Dynamics in Tsc1 Haploinsufficient Mice

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PHD YEAR
Year 3

POSTER NO.
46

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Purkinje Cell Excitability
Action Potential Dynamics
Cerebellar Development

BACKGROUND

Cerebellar dysfunction is increasingly implicated in autism, with mutations in the TSC1 gene leading to dysregulated mTOR signalling and altered neuronal excitability. While changes in firing rate and excitation–inhibition balance are well documented in autism models, how action potential (AP) dynamics, including spike generation and temporal structure, are affected across development and between the sexes remains insufficiently characterized. Previous research using TSC autism mouse models with homozygous cell-specific mutations in Tsc1 showed decreased cerebellar Purkinje cell (PC) excitability across adulthood. However, it is unclear how cerebellar cell activity is affected across development into adulthood in patient-representative mutations and whether sex-differences play a role.

METHODS

Therefore, we performed ex-vivo patch-clamp recordings on PCs in cerebellar vermis lobules V–VI in female and male global Tsc1 mice and wildtype littermates. We measured spontaneous firing and AP properties at P7–P10 (pup), P18–P21 (juvenile), and P60–P80 (adult).

RESULTS

Tsc1 haploinsufficiency left overall maturation of excitability largely intact but produced subtle and transient sex-specific alterations in spiking behavior and AP dynamics. Male pup Tsc1 PCs showed altered action potential dynamics and an initial increased spontaneous firing rate Tsc1 that stagnates during the juvenile phase. Whereas female Tsc1 PCs showed only early AP dynamics differences that normalized by P10 but progressively increased their spontaneous firing rate during development from pup to adult. Additionally, we show baseline differences between male and female wildtype PCs.

CONCLUSIONS

These results indicate that Tsc1 haploinsufficiency interacts with pre-existing sex differences in PC physiology to shape divergent developmental trajectories of excitability.

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Bridging Neuronal Transmission and the Dynamic Restructuring of Glial Processes

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PHD YEAR: Year 2
POSTER NO.: 99
LOCATION: Zaal 24 Woudvleugel · Fri
KEYWORDS: Perisynaptic Astrocytic Processes (PAP's); Single Molecule Localization Microscopy (SMLM)

BACKGROUND

Peri-synaptic Astrocytic Processes (PAP) are minuscule leaflets which play a crucial role in maintaining the synaptic environment. For example, neuronal activity can induce the retraction of these processes, leading to neurotransmitters spillover and the activation of nearby synapses (Hennerberger et al., 2020). It is still unknown how exactly the composition of these peri-synaptic processes is regulated and how it's composition contributes to plasticity and memory. We hypothesize that Ezrin, an actin-binding protein associated to the plasma membrane, contributes to efficient signal transmission and astrocytic structural plasticity.

METHODS

Primary cultures were made from a Cas9 mouse line. CRISPR/Cas9 Knock-In's were designed to tag PAP proteins in astrocyte neuron co-cultures. Super-resolution microscopy techniques such as DNA-PAINT and dSTORM were applied to localize said proteins on the nanoscale.

RESULTS

We hypothesize that we will be able to confirm the co-localization of Ezrin and NHERF1. Additionally, we aim to co-localize Ezrin with previously determined NHERF1 binding partners, in particular G-protein coupled receptors (GPCR's) such as B2AR, P2YR and mGluR's.

CONCLUSIONS

We aim to resolve macromolecular complexes on the membrane of astrocytic processes, elucidating the role actin-binding proteins may play in neuron-astrocyte signal transmission. Future studies will focus on understanding the role of Ezrin and NHERF1 in the mobility, localization and endocytosis of various astrocytic GPCR.

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Cell-Type-Specific Responses to Oxidative Stress

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PHD YEAR
Year 4

TALK
Session 1B

WHEN · WHERE
Thu 10:45–11:45 · Zaal 30

KEYWORDS
Neuron-Astrocyte | Oxidative Stress | Tau

BACKGROUND

Oxidative stress (OS) is a hallmark of neurodegenerative diseases including Alzheimer's Disease (AD) and is characterised by an elevation in toxic reactive oxygen species (ROS) that drive neurodegeneration. Although most studies on AD have been neurocentric, astrocytes are now recognised as active participants in pathogenesis. They are essential in managing ROS through redox cycling and antioxidant defence, functions critical for neuroprotection and maintaining homeostasis. We have previously shown that astrocytes display non-autonomous responses to tau aggregation in neurons, a characteristic of AD, with an increase in ROS and activation of the Integrated Stress Response (ISR) pathway. Here we aimed to identify the mechanistic link between ROS and ISR activation in addition to investigating cell-autonomous and non-autonomous responses in neurons and astrocytes to OS.

METHODS

We employed co-culture and monoculture models of iPSC-derived neurons and human foetal astrocytes alongside genetic and pharmacological interventions to isolate key molecular players. Additionally, we used high-content and confocal microscopy to validate target expression.

RESULTS

Astrocytes and neurons exhibited distinct cell-specific responses to OS. In astrocytes, elevated ROS and ATP depletion both triggered ATF4 activation via the mitochondrial stress sensor DELE1 and the ISR kinase HRI. HRI inhibition under OS resulted in marked ROS accumulation and significantly compromised astrocyte viability. In contrast, while neurons also activated ATF4 via the DELE1-HRI axis during ATP inhibition, they did not activate this pathway in response to elevated ROS alone.

CONCLUSIONS

Mapping cell-type-specific responses to oxidative stress revealed distinct mechanisms of DELE1-HRI-ATF4 axis regulation in neurons versus astrocytes. These findings highlight selective vulnerability in astrocytes and identify this pathway as a potential target to restore homeostasis in neurodegenerative diseases. With these findings, we are currently investigating how tau pathology alters stress management.

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Defining Non-Cell-Autonomous Astrocytic Stress States in Response to Neuronal Tau Pathology

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PHD YEAR: Year 3
POSTER NO.: 93
LOCATION: Zaal 22 + 23 Woudvleugel · Fri
KEYWORDS: Stress Pathways, Neuron-Glia Signalling, Tau Pathology

BACKGROUND

Intraneuronal tau aggregation is a defining feature of Alzheimer's Disease (AD) and related tauopathies, yet its impact extends beyond neurons. Astrocytic stress pathways are increasingly implicated in neurodegeneration, including the integrated stress response (ISR), oxidative stress and astrocyte reactivity. However, how neuronal tau pathology triggers these astrocytic responses is unknown. This study investigates how neuronal tau accumulation drives astrocytic stress signalling and how distinct stress states can arise.

METHODS

We established a human iPSC-derived neuron-astrocyte co-culture model with neuron-specific tau accumulation. In parallel, astrocyte reactivity was induced in monocultured astrocytes using the cytokines TNF, IL1 and C1q (TIC). Astrocytic stress responses were assessed in both models, using markers for ISR, oxidative stress and reactivity. Single-cell analysis was performed to delineate astrocytic stress states.

RESULTS

In co-culture, intraneuronal tau pathology induced astrocytic ISR activation, oxidative stress and reactivity. Notably, pathway activation was limited to a subset of astrocytes. In monoculture, TIC treatment alone triggered both ISR and oxidative stress, demonstrating that reactivity signalling can act as an upstream driver. Furthermore, single-cell profiling revealed that uniform TIC exposure generates distinct astrocytic stress states, ranging from restricted reactivity to complete stress pathway activation.

CONCLUSIONS

Neuron-specific tau accumulation drives non-cell-autonomous astrocytic stress responses. Astrocyte reactivity independently induces similar stress responses, pointing to shared signalling mechanisms. Crucially, both conditions trigger heterogeneous responses, indicative of distinct astrocytic stress states. Together, these findings uncover a mechanistic link between tau pathology and glial stress signalling.

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Determining the Role of the Complement System in Neuropsychiatric Disorders

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PHD YEAR
Year 2

POSTER NO.
118

LOCATION
Zaal 25 Woudvleugel · Fri

KEYWORDS
Complement · Major Depressive Disorder · Microglia

BACKGROUND

The etiology of major depressive disorder (MDD) is poorly understood, but a leading hypothesis implicates neuroinflammation of cortical circuits of emotional regulation. In the brain, the complement system bridges the innate immune system with synaptic plasticity, neurodevelopment and neurodegeneration. The system is an evolutionarily highly conserved protein cascade comprising over forty different proteins, with a crucial role in immune defense against pathogens. Previous clinical studies have reported elevated levels of C1q, C3, and C4 in the serum of individuals with MDD compared to healthy controls.

METHODS

To directly test the role of complement in the synaptic and cellular features of the neural circuits involved in MDD, we are performing immunohistochemical staining on a cohort of postmortem grey matter from the frontal cortex of MDD patients, obtained from the Netherlands Brain Bank–Psychiatry. Since complement proteins can be locally produced in the brain by neurons and glial cells, in particular by microglia, we will stain for neuronal cell types and microglia. Using age-matched non-neurological controls, we will investigate complement expression and its association with microglial activation as well as its colocalization with inhibitory synapses. In parallel, to test for causality we are investigating complement expression and its relation to microglia during the development of cortical organotypic slice cultures. The platform will be used in future studies to manipulate complement pathways using novel chemical tools to label complement proteins and enable functional analyses of this system.

CONCLUSIONS

By combining these two approaches, we expect that our results will provide molecular insights into the mechanistic role and therapeutic potential of complement in MDD.

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Guts2Beat Depression: Linking Gut Microbial Metabolites to Brain Plasticity and Neuroimmune Mechanisms in Depression.

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PHD YEAR	POSTER NO.	LOCATION	KEYWORDS
Year 2	82	Foyer top floor · Fri	Brain Organoids · Depression · Gut-Brain Axis

BACKGROUND

Depression is a complex and multifactorial disorder in which stress-related molecular and cellular processes, including inflammation, play a central role. Increasing evidence suggests that the gut microbiome contributes to depressive symptoms via microbial metabolites that influence immune signaling and neuronal functioning, yet the causal mechanisms remain unclear. This project, conducted within the Guts2Beat Depression consortium, combines large-scale human cohort analyses with advanced experimental models to study microbiome-brain interactions and develop novel intervention strategies.

METHODS

We first analyze international cohorts to identify microbial taxa and their metabolic products that are depleted in individuals with depression. These microbiome-derived metabolites are selected as candidates for functional testing. Their effects are investigated in a stress-induced human cerebral organoid model incorporating microglia, enabling the study of neuroimmune interactions under controlled stress conditions. Stress is induced via glucocorticoid receptor stimulation and pro-inflammatory cytokines to model cellular aspects of depression-related pathology. Metabolite supplementation is then evaluated for its ability to counteract stress-induced changes in microglial activation and inflammatory signaling. In parallel, an in vivo mouse model combining early-life adversity and chronic mild stress evaluates whether metabolite supplementation reduces depressive-like behavior and modulates neuroinflammatory processes.

RESULTS

NVT, only experimental design (Arial 10 pt)

CONCLUSIONS

We hypothesize that specific microbiome-derived metabolites can restore stress-induced cellular dysfunction and alleviate depressive-like phenotypes. By integrating human cohort discovery with mechanistic validation in complementary model systems, this project aims to provide insight into the role of the gut–brain axis in depression and identify novel metabolite-based intervention strategies.

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Human-Specific Adaptations in Astrocyte-Synapse Interactions

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PHD YEAR
Year 2

POSTER NO.
120

LOCATION
Foyer top floor · Fri

KEYWORDS

Human astrocytes show unique evolutionary features compared to mouse astrocytes. They are larger, present extended territorial domains and faster intracellular calcium responses to glutamate. Furthermore, human presynaptic boutons exhibit larger vesicle pools, suggesting greater glutamate release that places higher demands on astrocytic uptake. While perisynaptic astrocytic processes (PAPs) dynamics are well characterized in rodents to be highly mobile and remodel in response to neuronal activity, particularly retracting after long-term potentiation (LTP), little is known about their behaviour in the human brain. In the current research we aim to determine (1) whether human astrocytes clear synaptically released glutamate more efficiently than mouse astrocytes and (2) whether human PAPs show activity-dependent mobility comparable to that of mouse. To investigate these questions, we combine live two-photon imaging with cultured mouse and human cortical slices with viral labeling approaches to monitor real-time glutamate dynamics and astrocyte-synapse interactions under different patterns of neuronal activity. Preliminary data suggests species-specific glutamate clearance kinetics and sensitive PAP morphology to changes in the extracellular environment. These findings may reveal human-specific adaptations of astrocyte synapse interactions. (176 words)

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Microglial Morphological Changes Near Engram Dendrites Accompany Memory Impairment in Alzheimer's Disease

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PHD YEAR	TALK	WHEN · WHERE	KEYWORDS
Year 4	Session 4A	Fri 13:50–15:20 · Zaal 30	Microglia, Engram, Alzheimer's Disease

BACKGROUND

Alzheimer's disease (AD) is characterized by amyloid-β (Aβ) accumulation, neuroinflammation, and cognitive decline. Microglia initially protect the brain by clearing Aβ, but later become reactive, contributing to synapse loss. Microglia can modulate memory recall during physiological forgetting and memory extinction. We wondered whether bidirectional communication between engram neurons and microglia occurs during AD and influences dementia development.

METHODS

We investigated this by measuring microglial morphology and phagocytosis near Aβ plaques and engram dendrites in APP/PS1 Arc::dVenus (AdV) mice. Staining for IBA1, CD68, Aβ (AB6E10), and dVenus was combined with confocal imaging. 3D lysosomal quantification was performed in IMARIS. Microglial morphology was assessed using microglial morphometric analysis. We analysed the changes on both the animal and the cellular levels using Linear Mixed Effects Models (LMEs).

RESULTS

At 4M, memory recall was unaffected, but at 6M and 9M, APP/PS1 AdV mice had impaired contextual fear memory, with concurrent deficits in engram reactivation (6M) and formation (9M). Microglia near engram dendrites in APP/PS1 AdV mice transiently increased their branching complexity at 6M, compared to microglia far from engram dendrites. This morphological change at the earliest timepoint at which memory recall was impaired suggests that microglia may be involved in memory loss development during the early, cellular phase of AD.

CONCLUSIONS

Microglia respond to engram dendrites by increasing branching complexity, suggesting increased surveillance of these dendrites and synapses in WT AdV mice. This response is present transiently in APP/PS1 AdV mice and correlates with the appearance of memory recall deficits.

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Molecular and Functional Identification of CD200-CD200R Interactions in Neuron-Glia Signaling

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PHD YEAR: Year 2
POSTER NO.: 18
LOCATION: Foyer ground floor · Thu
KEYWORDS: CD200 · Microglia · Neuronal Activity

BACKGROUND

Microglia, resident macrophages of the brain, continuously surveil surrounding cells to maintain circuit functions. One of the molecules governing these interactions is CD200 and its receptor CD200R. Checkpoint molecule CD200 is widely expressed in the brain by neurons, oligodendrocytes and astrocytes, while the CD200R is exclusively expressed by microglia. After binding, microglial activation is inhibited. Dysregulation of this pathway has been implicated in neurodegenerative diseases and neuropsychiatry but its physiological role remains unclear. RNA sequencing and proteomics data show that CD200 is expressed by most CNS cells but the endogenous subcellular expression pattern has been difficult to study likely due to high level of soluble CD200 in the extracellular space.

METHODS

We developed various CRISPR/Cas9 knockin plasmids to label endogenous CD200. Additionally, we have developed CD200 overexpression plasmids to further probe this signaling cascade. Lastly, we probed neuronal activity with whole-cell patch-clamp recordings to study the effect of soluble CD200Fc (CD200R agonist).

RESULTS

We show effective AAV transduction of our CRISPR/Cas9 and overexpression plasmids in organotypic cortical slice cultures (OSC). Our knockin plasmids revealed sparse, but selective, labeling of various cell types. Moreover, the low concentration of CD200Fc was ineffective in reducing microglial activity. Consequently, neuron function was unaltered.

CONCLUSIONS

For the first time we show endogenous protein expression and localization of CD200 across neurons and glial cells. Further experiments will include overexpression plasmids of CD200 to further probe the temporal component of CD200-CD200R signaling with the aim to gain further insights on how CD200-CD200R signaling affects neuronal, glial and network function.

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Proteomic Analysis of Learning-Induced Changes in Perisynaptic Astrocytic Processes

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PHD YEAR
Year 4

TALK
Session 2A

WHEN · WHERE
Thu 16:00–17:30 · Woudzicht (108)

KEYWORDS
Astrocyte Tripartite Synapse Proteome

Polarized protoplasmic astrocytes extensively interact and communicate with neuronal synapses using their perisynaptic astrocytic processes (PAPs); an interplay required for synaptic plasticity. For example, astrocytes dynamically retract their PAPs from the synaptic cleft to gate fear memory strength. Our understanding of the molecular mechanisms underpinning this and other plasticity processes regulated by astrocytes, is limited by the sparsity of data on the proteins residing in PAPs. While the proteomic composition of the neuronal compartments of the tripartite synapse, i.e. pre- and post-synapse, are extensively studied, the proteomic composition of the PAP remains -largely- elusive. In the present study, we use mass spectrometry-based proteomics combined with correlation profiling across different murine hippocampus brain fractions to identify proteins present in the PAP. First, we show that canonical PAP proteins, such Glt-1, show a clear expression profile across subcellular fractions. Then, we employ this profile to identify proteins showing a similar profile. Next, we filter based on astrocytic enrichment to increase confidence in assigning the proteins to the PAP. In total, we identify 70 putative PAP proteins, of which 60 proteins were not previously assigned to the PAP. Next, we show that the expression of the identified putative PAP proteins, in synaptic fractions, is regulated by fear conditioning in a translation-dependent manner. Finally, we show that the majority of these proteins are locally translated. Together, we identified novel putative PAP proteins that are regulated in learning. Current efforts include confirming the PAP localization for a selection of these proteins using expansion microscopy, and to determine their role in synaptic function by genetic manipulation in vitro and in vivo.

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Towards the Detection of Subcompartment-Specific Proteomes in Astrocytes

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PHD YEAR
Year 2

POSTER NO.
67

LOCATION
Foyer ground floor · Fri

KEYWORDS
Astrocytes | Cellular Subcompartment | Proteomics

BACKGROUND

Astrocytes have a complex morphology, forming two types of specialized subcompartments: the perisynaptic astrocyte processes (PAPs) contacting neuronal synapses and astrocyte endfeet ensheathing the brain's vasculature. This places astrocytes in a unique bridging position, enabling them to control neuronal signal transmission on the one hand while tuning regulation of brain metabolism and fluid homeostasis on the other. However, the underlying molecular architecture governing these functions, as well as the extent to which it is PAP or endfeet specific remains poorly understood. Therefore, we aim to map the proteome of astrocyte PAPs, endfeet, and the astrocyte as a whole, in order to begin unraveling subcompartment-enriched molecular signatures and pathways.

METHODS

To achieve this, we make use of proximity-based proteomics using the biotinylase TurboID, which allows for unbiased, circumjacent labeling and subsequent enrichment of cell-type specific proteins. Combining proximity-based proteomics with specific isolation of synaptogliasomes and brain vessels enables the analysis of PAPs and endfeet, respectively.

RESULTS

However, the successful integration of these techniques appears highly dependent on methodological details, such as labeling time and method, biotinylated protein isolation and enrichment, and mass spectrometry sample preparation parameters. By systematically optimising these variables for both in vitro and in vivo applications, we developed a protocol that achieves deep proteomic coverage and a high signal-to-noise ratio.

CONCLUSIONS

The optimized protocol paves the way for future studies of activity-dependent molecular changes in astrocyte subcompartments.

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02

THEME

Cognition and Behavior

Human Cognition and Behavior p. 56

Animal Cognition and Behavior p. 61

Motivation and Emotion p. 67

Learning p. 68

Arousal Modulates Performance but Not Decodable Visual Representations in EEG

Margot C.E. Steijger[1], Sean D. van Mil[1], Samuel Noorman[1,2], Lola Beerendonk[1], Timo Stein[1], Johannes J. Fahrenfort[1,3], Simon van Gaal[1]

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PHD YEAR
Year 4

TALK
Session 4C

WHEN · WHERE
Fri 13:50–15:20 · Zaal 15 (45 places)

KEYWORDS
Pupil-Linked Arousal · EEG Decoding · Sleep Deprivation

BACKGROUND

Arousal modulates behavioral performance, often following an inverted U-shaped pattern in which performance is best at intermediate arousal levels. It remains unclear whether such effects reflect changes in sensory and perceptual representations, or later decision-related stages. Here, we tested whether arousal influences early visual encoding or later perceptual integration.

METHODS

Participants performed a perceptual task in which they detected Kanizsa illusory figures and discriminated local contrast in masked stimuli while EEG and pupillometry were recorded. We used multivariate pattern analysis (MVPA) to decode stimulus contrast as an index of early visual encoding and illusory shape perception as an index of perceptual integration, and related decoding performance to trial-by-trial fluctuations in pupil-linked arousal. To assess more sustained arousal changes, we additionally analyzed an independent dataset using sleep deprivation.

RESULTS

Behaviorally, performance was optimal at intermediate arousal levels for both accuracy and reaction time. In contrast, EEG decoding of stimulus contrast and illusory percepts remained stable across trial-by-trial fluctuations in pupil-linked arousal, indicating that neither early sensory encoding nor later perceptual integration was systematically affected. Likewise, reduced arousal following sleep deprivation did not reliably alter perceptual representations.

CONCLUSIONS

Together, these findings suggest that arousal-related changes in performance are unlikely to reflect modulation of visual representations. Instead, arousal may primarily influence post-perceptual processes, such as the transformation of perceptual evidence into decisions or responses. Ongoing analyses are testing this decision- and response-stage account directly.

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Change-Point Oddball: Introducing Volatile Statistics to Study Learning from Unexpected Outcomes

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PHD YEAR
Year 3

POSTER NO.
10

LOCATION
Foyer ground floor · Thu

KEYWORDS
Pupillometry | Belief Updating | Oddball

BACKGROUND

The (auditory) oddball protocol is one of the most widely used tools in cognitive and systems neuroscience. Although the design reliably elicits mismatch responses towards oddball stimuli, a key limitation is that these responses do not drive learning, as stimulus statistics are stationary. This is at odds with the premise that unexpected outcomes should prompt learning to enable adaptive behaviour. To address this contradiction, we developed “change-point oddball”

METHODS

We started with a conventional passive oddball design with high- and low-frequency tones (standard, 90%; oddball, 10%; frequencies, 1kHz and 2kHz; tone duration, 0.5s; inter-tone-interval, 1s). Critically, we introduced a 5% chance of a state change after every stimulus. A state change reversed the mapping between frequency and oddball status. We hypothesized that after every state change participants would update their predictions to the new stimulus statistics. We showcase the appeal of our protocol by measuring pupil-linked arousal in human participants (N=20).

RESULTS

We observed multiple pupil-based signatures of prediction updating: (i) larger tone-evoked pupil responses for state-dependent oddballs vs standards ($p<0.001$), (ii) exponentially decreasing pupil responses to standards after state changes ($tau=0.86$), and (iii) a linear relationship between pupil responses and the “change point probability” ($p<0.001$), derived from a Bayesian belief updating model.

CONCLUSIONS

We conclude that phasic pupil-linked arousal supports the updating of predictions after unexpected outcomes. We advocate for the implementation of this novel change-point oddball protocol in study contexts ranging from animal models, to investigate underlying mechanisms, to clinical populations, to characterize aberrant prediction updating.

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Decomposing Pupil-Linked Arousal Across Multiple Timescales Demonstrates Differing Relations to Performance

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PHD YEAR
Year 3

POSTER NO.
57

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Yerkes-Dodson
Time-on-Task Effects
Frequency Decomposition

BACKGROUND

The Yerkes-Dodson law describes an inverted-U relationship between pupil-linked arousal and perceptual performance, but human evidence is mixed, with studies reporting both inverted-U and linear relationships. We asked (1) whether slow block-level, putatively fatigue-related trends in pupil and performance can drive a spurious linear relationship, and (2) whether the shape of the arousal-performance relationship depends on the timescale of fluctuations considered.

METHODS

N = 99 participants across two experiments performed an auditory discrimination task while pupil size was recorded. Tone volume was titrated per session to fixed accuracy levels using a staircase. We related pupil-linked arousal to perceptual sensitivity (d′) using polynomial regression, systematically varying the filter cutoffs to localise the relationship across frequency bands (ultraslow, <0.01 Hz; infraslow, 0.01–0.1 Hz; slow, 0.1–1.0 Hz; fast, >1.0 Hz).

RESULTS

Across the low-pass-filtered signal, the arousal-performance relationship was non-monotonic with a strong positive linear component, rather than inverted-U shaped. This reflected a shared within-block decline in pupil size and performance: the highest pupil bins were disproportionately populated by early, high-accuracy trials. Excluding early trials, or removing ultraslow (<0.01 Hz) fluctuations by band-pass filtering, recovered the classic inverted-U. The quadratic relationship was present only in ranges that included the infraslow band (0.01–0.1 Hz), aligning with a growing literature implicating this timescale in organism-wide arousal dynamics.

CONCLUSIONS

The arousal-performance relationship is timescale-dependent. Slow time-on-task trends can impose a spurious linear component, whereas the inverted-U emerges specifically in infraslow pupil fluctuations. We recommend reporting within-block trends and considering frequency-based decomposition of pupil signals.

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How External Goals Shape Learning Under Moral Conflict

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PHD YEAR
Year 4

TALK
Session 4C

WHEN · WHERE
Fri 13:50–15:20 · Zaal 15 (45 places)

KEYWORDS
Reinforcement-Learning · Morality · Self-Other

BACKGROUND

Successfully navigating social life requires more than learning which actions lead to good outcomes; it also requires adjusting how much different outcomes are valued depending on situational demands and expectations. This challenge is especially pronounced in moral conflict situations, where actions that benefit oneself may simultaneously harm others, and where external rules or instructions may require people to act against their usual moral values.

METHODS

We use a learning task in which each choice produces two outcomes: money for the self and physical pain for another person (Fornari et al., 2023). Participants received different goal-directed instructions, such as maximizing personal reward or minimizing other's pain. Using behaviour, computational modelling, and neuroimaging (fMRI) analyses, we examine how these instructions shape how the brain integrates these outcomes during learning and decision-making.

RESULTS

Behavioural results (N = 85) show pain-focusing instructions induced stronger, more reliable effects than money-focusing instructions. Notably, even highly prosocial individuals followed instructions to increase another person's pain. This suggests moral value representations can be flexibly regulated, though not symmetrically across goal types. Trial-by-trial learning emerged selectively under pain-related goals, and choice behaviour was best explained by an interaction between instruction compliance and pain saliency. In addition, recall for symbol–outcome associations was selectively biased toward pain outcomes. At the neural level this seems to be captured by an attentional shift towards pain outcomes.

CONCLUSIONS

These findings highlight how externally imposed goals dynamically reshape moral valuation and learning, providing insight into how social demands can override or amplify moral preferences in everyday decision-making.

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Identifying Key Predictors of Exercise Persistence and Habit Formation in First-Year Students: A Longitudinal Analysis.

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PHD YEAR
Year 2

POSTER NO.
34

LOCATION
Zaal 22 + 23 Woudvleugel · Thu

KEYWORDS
Physical Activity | Mental Health | Network

BACKGROUND

Almost half of Dutch students report mild-to-severe depression and anxiety complaints. Physical activity (PA) is a low-cost behavioral strategy that promotes mental health and wellbeing by increasing stress resilience and is associated with transdiagnostic protective factors. The strength of these effects depends on the intensity and frequency of PA and is influenced by demographic, psychosocial and environmental factors. We aimed to implement a complex system approach to determine relationships between PA, mental health, substance use, and urbanicity in Dutch students.

METHODS

Approximately 11 000 students from nine Dutch universities responded to a cross-sectional survey. Validated scales were used to measure PA (vigorous, moderate, light, sedentary behaviour), depression, generalised anxiety, perceived stress, academic stress, loneliness, procrastination, wellbeing, insomnia, self-esteem, substance use, and urbanicity. We used network analyses to detect direct and indirect associations between physical activity and the remaining factors.

RESULTS

The Gaussian Graphical Model of partial correlations revealed stable negative associations between vigorous PA and perceived stress, and a positive association with alcohol consumption, which in turn was associated with lower loneliness. Moderate PA was associated with better wellbeing, while more sedentary hours were associated with more procrastination. Depression and stress had the highest strength centrality, while the PA nodes were sparsely connected with the rest of the network.

CONCLUSIONS

This study provides novel insights on the complex relationships between physical activity and student's mental health. Its findings will inform future longitudinal investigations and RCTs aimed to better understand potential working mechanisms of the effects of physical activity on stress, depression and anxiety.

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A Role for the AMPAR Subunit GluA3 in Sleep and Memory

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PHD YEAR: Year 4
TALK: Session 1A
WHEN · WHERE: Thu 10:45–11:45 · Woudzicht (108)
KEYWORDS: Memory, Sleep, GluA3 AMPAR

BACKGROUND

Sleep is a fundamental process for memory consolidation. Memory formation heavily relies on the plasticity of synaptic AMPA receptors (AMPAR), which undergo sleep-related regulation. Impairment of sleep-related neural plasticity could potentially hin der memory consolidation and processing. The AMPAR subunit GluA3 has been previously implicated into mediating slow wave activity during sleep.

METHODS

Here, we investigate how the GluA3 AMPAR subunit influences sleep and memory. Using global GluA3 knockout (GluA3 KO) mice, localized knockout models, the object location memory task, and immediate-post learning 6-hour sleep deprivation (SD), we evaluated the role of GluA3 in spatial memory consolidation and sleep. Additionally, using electrocorticography, local field potentials and electromyograms, we investigated changes in sleep.

RESULTS

GluA3 KO mice exhibited preserved short-term memory, but impaired 24-hour memory consolidation and sleep, indicating an overnight impairment of memory consolidation. In contrast, localized GluA3 KO in the hippocampus resulted in an intact 24h memory that was resilient against SD. Indicating a role for the AMPAR subunit GluA3 for both spatial memory consolidation, and sleep deprivation induced memory impairment. While GluA3 KO mice showed similar sleep architecture to WT littermates, their spectral power was significantly decreased in the hippocampus during both rapid eye movement sleep (REMs), and non-REMs, while spectral power was conserved in the cortex. Indicating a role for GluA3 in the oscillations during sleep.

CONCLUSIONS

Our findings underscore the potential significance of the GluA3 subunit in sleep-mediated hippocampal memory processing, shedding new light on the complex mechanisms underlying memory consolidation.

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Investigating the Representations of Outcome Controllability in Dopamine and Serotonin Signals in the Ventromedial Striatum

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PHD YEAR
Year 3

POSTER NO.
45

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Serotonin · Dopamine · Decision-Making · Valence · Controllability · Fiber-Photometry

BACKGROUND

Controllability, the degree to which actions can influence outcomes, is central to adaptive decision making and stress resilience. In humans, impaired perception of control is implicated in psychiatric disorders such as depression, obsessive-compulsive disorder, and pathological gambling, suggesting that altered controllability perception has transdiagnostic relevance and may contribute to maladaptive decision making and pathological behavioral patterns. Animal studies have shown that experience with controllable or uncontrollable aversive stimuli can alter later avoidance or escape responses. However, most of this work has focused on aversive controllability alone and often using between-subject designs. It therefore remains unclear whether controllability is represented as a general action-outcome feature across appetitive and aversive contexts, or whether its neural representation depends on outcome valence. The serotonergic and dopaminergic systems are implicated in functions that relate to outcome controllability. Serotonergic signaling is implicated in behavioral inhibition, aversive-outcome controllability, and stress sensitivity. Dopaminergic signaling is involved in reinforcement learning, value encoding, and motivated behavior across valences. The ventromedial striatum (VMS) is particularly interesting for studying controllability across appetitive and aversive outcomes, as it receives both dopaminergic and serotonergic input and integrates information about value, valence, and action.

METHODS

In this study, we developed a behavioral paradigm to compare controllable and uncontrollable conditions for both appetitive and aversive outcomes within the same animal and experimental session. This design includes four trial types: appetitive controllable, appetitive uncontrollable, aversive controllable, and aversive uncontrollable. By comparing these conditions within the same animal and experimental session, the task reduces between-subject and across-session variability, enabling a more direct assessment. We are performing simultaneous fiber-photometry recordings to capture serotonin and dopamine signals in the VMS using a dual-color genetically encoded sensor approach.

RESULTS

Our behavioral results suggest that rats learned the task structure and adjusted their behavior according to trial type. This behavioral paradigm will be combined with fiber photometry recordings to simultaneously monitor VMS serotonin and dopamine using a dual sensor approach already established in our group.

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Learning Where Danger Lies: Observational Fear Learning in Rats

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PHD YEAR: Year 3
POSTER NO.: 48
LOCATION: Zaal 24 Woudvleugel · Thu
KEYWORDS: Observational Learning, Social Fear, Spatial Behavior

BACKGROUND

Learning by observing others can provide animals with information about environmental danger without direct experience. Here, we investigate whether rats use the observed outcome of a conspecific's experience to guide their subsequent spatial behavior.

METHODS

Observer rats were familiarized with an arena containing two compartments in opposing corners. During observation, observers watched a conspecific receive footshocks in one compartment, while another conspecific remained safely in the opposite compartment. Demonstrators were visible through transparent, perforated dividers. Twenty-four hours later, observers were re-exposed to the arena alone. Spatial occupancy and freezing were quantified. A spatial bias score, normalized to total arena occupancy, assessed changes in preference for shock- versus safe-associated regions from baseline to test.

RESULTS

Preliminary data from 12 observers (6 females, 6 males) revealed three profiles based on changes in spatial bias: avoiders, approachers, and ambiguous animals. Most observers spent more time in the safe-associated region during test, whereas some increased occupancy near the shock-associated region and others showed little change. Avoiders displayed more freezing during shock observation than approachers and ambiguous animals. Across animals, greater freezing during observation was associated with stronger subsequent avoidance of the shock-associated region, with this relationship especially strong in males.

CONCLUSIONS

These preliminary findings suggest that rats can use socially acquired information about threat to modify their own spatial behavior. The association between freezing during observation and subsequent avoidance may indicate that arousal elicited by observing threat contributes to encoding socially acquired spatial information. Ongoing experiments will test the robustness of these effects in larger samples.

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Measuring Neuronal Activity in the Medial Orbitofrontal Cortex During Anxiety-Like Behavior in a Mouse Model for OCD

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PHD YEAR: Year 3
POSTER NO.: 4
LOCATION: Foyer ground floor · Thu
KEYWORDS: Obsessive-Compulsive Disorder, Anxiety, Calcium Imaging

BACKGROUND

Mutations in Brwd1 substantially increase risk for obsessive-compulsive disorder (OCD), but how Brwd1 loss alters brain activity and behavior to drive this risk is unknown. The orbitofrontal cortex (OFC) is implicated in compulsivity and reversal learning, yet its role in anxiety encoding—well established in ventral hippocampus (vH), an OFC input region—remains underexplored. We asked whether Brwd1-heterozygous (Brwd1-het) mice show OCD-like anxiety and avoidance, and whether the medial OFC (mOFC) contributes to anxiety coding.

METHODS

We injected a GCaMP7f-expressing virus and implanted a GRIN lens in mOFC of Brwd1-het and wild-type (WT) littermates, then used miniscopes to record mOFC single-cell activity during 10-minute elevated plus maze (EPM) exploration. Behavior was tracked with an overhead camera and Bonsai, and arm entries and head-dips were manually scored. Neural activity was aligned to these behavioral events.

RESULTS

Brwd1-het mice made fewer open-arm entries than WT, indicating increased anxiety consistent with an OCD-like phenotype. In WT mice, mOFC neurons responded to specific EPM compartments, but no consistent preference for open-arm exploration emerged across animals. Instead, subsets of neurons fired differentially during exploration versus safety-seeking despite matched location. Similarly, during head-dipping, activity diverged according to the animal's subsequent choice to continue exploring or retreat to closed arms.

CONCLUSIONS

These findings suggest mOFC does not simply encode anxiety, but instead contributes to arbitrating approach-avoidance decisions during conflict. Ongoing recordings in additional Brwd1-het and WT mice will clarify genotype differences in this circuit, offering insight into mechanisms underlying elevated OCD risk.

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Mice Emit High Frequency Vocalizations Above 100 kHz in Response to Being Tickled

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PHD YEAR: Year 3
POSTER NO.: 29
LOCATION: Zaal 22 + 23 Woudvleugel · Thu
KEYWORDS: Tickling, Social Behaviour, Fragile X Syndrome

BACKGROUND

Social play is a widespread behaviour among juvenile mammals and is important for the development of social skills. One form of social play is tickling, which comprises unpredictable elements of social touch in a safe environment, leading to involuntary laughter-like vocalizations.

METHODS

Tickling animals in the lab resembles relatively naturalistic and freely moving social behaviour while the tickling bouts can be controlled by the experimenter. Rats which are being tickled by an experimenter emit ultrasonic vocalizations (USVs) at 50 kHz, typical for a positive affective state. However, extending such research to mice would open up a greater number of genetic tools to investigate the neuronal mechanisms of social play.

RESULTS

Here we show for the first time that wildtype C57Bl6 mice elicit unique vocalizations in response to being tickled. Furthermore, these tickling-induced USVs are in the ultrahigh frequency range of 100 – 150 kHz and differ from the vocalizations made in a subsequent free interaction test between two mice.

CONCLUSIONS

Fmr1-knockout mice, modelling the neurodevelopmental disorder Fragile-X, also respond to being tickled. We are currently looking into their specific vocalization frequency and repertoire. In preference tests, all mice prefer tickling over access to the hut from their home cage, suggesting that mice are not aversive to tickling, but prefer solitary motor play over tickling. Our results first of all challenge existing views on the sociability and play behaviour of mice, and secondly open up opportunities to use mouse-specific tools to investigate neuronal mechanisms of social play during controlled yet more naturalistic social behaviour.

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Thinking Thalamic

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PHD YEAR
Year 2

POSTER NO.
100

LOCATION
Zaal 24 Woudvleugel · Fri

KEYWORDS
Thalamus · Thalamic Reticular Nucleus (TRN) · Electrophysiology

BACKGROUND

The thalamus is an egg-shaped structure deep in the brain, composed of multiple nuclei and central to cognition. Several of its properties make it an ideal ”waist” for orchestrating brain-wide activity. First, it comprises far fewer neurons than cortex, yet thalamic inputs drive cortical activation far more strongly than cortico-cortical inputs. Second, thalamic neurons integrate inputs from many cortical and subcortical sources, so thalamic activity represents a lower-dimensional, integrated version of those inputs. Coordination across thalamic nuclei may therefore be a computationally efficient way of organising brain activity. The narrowness of the waist also provides a convenient point of action: a hypothesised control system (e.g. TRN and ZI) can exert fine control over the compactly gathered nuclei via inhibitory projections.

METHODS

We investigate the role of the TRN in coordinating activity across thalamic nuclei by optogenetically inducing different rhythms in the TRN of VGAT-ChR2 mice, while simultaneously recording across first-order and higher-order thalamic nuclei (dLGN, VPM, POm, LP) with quad-base Neuropixels probes. Recordings additionally extend to the cortex, allowing us to track the consequences of TRN perturbation throughout the thalamocortical loop.

RESULTS

Data collection is ongoing. This design lets us quantify (i) how distinct TRN perturbations differentially affect FO and HO nuclei, (ii) the degree of cross-nuclei synchronisation induced by each perturbation, and (iii) the propagation of these effects to cortex.

CONCLUSIONS

This approach allows us to test directly whether the TRN acts as a controller of cross-nuclei synchronisation, and thereby to evaluate the thalamus’s proposed function as a ”waist” for coordinating brain-wide activity.

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The Structure of Empathic Lived Experience: An Experimental Phenomenological and Computational Topic Modelling Study

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PHD YEAR
Year 3

POSTER NO.
25

LOCATION
Foyer top floor · Thu

KEYWORDS
Affective Empathy · Social Network · Prosocial Decision-Making

BACKGROUND

Navigating our social world requires the interplay of individual characteristics, like affective and cognitive brain processes - and social environment factors, both of which can influence behavior and relationships. This study explores the relationship between individual differences in affective empathy, prosocial decision-making, and social network positioning over time.

METHODS

We will combine behavioral data, neuroimaging (fMRI), and social network analysis, measuring brain activity and prosocial decision-making in 250 young adults across two experimental tasks while mapping their complete social network. The first task, a naturalistic movie-watching paradigm, captures spontaneous emotional responses (adapted from Jimenez et al., 2020). Using an inter-subject correlation approach, we will assess individual differences and explore links with social network proximity (Parkinson et al. 2018) and centrality. The second task, an adapted social delay discounting task (van de Groep et al. 2023), will estimate parameters reflecting participants' preferences in benefiting themselves, friends, or others, via computational modeling (Yang et al. (in prep)). We will then examine whether these prosocial parameters correlate with social network positioning. Additionally, by combining the two tasks, we aim to determine if spontaneous affective empathy neural responses in the movie task predict prosocial tendencies in decision-making.

RESULTS

We hypothesize a positive correlation between social network proximity, emotional neural response similarity, and prosocial tendencies, with a higher centrality for individuals showing stronger brain activations during the movie and social delay discounting tasks. Moreover, we expect spontaneous affective empathy to predict prosocial decision-making.

CONCLUSIONS

Together, these studies may help in understanding the processes underlying the formation and maintenance of social relationships.

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How Action Representations Support Temporal Inference

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PHD YEAR
Year 3

POSTER NO.
14

LOCATION
Foyer ground floor · Thu

KEYWORDS
Timing Behavior Dopamine

BACKGROUND

Time is commonly represented in reinforcement-learning models through clocks, accumulators, or evolving temporal features. However, animals may also infer temporal position from their own actions. If behavior contributes to timing, a key question is how temporally informative actions emerge during learning.

METHODS

We developed an actor–critic framework in which noisy temporal microstimuli provide one source of information about latent temporal state. The actor does not receive explicit temporal information. Instead, actions are represented in an overlapping motor space, allowing reinforcement of a rewarded action to generalize to similar anticipatory actions.

RESULTS

The framework predicts that reinforcement of a terminal action can lead to the emergence of stereotyped anticipatory behavior without explicitly assigning that behavior a timing function. Once established, these actions can provide coarse information about progression through an interval and complement noisy microstimulus-based timing. Action-driven belief updates can therefore alter expected value and generate temporal-difference errors in the absence of external events or reward.

CONCLUSIONS

This framework links the development of anticipatory behavior with temporal inference using overlapping action representations that explain how timing-relevant actions may emerge. The model provides a potential account of dopamine dynamics that are not explained by temporal representations alone, without requiring an explicit internal clock.

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Temporal Dynamics of ATF3-Expressing Neuronal Ensembles Induced by Fear Conditioning

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PHD YEAR	TALK	WHEN · WHERE	KEYWORDS
Year 4	Session 2B	Thu 16:00–17:30 · Zaal 30	ATF3 · Learning · Memory

BACKGROUND

The encoding of new memories relies on learning-induced activation of sparse neuronal ensembles (engram cells) that undergo time-dependent waves of gene transcription and protein synthesis. They are typically identified by expression of Immediate Early Genes (IEGs), such as c-Fos and Npas4. We previously found that Activating Transcription Factor 3 (ATF3) is robustly upregulated in dentate gyrus (DG) engram cells after learning. However, little is known about its temporal expression profile after a behaviorally-relevant stimulus, and whether it is co-expressed in c-Fos$^+$ and/or Npas4$^+$ ensembles in the DG. To address this, we investigated the profile of ATF3, Npas4 and c-Fos expression in the DG following contextual fear conditioning (CFC).

METHODS

Wild-type mice remained in their home-cage or underwent CFC and were sacrificed at different timepoints after conditioning. Using immunofluorescence, we quantified cells expressing ATF3, Npas4 and c-Fos in the DG and measured the degree of overlap between these populations across multiple timepoints.

RESULTS

In the DG, ATF3 is rapidly and transiently induced by CFC, and comprises a neuronal ensemble that partially overlaps with c-Fos+ and Npas4+ populations. Interestingly, almost 50% of the ATF3$^+$ population did not co-express Npas4 or c-Fos. In contrast, of the Npas4$^+$ and of the c-Fos$^+$ populations, a large majority (~80%) also expressed ATF3 after CFC.

CONCLUSIONS

Our data indicate that, in addition to representing well-established DG subengrams, ATF3 is uniquely expressed in a distinct sparse ensemble, potentially pointing to a novel subengram within the DG.

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03

THEME

Development

Axon and Dendrite Development and synaptogenesis p. 71

Development of Motor, Sensory and Limbic Systems p. 75

Elucidating the Role of Shank2 in Neuronal Development

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PHD YEAR
Year 3

POSTER NO.
47

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Neuronal Development
Polarity

BACKGROUND

Shank proteins are core scaffolding molecules of the postsynaptic density (PSD) of excitatory synapses. They are large proteins that contain multiple domains which allow them to link glutamatergic receptors to the actin cytoskeleton. In mature synapses, Shanks interact with actin via Cortactin to dynamically regulate synapse morphology and function. Mutations in Shank genes are known risk factors for various neurodevelopmental disorders, like autism spectrum disorder. While previous research has primarily focused on the role of Shanks in mature synapses, their role in early development remains elusive. Shank2 is the earliest Shank isoform to be expressed during neuronal development and its subcellular distribution changes as neurons mature, from the nascent growth cones to the cytoplasm and the growing neurites to finally localize at the PSD. Here, we hypothesized that Shank2 is involved in early polarization processes in neurons.

METHODS

To address this hypothesis, we used primary rodent cultures to study the role of Shank2 during the early stages of neuronal development.

RESULTS

shRNA-mediated knockdown (KD) of Shank2 in immature neurons led to defects in cytoskeletal organization. TRIM46, a microtubule-associated protein that exclusively localizes at the axon initial segment in control neurons, was found in several dendrites upon Shank2 silencing, revealing an alteration of neuronal polarity. As TRIM46 associates with parallel microtubules, we next investigated the orientation of microtubules in Shank2 KD neurons. Unlike control neurons, where dendrites have a mixed orientation, in the absence of Shank2, minor neurites acquired a parallel organization, as found in the axon. This finding suggests that Shank2 KD alters the organization of the microtubule network in developing neurons. These defects were associated with an impaired localization of the KIF5 motor, which was abnormally accumulated at the tip of dendrites.

CONCLUSIONS

From these results, we hypothesize that the polarity defects in Shank2 KD neurons could disrupt the distribution of axonal and somatodendritic proteins, thereby participating in impaired synaptic function in mature neurons. This work will provide valuable insights into the potential role of Shank2 in instructing early neuronal polarization processes, thereby advancing our understanding of the pathogenesis of Shank-related neurodevelopmental disorders.

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Fueling Cortical Development: Linking Neuronal Activity and Metabolism in Health and Disease

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PHD YEAR: Year 2
POSTER NO.: 53
LOCATION: Zaal 25 Woudvleugel · Thu
KEYWORDS: Energy Metabolism, Neuronal Activity, FLIM

BACKGROUND

Developing neural circuits requires energy for neuronal activity, synapse formation, and circuit refinement. Mitochondrial dysfunction can therefore have major consequences for brain development. Leigh syndrome is a severe mitochondrial neurodevelopmental disorder frequently associated with impaired complex I function. We aim to determine how neuronal activity and energy metabolism are coupled during cortical development and how this relationship changes with mitochondrial dysfunction.

METHODS

We combine two-photon fluorescence lifetime imaging microscopy (FLIM) of endogenous NAD(P)H and FAD with calcium imaging in acute and organotypic mouse visual-cortex slices. Pharmacological manipulation of mitochondrial respiration (rotenone, FCCP), glycolysis (2-deoxy-D-glucose), and substrate availability (pyruvate, lactate) is used to characterize metabolic responses in neurons and astrocytes. Ongoing experiments use conditional Ndufs4 knockout mice to compare complex I-deficient and control tissue.

RESULTS

Mitochondrial inhibition (rotenone) and uncoupling (FCCP) produced consistent increases in FAD mean arrival time in neurons, with larger rotenone-induced changes after longer exposure. NAD(P)H responses to substrate manipulation differed markedly between neurons and astrocytes, sometimes in opposite directions. In addition, metabolic responses varied within individual cells and between cells.

CONCLUSIONS

These results establish a framework for measuring metabolism during cortical development. We are extending this approach to simultaneous calcium imaging and FLIM to study activity–metabolism coupling in healthy and Ndufs4-deficient developing circuits.

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Mind the VAP: How Endoplasmic Reticulum Contact Sites Regulate Axonal mRNA Localization.

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PHD YEAR: Year 2
POSTER NO.: 32
LOCATION: Zaal 22 + 23 Woudvleugel · Thu
KEYWORDS: ER, Axon, mRNA Localization

BACKGROUND

The neuronal proteome must quickly adapt to internal and external changes to ensure a proper neuronal function. This process is more complex in subcellular compartments due to the large distance between the soma and neuronal projections, such as the axon. Therefore, neurons transport, store, and translate mRNAs at exact locations and times to achieve rapid changes to the subcellular proteome. Although we know that the location of mRNA and its local translation are required for neuronal development and maintenance, the molecular mechanisms by which neurons control these processes, especially in axons, are unknown. Recent research indicates that organelles play an important role in mRNA localization. mRNAs can be transported on endolysosomes and mitochondria via a process termed hitchhiking. In addition, we previously found that the axonal endoplasmic reticulum (ER) can be a key player orchestrating local translation by interacting with ribosomes and mRNA. However, it is unclear how ER cooperates with other organelles to regulate mRNA localization and translation in axons.

RESULTS

We demonstrate that VAP proteins might facilitate RNA granules transport into the axon in primary neuronal cultures. By modifying VAP-mediated interactions (increasing, decreasing or inhibiting the binding), we observed, through high-resolution microscopy, that the abundance of RNA granules decreases. Currently, we are exploring the mechanisms behind this decrease, investigating whether defective RNA granule transport occurs due to an impairment in organelle-mRNA hitchhiking

CONCLUSIONS

Together, our work highlights an important role for the ER in regulating subcellular mRNA axonal localization.

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The Neuronal ER Proximity Proteome and Its Role in Local Translation

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PHD YEAR
Year 4

TALK
Session 3C

WHEN · WHERE
Fri 11:00–12:30 · Zaal 15

KEYWORDS
Local Translation | Endoplasmic Reticulum (ER) | Proximity-Based Proteomics

BACKGROUND

Proper neuronal function requires precise spatiotemporal control of the proteome in response to local demands, including in the most distal regions of the neuronal dendrites and axons. To achieve this, neurons rely on the transport, storage, and local translation of mRNAs. Although we now know that these processes are essential for neuronal health, development, and plasticity, our knowledge of the underlying molecular mechanisms remains limited. Specifically, we do not understand how the exact localization of mRNAs is coordinated within the neuron and how their selective translation is achieved with high spatiotemporal precision. We recently discovered that the endoplasmic reticulum (ER) may be a key player in these processes.

METHODS

Here, we have started to investigate the role of the ER in governing mRNA transport and subcellular translation. Specifically, we have mapped the ER proximity proteome in neurons using proximity-labeling proteomics.

RESULTS

This revealed not only novel ER-proximal proteins but also translation-dependent contacts with the ER. Among these, we further investigated the RNA-binding protein LARP6 as a potential ER-associated regulator of neuronal mRNA translation.

CONCLUSIONS

Together, our work highlights an important role for the ER in regulating subcellular mRNA localization and translation in neurons.

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Complementary Roles of External Sensory Input and Intrinsic Mechanisms in the Development of an Innate Reflex

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PHD YEAR
Year 3

POSTER NO.
5

LOCATION
Foyer ground floor · Thu

KEYWORDS
Cerebellar Development · Visual Deprivation · Purkinje Cell Intrinsic Activity

BACKGROUND

Innate reflex development is driven by genetically programmed mechanisms, through both cortical and subcortical structures, as well as sensory experience. Here, we investigate how visual input and different brain regions are together required to set up innate compensatory eye movements (CEMs) including the optokinetic reflex (OKR) and the vestibulo-ocular reflex (VOR).

METHODS

C57BL/6 mice were reared under a standard light and dark cycle or complete darkness, with CEMs assessed at multiple postnatal ages. Brain-wide neuronal networks activated during CEMs were mapped, using targeted recombination in active populations (TRAP2) mice. Bilateral primary visual cortex (V1) lesions were performed at P12 (before eye opening) and in adulthood to determine the contribution of V1 to CEM development. Purkinje cell (PC)-specific Kir2.1 mouse model were used to assess the interaction between PC intrinsic activity and visual input.

RESULTS

1. The OKR matures earlier in postnatal development than the VOR.
2. Visual deprivation increases OKR and reduces VOR eye movement amplitude.
3. CEM behavioral tasks engage a broad, distributed brain network.
4. V1 lesions at P12 produce a generalized but small CEM deficit (reduced OKR and VOR).
5. Silencing cerebellar PCs has the inverse effect of dark rearing, abolishing its effect when combined.

CONCLUSIONS

CEM development requires coordinated function of cortical and subcortical structures, together with appropriate visual input. While the absence of V1 has minimal impact on CEMs and CEM maturation, the presence of visual input and the activity of the cerebellar cortex have opposite roles.

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The Effect of in utero Exposure to THC on the Development of Midbrain Dopaminergic Neurons

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PHD YEAR: Year 2
POSTER NO.: 24
LOCATION: Foyer top floor · Thu
KEYWORDS: Neurodevelopment, Cannabis, Development, Dopamine, Rodent

Cannabis use during pregnancy has increased drastically over the past years, coinciding with increased legalization and a substantial rise in the Δ9-tetrahydrocannabinol (THC). THC readily crosses the placenta into the fetal brain where it can disrupt the finely tuned actions of the endocannabinoid system which plays a crucial role in neurodevelopment. Given that many behavioural outcomes following prenatal cannabis exposure are associated with dopamine dysfunction, this system appears particularly vulnerable. However, the mechanisms through which prenatal THC exposure alters brain development, remains unclear. This study aims to investigate how THC affects the development of midbrain dopamine neurons. Pregnant dams were exposed to THC or vehicle via intraperitoneal injection during gestation, and embryos were isolated at embryonic day 14.5. RNA sequencing was performed on midbrain dopamine neurons isolated by FACS-sorting using the Pitx3-GFP reporter allele. In addition, the expression profile of cannabinoid receptor 1 (CBR1) was assessed in tyrosine hydroxylase (TH) expressing neurons. This study provides valuable insight into how prenatal THC exposure affects the development of mdDA neurons. Our transcriptome analysis will aid in identifying affected pathways, laying the groundwork for future studies. This study is the first in a series of studies on the short- and long-term consequences of prenatal THC exposure, aiming to map developmental trajectories and vulnerabilities. Collectively, we strive to clarify the risks associated with cannabis use during pregnancy and further elucidate the role of the endocannabinoid system in neurodevelopment.

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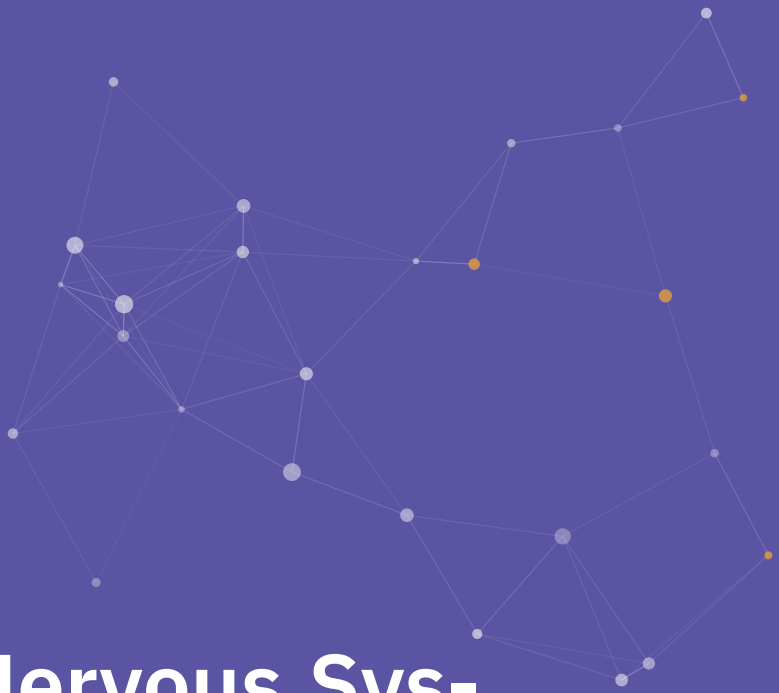

04

THEME

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G-Protein Coupled Receptor 5-B at Astrocyte Endfeet: Novel Regulator of Brain Fluid Homeostasis in MLC

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PHD YEAR
Year 2

POSTER NO.
69

LOCATION
Foyer ground floor · Fri

KEYWORDS
Astrocytes · Leukodystrophy · G-Protein-Coupled Receptors

BACKGROUND

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a genetic white matter disorder marked by white matter edema. Patients develop macrocephaly in the first year of life. Clinical symptoms include motor dysfunction, epilepsy, and mild cognitive decline. There is no curative treatment. Most cases are caused by pathogenic variants in MLC1 or GLIALCAM, encoding astrocytic endfoot membrane proteins that regulate ion and water homeostasis. Recently, patients without variants in MLC1 or GLIALCAM were found to carry heterozygous variants in GPRC5B, which interacts with GlialCAM and MLC1. Since GPCRs are excellent drug targets, identifying one in MLC could aid therapy development.

METHODS

A mouse model was generated based on a patient GPRC5B variant. These mice are heterozygous for an amino acid duplication observed in two MLC patients (p.Ile176dup). The sequence of the 4th transmembrane segment of the receptor with this duplication is largely conserved between human and mouse. In addition, transgenic mice with a brain specific knockout of Gprc5b (Gprc5bflox/floxxNestin-Cre) were generated to compare the phenotype of carrying the patient variant to a full loss of this receptor.

RESULTS

Preliminary data reveal that these mice exhibit an MLC-like phenotype, with increased brain water content and mild motor impairment. Furthermore, the localization of MLC1 to astrocyte endfeet is preserved, suggesting that the mutation does not disrupt the full MLC1-GlialCAM-GPRC5B complex, but may disrupt local signaling.

CONCLUSIONS

Characterization of these novel MLC mice will yield important insight into the role of GPRC5B and help provide a model to test future GPRC5B-based therapies

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A Scoping Review of Artificial Intelligence in Speech and Language Analysis for Frontotemporal Dementia

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PHD YEAR
Year 3

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40

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Frontotemporal Dementia · Artificial Intelligence · Speech · Language · Digital Markers

Speech and language impairments are core features of frontotemporal dementia (FTD), yet traditional clinical assessments are insensitive to early change, time-intensive, and prone to rater subjectivity. AI-powered digital speech analysis offers a scalable alternative, though its clinical readiness for FTD diagnosis remains unevaluated. This scoping review examines which digital speech and language features aid FTD detection and how they contribute to diagnostic accuracy and clinical applicability. Across 28 included studies, acoustic features (fundamental frequency, pause dynamics, articulation rate) and linguistic features (syntactic complexity, lexical diversity) most consistently distinguished FTD from healthy controls, with AI classifiers showing high to excellent performance. However, only three studies (11%) used explainability frameworks — a critical gap, since without it clinicians cannot identify which markers drove diagnoses, audit errors, or align results with known FTD neurolinguistic profiles. External validation and longitudinal evidence remain similarly sparse. Large-scale, explainability-focused validation is needed to establish trustworthy AI-based speech biomarkers.

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AAV-Mediated Gene Therapy for Vanishing White Matter

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PHD YEAR
Year 2

POSTER NO.
78

LOCATION
Foyer ground floor · Fri

KEYWORDS
Vanishing White Matter · Leukodystrophy · Gene Therapy

BACKGROUND

Vanishing white matter (VWM) is a rare autosomal recessive leukodystrophy characterized by chronic neurological deterioration and stress-induced episodes of rapid decline. It is caused by pathogenic variants in any of the five genes encoding eukaryotic translation initiation factor 2B (eIF2B) subunits, impairing eIF2B function and dysregulation the integrated stress response (ISR). Although pharmacological ISR modulation has shown beneficial effects, gene therapy targets the underlying genetic defect. Previous studies demonstrated therapeutic benefits of AAV-mediated EIF2B5 gene augmentation in presymptomatic VWM mice. Here, we investigate its therapeutic potential in symptomatic mice.

METHODS

AAV9-CBh-EIF2B5 and AAV9-CBh-GFP vectors were produced in suspension HEK293T/17 cells and purified by polyethylene glycol precipitation and iodixanol gradient centrifugation. Viral titers were determined by quantitative PCR, and vector functionality was assessed by Western blot in transduced Neuro-2a cells. Eif2b5R^{191}H mutant mice, a model of VWM, were longitudinally characterized to determine disease onset through body-weight monitoring and neurological assessment using a composite ataxia score (CAS). Following disease onset, 4×10^{11} vg of AAV9-CBh-GFP was administered by unilateral or bilateral intracerebroventricular (ICV) injection. Vector biodistribution was subsequently assessed by GFP immunohistochemistry 3 weeks post-injection.

RESULTS

AAV9-CBh-EIF2B5 yielded titers of 1×10^{13}–1×10^{14} vg/mL, with eIF2Bε expression confirmed by Western blot. Symptomatic VWM mice were classified from 7 months of age based on gait and ledge test deficits (CAS >0). Unilateral ICV administration achieved bilateral transduction, supporting its potential for widespread brain delivery.

CONCLUSIONS

These findings support unilateral ICV administration of AAV9-EIF2B5 to evaluate therapeutic efficacy and safety in symptomatic VWM mice, advancing preclinical gene therapy development.

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Altered Age-Dependent Somatic Mutational Trajectories in ALS Motor Cortex Neurons

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PHD YEAR
Year 4

TALK
Session 4A

WHEN · WHERE
Fri 13:50–15:20 · Zaal 30

KEYWORDS
Somatic Mutation · Aging · Amyotrophic Lateral Sclerosis

BACKGROUND

Amyotrophic lateral sclerosis (ALS) is a lethal neurodegenerative disease characterized by progressive degeneration of motor neurons in the spinal cord and motor cortex. Although inherited genetic variants contribute to ALS risk, most cases are sporadic and arise in late adulthood, suggesting that age-associated and environmental processes may also contribute to disease onset and progression. Somatic mutations accumulate throughout life and may provide a cumulative molecular record of aging- and exposure-associated processes acting on neuronal genomes.

METHODS

Single-cell DNA sequencing studies have reported increased neuronal somatic mutation burden in neurodegenerative diseases, but these analyses have been limited by the numbers of donors and neurons profiled. To investigate neuronal somatic mutational patterns at larger scale, we harmonized three publicly available 10X single-nucleus datasets from ALS and control motor cortex, comprising 118 donors and 885,929 cells. Raw sequencing data were uniformly processed, and somatic single-nucleotide variants were identified using SComatic. Because 10X sequencing interrogates a restricted mutation-detectable genomic window, we benchmarked variant detection using SomatoSim simulations and interpreted downstream burden analyses within this effective callable space.

RESULTS

Our 10X-derived variant calls recapitulated established features of neuronal somatic mutagenesis. Neurons exhibited the highest detectable somatic mutation burden among major brain cell types, control neurons showed an age-associated increase in mutation burden, and mutational signature analysis recovered SBS5, a clock-like signature associated with age-related somatic mutation accumulation. Within the 10X-detectable genomic window, ALS and control neurons exhibited distinct age-dependent mutational trajectories. Rather than a uniform increase in somatic mutation burden in ALS, the difference between ALS and control neurons varied with age, indicating a reshaping of neuronal somatic mutation accumulation across the lifespan. Signature-specific analyses further identified SBS5 as the major mutational component underlying the observed age-by-diagnosis interaction.

CONCLUSIONS

These findings suggest that ALS is associated with an altered age-dependent trajectory of somatic mutagenesis in motor cortex neurons, rather than a uniform increase in neuronal somatic mutation burden. More broadly, our study demonstrates the utility of existing large-scale single-cell datasets as a complementary framework for cohort-scale investigation of neuronal somatic mutagenesis across aging and neurodegeneration. Lastly, our results suggest that more studies are needed one the role of somatic mutations not only in upper motor neurons

but also lower motor neurons.

APOE as a Regulator of Lysosomes in iAstrocytes

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PHD YEAR
Year 3

POSTER NO.
86

LOCATION
Zaal 22 + 23 Woudvleugel · Fri

KEYWORDS
APOE · Multi-Omics · Lysosomes

BACKGROUND

Apolipoprotein E(APOE) is the strongest genetic risk factor for sporadic Alzheimer's disease(sAD). While APOE is primarily known as a secreted lipid carrier, recent evidence suggests additional intracellular functions. Moreover, protective and pathogenic APOE variants influence diverse cellular pathways, underscoring the need to investigate its global effects on cellular homeostasis.

METHODS

To uncover these functions, we performed transcriptomics, proteomics, and lipidomics on APOE knock-out(KO) human iPSC-derived astrocytes(iAs) and compared them with isogenic protective(APOE2), neutral(APOE3), and pathogenic(APOE4) variants associated with AD risk.

RESULTS

APOE loss consistently upregulated lysosomal pathways in both RNA-seq and proteomics datasets across comparison of KO with any of the APOE variants. Cathepsins were among the top upregulated proteins, whereas lysosomal abundance(assessed using LAMP1 and LAMP2), increased only modestly. Other lysosomal proteins like NPC1, PSAP,and SMPD1 were also elevated, suggesting enhanced lysosomal activity rather than lysosomal biogenesis alone. APOE KO lysosomes remained acidic and functional, as evaluated by mature cathepsin-B(CTSB) levels. Moreover, increased CTSB expression was rescued by APOE supplementation from APOE3 iAs in an indirect co-culture system. Lipidomics further revealed accumulation of storage lipids, in accordance with APOE's secretory role. Interestingly, sphingomyelins were reduced and ceramides were increased, consistent with increased SMPD1 and PSAP expression.

CONCLUSIONS

These findings reveal a direct role for APOE as a regulator of lysosomal machinery, potentially explaining beneficial effects of APOE reduction in resolving Alzheimer's disease pathology. Future experiments will determine the precise mechanisms by which APOE regulates lysosomal activity.

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Blood-Derived EV-miRNAs as Candidate Molecular Links for Long COVID-Associated Neurodegeneration

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PHD YEAR
Year 3

POSTER NO.
31

LOCATION
Zaal 22 + 23 Woudvleugel · Thu

KEYWORDS
Long COVID · Neurodegeneration · EV-miRNA

BACKGROUND

Viral infections have been linked to increased neurodegenerative disease risk and lasting neuroimmune disruption. Long COVID is a relevant model, as persistent neurological symptoms can overlap with features of Alzheimer's and Parkinson's disease. Its heterogeneity and overlap with ME/CFS complicate distinction of shared from condition-specific post-viral changes. Extracellular vesicles carry regulatory miRNAs capable of influencing multiple upstream molecular pathways and can cross the blood–brain barrier; blood-derived EV-miRNAs may therefore provide a minimally invasive window into CNS-related changes. We aimed to evaluate their potential as indicators of post-viral neurological heterogeneity by defining profiles associated with neurological outcomes in long COVID, comparing shared and distinct patterns with ME/CFS, and determining how age, viral variant and time since infection influence their interpretation.

METHODS

Seven plasma EV-miRNAs were prioritised : five shared between acute COVID-19 and Alzheimer's or Parkinson's disease in published studies, and two dysregulated three months after SARS-CoV-2 Delta infection in macaques. EVs were isolated by size-exclusion chromatography from plasma of individuals with long COVID, ME/CFS and healthy controls; EV-miRNAs were quantified by RT-qPCR. PCA integrated neurological symptom severity scores and EV-miRNA expression. Further, linear regression assessed clinical-group, age and sex effects. To provide temporal and variant context, the same panel was profiled from pre-infection to 12 months after Omicron and delta infection in macaques.

RESULTS

PCA separated controls from both patient groups, while long COVID and ME/CFS partially overlapped. PC1 explained 38.9% of variance, with neurological symptom severity and EV-miRNAs contributing in opposing directions. Selected EV-miRNAs showed age-associated variation within long COVID. Macaque trajectories were dynamic, non-linear and individual-specific across post-infection timepoints.

CONCLUSIONS

Neurological long COVID was associated with altered blood-derived EV-miRNA profiles, with partial overlap in ME/CFS. Variation by age and time since infection highlights the need to interpret EV-miRNA biomarkers within comprehensive clinical and temporal profiles.

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Cell-Type-Specific Effects of γ-Secretase Inhibition on Cholesterol Metabolism in Neural Cells

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PHD YEAR
Year 4

TALK
Session 4A

WHEN · WHERE
Fri 13:50–15:20 · Zaal 30

KEYWORDS
Alzheimer's Disease · Gamma-Secretase · Cholesterol Metabolism

BACKGROUND

Alzheimer's disease (AD) is characterized by alterations in lipid metabolism, particularly cholesterol homeostasis. Gamma-secretase, an enzyme involved in amyloid-beta (Aβ) generation, has recently been implicated in cholesterol metabolism in neurons. However, whether this function is neuron-specific or extends to other neural cell types remains unclear. Here, we investigated the role of gamma-secretase activity in cholesterol metabolism in neurons, astrocytes, and oligodendrocytes.

METHODS

Cell maturity was assessed by qPCR and immunocytochemistry of cell type-specific markers. Secreted Aβ and APOE were measured by ELISA. Cholesterol levels were assessed using a cholesterol assay, cholesterol biosynthesis enzyme expression by qPCR, and lipid droplets by BODIPY staining.

RESULTS

γ-secretase inhibition (GSI) reduced secreted Aβ and Notch activity in neurons, astrocytes, and oligodendrocytes. GSI increased expression of cholesterol biosynthesis enzymes in neurons and oligodendrocytes, but not astrocytes. Free cholesterol levels remained unchanged, whereas cholesteryl ester (CE) levels were altered in neurons and oligodendrocytes. In oligodendrocytes, GSI also promoted maturation, characterized by increased expression of oligodendrocyte markers and MBP-positive cell area. Direct Notch inhibition similarly increased cholesterol biosynthesis and CE levels in neurons and oligodendrocytes.

CONCLUSIONS

γ-secretase inhibition affects cholesterol metabolism in a cell-type-specific manner, with responses observed in neurons and oligodendrocytes but not astrocytes. The similar effects of gamma-secretase and Notch inhibition are consistent with Notch signaling contributing to this response. In oligodendrocytes, changes in cholesterol metabolism occur alongside increased maturation and cell area, suggesting an association with the increased membrane demands accompanying maturation.

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Ceramide Levels Elucidated in Astrocyte Reactivity during Alzheimer's Disease

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PHD YEAR
Year 3

POSTER NO.
119

LOCATION
Zaal 25 Woudvleugel · Fri

KEYWORDS
Alzheimer Disease's
Inflammation
Lipid Mediators

Alzheimer's disease (AD) is a fatal neurodegenerative disease with no effective treatment. Accumulating evidence suggests that reactive astrogliosis occurs early during AD progression and precedes amyloid beta and tau accumulation, providing a window for early intervention. Previous studies have demonstrated an important role for bioactive sphingolipids, particularly ceramides, in astrocyte reactivity during AD. Ceramides are considered key molecules in the complex sphingolipid biology. They can either contribute to inflammation and cell death or promote pro-survival signalling, depending on their chain-length. Our previous work has indicated that specifically reactive astrocytes are important producers of pro-apoptotic ceramides in the context of AD. However, the regulation of distinct ceramide species and their biosynthetic enzymes in astrocytes during neuroinflammation remains poorly understood. In this study, we aim to investigate how astrocytes regulate distinct ceramide species and whether restoring ceramide homeostasis can reduce astrogliosis. .

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Changes in Tau Alter Lipid Metabolism in Neurons

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PHD YEAR
Year 3

POSTER NO.
115

LOCATION
Zaal 25 Woudvleugel · Fri

KEYWORDS
Tau Lipid Peroxidation

BACKGROUND

Altered lipid metabolism has been implicated in many neurodegenerative diseases. However, the role lipids play in primary tauopathies is still unclear. Tau has previously been associated with mitochondrial dysfunction and increased ROS levels in neurons, which are known to alter lipid metabolism and can lead to lipid peroxidation. Therefore, we aim to assess how MAPT mutations alter lipid metabolism in neurons and how this may contribute to disease progression.

METHODS

An isogenic CRISPR-edited set of the Kolf2.1j iPSC line and isogenic sets of iPSCs from patients with the R406W MAPT mutation were differentiated to NGN2 neurons. A characterization of both tau and lipid profiles was performed on these neurons through Western blotting and liquid chromatography – mass spectrometry. Additional biochemical assays were performed for further analyses.

RESULTS

Neurons with the R406W mutation show no differences in total tau or phosphorylated tau levels when compared to controls. However, mutant neurons display increased levels of tau species that are 48kDa in molecular weight. This is the same molecular weight as hypo-phosphorylated tau, as evidenced by phosphatase treatment of these same lysates. Furthermore, although there are no robust changes in lipid abundance at class level between mutant neurons and controls, neurons homozygous for the R406W mutation contain lower levels of polyunsaturated fatty acid (PUFA) – containing phospholipids.

CONCLUSIONS

R406W mutant neurons show increased levels of 48kDa tau which might point towards an increase in hypo-phosphorylated tau. Additionally, the decrease in PUFA-containing phospholipids that we observe may indicate increased lipid peroxidation, consistent with increased mitochondrial dysfunction.

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Characterising Ubiquitin-Dependent Regulators of Mutant Huntingtin to Restore Its Degradation

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PHD YEAR
Year 2

POSTER NO.
62

LOCATION
Foyer ground floor · Fri

KEYWORDS
Huntington's Disease (HD)
High Throughput Screening Platform
Protein Degradation

BACKGROUND

Huntington's disease (HD) is a neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin (HTT) gene. The resulting mutant huntingtin (mHTT) protein contains an expanded polyglutamine (polyQ) tract prone for aggregation. Although aberrant proteins are normally targeted for proteasomal degradation or autophagy, mHTT escapes efficient degradation and forms insoluble intracellular aggregates overtime. Here, we focus on improving the selective degradation of mHTT prior aggregation as a novel therapeutic strategy to prevent or delay the onset of disease.

METHODS

A screening platform was developed using our dox-inducible HTTexon1 cell line paired with automated inclusion detection in combination with siRNA knockdowns. Downstream assays such as Western Blot, Filtertrap, CRISPRi/a allow us to differentiate the effects on soluble versus insoluble mHTT species, define specificity and determine the mechanism of action.

RESULTS

56 ubiquitin-dependent enzymes were previously identified form an IP with mHTTexon1. With these an siRNA screen was done using our mHTT modulating screening platform. Downstream this pipeline, two strong hits remained that both significantly reduce HTexon1Q97 levels: Arih1 and Kcmf1.

CONCLUSIONS

These two proteins are currently under further investigation for their mechanism of action. Additionally, new techniques are added to the pipeline to improve the discovery of selective mHTT modulators.

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Deep Brain Stimulation Mechanisms in Parkinson's Disease Using in vivo Optical Voltage Imaging

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PHD YEAR: Year 3
POSTER NO.: 3
LOCATION: Foyer ground floor · Thu
KEYWORDS: Voltage Imaging, Deep Brain Stimulation, Parkinson's Disease

BACKGROUND

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by debilitating motor impairments that affect millions of people worldwide. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for alleviating motor symptoms in advanced PD. However, despite its widespread clinical use, the neuronal mechanisms underlying its therapeutic effects remain incompletely understood, partly due to stimulation artifacts that hinder direct electrophysiological recordings during DBS.

METHODS

To overcome these limitations, we combined bilateral high-speed fiber photometry with soma-targeted genetically encoded voltage indicators (GEVIs) in awake, behaving healthy and PD mice. This approach enabled artifact-free, millisecond-resolution recordings of population-level membrane voltage dynamics during STN-DBS, allowing us to directly examine how stimulation modulates neuronal activity within and beyond the stimulated nucleus.

RESULTS

STN-DBS induced a rapid, frequency-dependent transient depolarization of STN neurons, followed by 1:1 entrainment to the applied stimulation pattern. These responses were spatially restricted, as neither transient depolarization nor high-frequency entrainment was observed in the contralateral STN or the adjacent zona incerta. The observed membrane voltage dynamics demonstrate that DBS directly drives neuronal activity within the stimulated STN rather than producing widespread or bilateral activation.

CONCLUSIONS

Our findings provide direct evidence that STN-DBS elicits transient local membrane depolarization and frequency-dependent neuronal entrainment without causing somatic inhibition. These results offer new mechanistic insight into the cellular actions of STN-DBS and establish optical voltage imaging as a powerful tool for investigating DBS mechanisms, supporting the development of more targeted stimulation strategies for Parkinson's disease.

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Expanding the Clinical Spectrum of TDP-43/ANXA11 Co-Pathology in FTLD-TDP

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PHD YEAR
Year 2

POSTER NO.
71

LOCATION
Foyer ground floor · Fri

KEYWORDS
FTLD ANXA11 TDP-43

BACKGROUND

TDP-43/ANXA11 co-pathology (TAP) is a novel pathological entity within the frontotemporal lobar degeneration (FTLD)-spectrum, characterized by co-aggregation of annexin A11 (ANXA11) with TDP-43. To date, TAP has primarily been associated with language (svPPA) and motor (PLS/ALS) clinical presentations in sporadic FTLD-TDP. However, its prevalence and clinical presentations in Dutch FTLD-TDP donors remain unclear.

METHODS

To investigate the relationship between TAP and clinical phenotype, we examined a post-mortem cohort of donors with FTLD-TDP pathology (n=68) from the Netherlands Brain Bank. Cases were neuropathologically classified according to established FTLD-TDP criteria, and immunohistochemistry was performed to assess ANXA11 pathology alongside TDP-43 inclusions. Clinical records were reviewed to correlate pathological findings with clinical presentation.

RESULTS

Consistent with previous studies, all FTLD-TDP type C donors (12/12) showed TAP. TAP was also identified in a subset of type A (2/19), type B (5/19), FTLD-MND (1/4), and ALS (2/4) donors. In contrast to earlier reports linking TAP predominantly to PPA and motor phenotypes, several TAP-positive cases presented with prominent behavioural symptoms, including apathy, disinhibition, and compulsive behaviours, with some fulfilling clinical criteria for behavioural variant FTD (bvFTD). In addition, multiple TAP-positive donors exhibited prosopagnosia, a hallmark feature of right temporal variant FTD (rtvFTD).

CONCLUSIONS

These findings expand the clinical spectrum associated with TAP in FTLD-TDP and suggest that TAP-related pathology is linked to a broader range of clinical phenotypes than previously recognized. Further studies are needed to better define these clinicopathological associations.

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Harnessing Exercise to Amend Neuroinflammation in AD

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PHD YEAR
Year 3

POSTER NO.
19

LOCATION
Foyer ground floor · Thu

KEYWORDS
Alzheimer · Microglia · iPSC · Physical Exercise

BACKGROUND

AD cannot be prevented or cured. Physical exercise improves memory, delays age-related cognitive decline, reduces dementia risk and neuroinflammation. Microglia are central to the regulation of brain inflammation and their altered activation is an AD hallmark, rendering them an obvious target for intervention. However, microglia are highly heterogeneous and probing their complexity in human-relevant AD systems has been challenging. Exercise modulates microglial activation and cognition in healthy and AD mouse brain. Yet, the mechanisms via which exercise impacts human microglial states are unknown. We hypothesize that running-induced, blood-derived factors modulate microglial activation equilibrium in AD via distinct mechanisms, the targeting of which can relay the effects of exercise, reduce neuroinflammation and modulate AD.

METHODS

We employ induced pluripotent stem cell (iPSC)-derived microglia (iMics) generated from individuals with sporadic Alzheimer's disease (sAD) and age-matched healthy controls. The iMics are exposed to blood serum collected from sedentary and physically active individuals to investigate the effects of systemic exercise-associated factors on microglial function. Comprehensive multidimensional phenotyping is performed, including transcriptomic profiling, phagocytosis assays, inflammatory gene expression analysis, secretome characterization, and serum proteomics. Finally, multi-omics data integration will be used to identify molecular pathways and circulating factors that mediate exercise-induced modulation of microglial phenotypes and their relevance to sporadic Alzheimer's disease.

RESULTS

iMics from sAD patients display differential transcriptomic profiles. iMics respond to serum in a dose-dependent manner, with microglial activation state remaining unchanged within a specific concentration range. Exercise serum partially reverts disease-dysregulated transcriptomic signatures.

CONCLUSIONS

We established and profiled a human-relevant model consisting of iMics derived from sAD patients, which displays AD-specific transcriptomic and functional signatures. Moreover, we obtained preliminary readouts from our novel iMic serum assay. This model can be used for studying the impact of lifestyle interventions on AD.

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Increased Functional Connectivity Is Associated with Future Amyoid Aggregation in Cognitively Normal Older Individuals

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PHD YEAR
Year 3

POSTER NO.
79

LOCATION
Foyer ground floor · Fri

KEYWORDS
Amyloid | Functional Connectivity | Proteomics

BACKGROUND

Cross-sectional studies suggest increased functional connectivity (FC) in the posterior default mode network (pDMN) may precede amyloid-β (Aβ) accumulation. We investigated whether FC predicts longitudinal Aβ decline and used CSF proteomics to study molecular processes underlying FC changes, using a monozygotic twin staging approach.

METHODS

We included 104 cognitively normal older twins from the Twin60++ cohort with resting-state fMRI and CSF proteomics, a subset with longitudinal CSF Aβ42/Aβ40 measurements (Aβ-abnormality as Aβ42/40<0.071). pDMN FC was defined as the number of functional connections between the precuneus/posterior cingulate to other brain regions. We compared FC across defined disease stages: 0 (concordant Aβ–), 1 (Aβ– of discordant pair, i.e. pre-amyloid), 2 (Aβ+ of discordant pair), and 3 (concordant Aβ+). Longitudinal mixed models tested whether FC predicted Aβ decline and generalized estimating equations tested which proteins related to pDMN FC.

RESULTS

pDMN FC increased from stage 0 to pre-amyloid stage 1, then decreased through stages 2 and 3. Higher FC predicted subsequent steeper decline in CSF Aβ42 levels in Aβ- individuals (β=-13.52,SE=5.26,p=0.0124). In stages 0-1, higher levels of 40 proteins enriched for neuronal development were associated with higher FC. In stages 1-3, reduced FC was associated with lower levels of 170 proteins enriched for synaptic plasticity and glucose metabolism.

CONCLUSIONS

We found that pDMN FC increases before Aβ becomes abnormal, which predicted subsequent Aβ42 decline. FC decreased after Aβ-abnormality, consistent with previous cross-sectional studies. Finally, both initial increase and later-stage decrease in pDMN FC were related to altered protein levels associated with plasticity.

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Integrated Functional Analysis of hiPSC Models for Personalized Prediction and Therapeutic

Angela Santiago Aranda

PHD YEAR
Year 4

POSTER NO.

LOCATION

KEYWORDS

Huntington's Disease (HD) is caused by a CAG repeat expansion in the HTT gene, with disease classification based on repeat length. While CAG repeat length is a key predictor of age of onset (AO), substantial inter-individual variability within the same CAG length suggests the influence of additional disease modifiers. This highlights the urgent need for comprehensive functional characterization to improve patient-specific predictions of disease onset, progression, and severity. We are establishing a functional characterization pipeline using human induced pluripotent stem cell (hiPSC) models to enhance predictive accuracy through phenotypic profiling. Our pipeline integrates metabolic, cellular, and neural network analyses. Using isogenic hiPSC lines with HD-relevant CAG repeat lengths, we analyze metabolic alterations through global metabolomics and real-time bioenergetic measurements of oxidative phosphorylation and glycolysis. High-throughput imaging enables unbiased quantification of synaptic density, neurite morphology, and culture composition in differentiated neurons. Neural connectivity is assessed at both single-cell and network levels using calcium imaging and multi-electrode array recordings. This comprehensive characterization pipeline will be applied to both isogenic and patient-derived hiPSC models with known AO, providing a controlled system to directly assess CAG-driven effects while capturing patient-specific variability. By integrating these complementary datasets, we aim to develop robust predictive models that will facilitate the validation of therapeutic strategies tailored to specific phenotypic profiles of HD patients.

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Intellectual and Cognitive Functioning in Leukodystrophy Patients

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PHD YEAR
Year 3

POSTER NO.
17

LOCATION
Foyer ground floor · Thu

KEYWORDS
Leukodystrophies · Cognitive Functioning · Intelligence

BACKGROUND

Vanishing White Matter (VWM) and Metachromatic Leukodystrophy (MLD) are leukodystrophies, causing cognitive decline, behavioral changes, motor dysfunction, and early death. Existing studies on cognition are limited by small samples, heterogeneous test batteries, and neglect of disease severity, hampering delineation of a distinct leukodystrophy-related cognitive profile. We aimed to characterize intellectual and cognitive functioning in VWM and MLD using standardized tests across disease severity stages.

METHODS

In this cross-sectional study, patients underwent testing targeting key domains: attention and processing speed, executive functioning, language, memory, social cognition and visuo-construction. Disease severity was graded by the Health Utilities Index.

RESULTS

16 MLD (1 pediatric, 15 adult) and 13 VWM (4 pediatric, 9 adult) patients were included. Greater disease severity was associated with lower performance (all p-values < 0.05). Processing speed and executive functioning were decreased from mild disease on, followed by decreased social cognition, while memory and verbal comprehension were relatively preserved in severer disease stages. No significant differences in profile were found between VWM and MLD patients or between pediatric and adult cases.

CONCLUSIONS

VWM and MLD are diffuse leukodystrophies, sharing a cognitive profile, characterized by impairments in processing speed and executive functioning from mild disease stage, followed by decreased social cognition in moderate stage, while memory and verbal comprehension are relatively preserved in severer disease stages. This profile contrasts with the well-known memory- and language-dominant dementias like Alzheimer disease. In leukodystrophies, the preserved verbal capacities mask deficits in rapid processing, execution of complex tasks, and understanding of social cues, causing overestimation of patients' capacities.

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Multi-Omics Approach for Defining the Disease Trajectory of FrontoTemporal Dementia

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PHD YEAR
Year 4

TALK
Session 4B

WHEN · WHERE
Fri 13:50–15:20 · Woudzicht

KEYWORDS
Dementia · Neurodegeneration · Multiomics

BACKGROUND

Neurodegeneration is known to spread progressively, yet our understanding of human pathophysiology relies heavily on late-stage post-mortem analyses. This often obscures molecular changes that are pivotal during the initial stages of the disease. Here we aim to unravel disease mechanisms of frontotemporal dementia (FTD), by using a within-subject multi-omics trajectory analysis through the cingulate cortex of type C FTD.

METHODS

Our workflow involves consecutive sectioning of the cingulate cortex from healthy and FTD donors, using specific histological staining to stage pathology. We aim to integrate 1) quantitative proteomics to identify differentially expressed proteins; 2) bulk and single-nuclei sequencing to characterize gene expression and cell-type-specific changes; 3) spatial transcriptomics to map these transcripts within the tissue architecture; 4) qPCR analyses to define regions-of-interest and validate candidate targets.

RESULTS

Preliminary results reveal a molecular signature in which neighbouring tissue exhibits a gradient of neurodegeneration, indicating that differential gene expression and protein abundance are driven by both disease pathology and anatomical positioning close to the atrophy epicenter. In addition, synaptic genes and proteins show a gradient-independent profile, suggesting that synaptic dysfunction may be a primary, overarching process in FTD pathology. Moreover, molecular profiles varied between patients at different disease stages, suggesting subject-tailored trajectories that mirror clinical severity.

CONCLUSIONS

Data-driven, multi-omic approaches are a promising strategy for mapping neurodegenerative progression and identifying early-stage biomarkers or personalized therapeutic targets. Future single-cell and spatial analysis will determine whether these trajectory-related changes are linked to specific cellular vulnerabilities. Key words:

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Network Mechanisms Underlying Progression of Subtype-Specific Amyloid Deposition

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PHD YEAR
Year 3

POSTER NO.
108

LOCATION
Zaal 24 Woudvleugel · Fri

KEYWORDS
Alzheimer's Disease · Amyloid-PET · Network Neuroscience · Connectomics · Subtypes · Epicenters

BACKGROUND

Recent evidence demonstrates distinct cortical amyloid-β (Aβ) accumulation subtypes with different epicenters and progression patterns in Alzheimer's disease (AD). We aimed to identify such subtypes in a preclinical population and determine whether longitudinal Aβ accumulation follows distinct network propagation mechanisms.

METHODS

We included 3,537 cognitively unimpaired participants from AMYPAD-PNHS, ADNI, and A4 with Aβ-PET and resting-state functional MRI. Cortical regions were defined using the 100-region Schaefer atlas. Regional Aβ-PET SUVR values were standardized using tracer- and site-specific Aβ-negative controls. Subtype and Stage Inference (SuStaIn) modelling identified data-driven Aβ subtypes. Linear mixed-effects models estimated annualized regional Aβ change, adjusting for age, sex, education, intracranial volume, cortical thickness, with random intercepts and slopes. Subtype-specific functional connectomes were used to derive neighborhood Aβ change, betweenness centrality, inverse clustering, and Euclidean distance from each subtype epicenter. Associations between network measures and regional Aβ accumulation were assessed using Spearman correlations and spin permutations.

RESULTS

SuStaIn identified frontal, parietal, and occipital Aβ subtypes with early abnormalities in orbitofrontal, medial parietal, and visual cortices. In the parietal subtype, regional Aβ accumulation correlated with neighborhood Aβ change (ρ=0.26, P_spin=0.047), betweenness centrality (ρ=0.22, P_spin=0.030), and Euclidean distance (ρ=0.34, P_spin=0.001). In the occipital subtype, accumulation correlated with inverse clustering (ρ=0.27, P_spin=0.004) and negatively with Euclidean distance (ρ=-0.28, P_spin=0.007). No associations were observed in the frontal subtype.

CONCLUSIONS

Early Aβ progression follows subtype-specific network mechanisms, highlighting mechanistic heterogeneity and supporting network-informed risk stratification and therapeutic targeting in preclinical AD.

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Neuronal Resilience to Tau Pathology: Sequestration of Active CK1δ Drives the Formation of Granulovacuolar Degeneration Bodies

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PHD YEAR
Year 4

TALK
Session 4A

WHEN · WHERE
Fri 13:50–15:20 · Zaal 30

KEYWORDS

BACKGROUND

Granulovacuolar degeneration bodies (GVBs) are proteolytically active lysosomes containing a dense protein core that form in a subset of neurons affected by tau pathology. While historically viewed as a marker of neurodegeneration, recent work from our lab shows that GVB-containing neurons are protected from tau-induced protein synthesis decline and neurodegeneration. The activity of the core GVB component casein kinase 1 delta (CK1δ) is a rate-limiting factor for GVB formation. Here, we investigate whether impaired proteasomal degradation of active CK1δ drives the biogenesis of GVBs in resilient neurons.

METHODS

Primary mouse neuronal cultures overexpressing spontaneously aggregating tau P301L/S320F were used. Genetic and pharmacological interventions were applied to selectively enhance, abolish, or mimic GVB formation, in combination with high-content, confocal, and super-resolution microscopy.

RESULTS

Turnover of active CK1δ is tightly regulated by the proteasome in healthy neurons. Combining CK1δ overexpression with proteasomal inhibition induced the formation of pPERK- and CK1δ-positive GVB-like clusters in the absence of tau pathology, a subset of which was surrounded by a lysosomal membrane. Using inactive and truncated CK1δ mutants as well as inhibition by small molecules, we found that enhanced levels of catalytically active CK1δ drive GVB-core formation and sequestration, whereas its intrinsically disordered C-terminal tail drives its targeting to the GVB core.

CONCLUSIONS

Taken together, our findings indicate that GVB formation is an active stress response, initiated by the accumulation of catalytically active CK1δ when it escapes proteasomal degradation. This triggers the clustering and subsequent sequestration of active CK1δ into the GVB via its C-terminal tail. This represents a novel, cell-autonomous proteostatic defense mechanism, driving neuronal resilience in tauopathies.

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Neuropathological Examination of the Mechanism Behind the Novel FTLD-TDP Biomarker AcTau174

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PHD YEAR: Year 2
POSTER NO.: 117
LOCATION: Zaal 25 Woudvleugel · Fri
KEYWORDS: Tau, Acetylation, TDP-43

BACKGROUND

Cerebrospinal fluid(CSF) levels of tau acetylated at lysine 174(AcTau174) are elevated in frontotemporal dementia patients with TDP-43 pathology(FTLD-TDP) relative to those with tau pathology(FTLD-Tau), serving as a novel biomarker to distinguish these groups (Nature Medicine, 2026). In contrast, brain acTau174 immunoreactivity is reduced in FTLD-TDP compared to AD and FTLD-Tau, suggesting that tau and TDP-43 pathologies differentially affect acTau174 retention. Here, we investigated the effect of tau and TDP-43 pathology on acTau174 brain immunoreactivity across tau and TDP-43 proteinopathies.

METHODS

Postmortem hippocampi from non-demented controls(N=8), AD(N=9), AD-TDP-43(N=19), FTLD-TDP(N=12), and FTLD-Tau(N=15) were stained using 5-plex immunofluorescence for AcTau174, pTDP-43-S409/410, pTau202/205, MAP2, and DAPI. High-throughput widefield imaging was used to assess colocalization and correlations.

RESULTS

Across the full cohort(N=70), acTau174 immunostaining correlated strongly with p-tau (rho=0.74, p<0.001) and colocalized with p-tau in neurofibrillary tangles, neuritic plaques, and Pick bodies. Overlap was highest in tau-rich pathologies(AD, AD-TDP, FTLD-Tau:50–90%). FTLD-TDP patients showed only minimal acTau174 and p-tau pathology. Therefore, the correlation between pTDP-43, acTau174 and pTau was assessed in AD-TDP patients which exhibit all three pathologies. In AD-TDP patients no significant correlations were found between pTDP-43 and p-tau or acTau174. A negative trend between pTDP-43 and acTau174 in pTDP-43-rich regions was observed, but seems partly driven by neurodegeneration after correction for neuron count.

CONCLUSIONS

Our data demonstrate a strong link between acTau174 and p-tau pathology. In contrast, no direct relationship between acTau174 and TDP-43 pathology was identified, with reduced acTau174 in TDP-43-rich regions likely reflecting TDP-43-induced neurodegeneration.

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Optimization of Patient Specific Extracellular Vesicle Isolation from Cerebrospinal Fluid

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PHD YEAR
Year 2

POSTER NO.
84

LOCATION
Foyer top floor · Fri

KEYWORDS
Alzheimer's Disease
Cerebrospinal Fluid
Extracellular Vesicles

BACKGROUND

Extracellular vesicles (EVs) hold the promise to act as potential biomarkers and improve molecular profiling in Alzheimer's disease (AD). Currently, the isolation of patient specific EVs is complicated by the higher amounts of cerebrospinal fluid (CSF) needed. This research aims to isolate EVs from 0.5mL CSF to allow patient specific proteomic based profiling, and subsequently by measurement of the EVs within the CSF, improve the specificity and depth of the analysis.

METHODS

Methods for the isolation of EVs from 0.5mL CSF will be compared and analyzed through LC/MS-MS. The used CSF pool contains samples with altered tau and beta-amyloid levels. The EVs are isolated by size based exclusion chromatography methods, which give the highest and purest EV yield. Further, a novel approach with magnetic beads will be tested as well, which would allow for high-throughput sample handling.

RESULTS

Preliminary results show the feasibility of EV isolations from 0.5mL of CSF. All isolation methods show enrichment of EV markers compared to CSF. Furthermore, increased protein depth is obtained for the isolated EVs compared to the CSF. In depth comparisons of the isolation methods will determine which method shows the most enrichment of EV markers, as well as the most selective.

CONCLUSIONS

Currently, the options for biomarkers and monitoring of disease progression in AD are limited. Our study optimizes the isolation of EVs from minimal amounts of CSF to improve patient specific molecular profiling. In the long term our project will provide new insights in the molecular processes in AD.

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Positive and Negative Predictive Value of Tau-PET for Clinical Progression and Cognitive Decline Across 12 Cohorts

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PHD YEAR
Year 3

POSTER NO.
122

LOCATION
Foyer ground floor · Thu

KEYWORDS
Tau-PET · Alzheimer's Disease · Prognosis · Cognitive Decline

BACKGROUND

Tau-PET is strongly associated with cognitive decline. However, most studies report group-level effects that do not convey how likely an individual is to decline or remain stable given a tau-PET result. We translated the tau–cognition relationship into probabilities of clinical progression and cognitive decline: positive predictive value (PPV), the probability of decline in tau-PET-positive individuals, and negative predictive value (NPV), the probability of remaining stable in tau-PET-negative individuals.

METHODS

We included 4,811 participants with tau-PET and longitudinal clinical follow-up from 12 cohorts (Table-1). Tau-PET positivity was defined per cohort as temporal meta-ROI SUVR ≥2 SD above the mean of CU amyloid-negative participants aged >50. We calculated the PPV and NPV of tau-PET for (i) clinical progression (CU to MCI/dementia; and MCI to dementia) using Kaplan–Meier survival analyses at 1–5 years, and (ii) cognitive decline using stage-specific thresholds for clinically meaningful annual MMSE decline (≥0.56/1.06/2.0 points/year for CU/MCI/dementia).

RESULTS

For clinical progression, tau-PET PPV increased markedly over time, while NPV decreased only slightly (Figure-1). In CU, PPV was 13%, 41%, and 59% at 1, 3, and 5 years post-tau-PET, respectively, while NPV was 98%, 91%, and 83%. In MCI, PPV increased more steeply, reaching 11%, 51%, and 76% at 1, 3 and 5 years post-tau-PET, with corresponding NPV's of 98%, 89%, and 79%. At year 3, tau-PET-positive individuals were thus more than four times as likely to progress as tau-negative individuals. For clinically meaningful MMSE decline, PPV increased and NPV decreased with syndromic stage: PPV was 27% (CU), 40% (MCI), and 50% (dementia), and NPV 92%, 88%, and 74% (Figure-2).

CONCLUSIONS

Our results indicate that a negative tau-PET scan signals a high probability of remaining clinically and cognitively stable, supporting tau-PET's rule-out value. The PPV for clinical progression and cognitive decline increased with advancing syndromic stage and with longer follow-up.

Table 1. Baseline participant characteristics

	Total (n = 4811)	CU (n = 3673)	MCI (n = 945)	DEM (n = 193)
Age at tau-PET, years	70.5 ± 7.9	70.0 ± 7.7	71.8 ± 8.1	73.3 ± 9.1
Sex, female	2841 (59.1)	2316 (63.1)	439 (46.5)	86 (44.6)
APOE ε4 carrier	1712 (37.6)	1215 (34.6)	379 (44.5)	118 (64.8)
MMSE	28.4 ± 2.2	28.9 ± 1.3	27.4 ± 2.3	22.9 ± 4.8
Amyloid-positive	1711 (38.4)	1100 (31.9)	418 (50.7)	193 (100)
Tau-PET-positive	759 (15.8)	313 (8.5)	295 (31.2)	151 (78.2)
Follow-up for clinical progression, years	3.3 ± 2.4	3.5 ± 2.4	2.3 ± 1.9	n/a
Follow-up for MMSE decline, years	2.9 ± 1.2	3.0 ± 1.2	2.5 ± 1.0	2.1 ± 0.9

Values are presented as mean ± SD or n (%). Data were pooled from 12 cohorts: A4/LEARN (n = 442), ADC (n = 99), ADNI (n = 882), ADNI-DOD (n = 84), Geneva Memory Center (n = 228), HABS (n = 253), HABS-HD (n = 657), OASIS-3 (n = 373), PREVENT-AD (n = 133), SCAN (n = 941), TRIAD (n = 185) and WRAP (n = 534). CU = cognitively unimpaired; MCI = mild cognitive impairment; DEM = dementia. Figure 1. Tau-PET positive and negative predictive value for clinical progression Pooled Kaplan–Meier estimates of PPV (blue: proportion of tau-PET-positive participants who progressed) and NPV (red: proportion of tau-PET-negative participants who remained stable) up to 5 years after tau-PET, with 95% CIs. At 3 years post-tau-PET, 41% of tau-PET-positive CU participants had progressed to MCI or dementia, and 91% of tau-PET-negative CU participants remained stable. In MCI, at 3 years post-tau-PET, 51% of tau-PET-positive participants had progressed to dementia, and 89% of tau-PET-negative participants remained stable. Figure 2. Tau-PET positive and negative predictive value for cognitive decline PPV (blue: proportion of tau-PET-positive participants who declined) and NPV (red: proportion of tau-PET-negative participants who did not decline) for clinically meaningful MMSE decline, with 95% CIs. Decline was defined as an MMSE slope of ≤ −0.56 (CU), ≤ −1.06 (MCI) or ≤ −2.0 (dementia) points per year. A positive tau-PET identified decliners in 27% of CU, 40% of MCI, and 50% of dementia participants. A negative tau-PET identified non-decliners in 92% of CU, 88% of MCI, and 74% of dementia.

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Restoration of Glial Function in AD by Correcting Lysosomal Lipid Dyshomeostasis

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PHD YEAR: Year 2
POSTER NO.: 85
LOCATION: Foyer top floor · Fri
KEYWORDS: APOE4 Astrocytes, Lysosomes, Lipids

BACKGROUND

APOE4 is the strongest genetic risk factor for Alzheimer's disease, with emerging evidence linking its expression in glial cells to lysosomal lipid dyshomeostasis and aberrant glial activity. However, the molecular mechanisms driving these deficits remain unclear and need further investigation for the development of targeted therapies that restore lipid metabolism and lysosomal function. A novel target to normalize lysosomal function in APOE4 glia is the bis(monoacylglycero)phosphate (BMP) phospholipase PLA2G15, that mediates lysosomal lipid metabolism.

METHODS

Using iPSC-derived astrocytes from one or two isogenic lines (Kolf and Bioni), we performed lipidomics, fluorescence microscopy, qPCR, and flow cytometry to compare APOE3/3 and APOE4/4 phenotypes and evaluate the effects of a selective lysosomal PLA2G15 inhibitor. Furthermore, we optimized a lyso-IP protocol to resolve organelle-specific lipidomic and proteomic alterations from whole-cell changes.

RESULTS

APOE4/4 astrocytes exhibited a distinct lipid profile compared to APOE3/3 controls, characterized by altered BMP species distribution and elevated intracellular cholesterol levels. Pharmacological inhibition of PLA2G15 rescued both BMP distribution ratios and cholesterol accumulation in APOE4 astrocytes. Additionally, qPCR revealed a downregulation of key lysosomal genes in APOE4 versus APOE3 astrocytes, which was partially restored following PLA2G15 inhibitor treatment.

CONCLUSIONS

PLA2G15 inhibition demonstrated target engagement and phenotypic rescue by restoring BMP profiles and normalizing cholesterol homeostasis in APOE4 astrocytes. These findings highlight PLA2G15 as a promising therapeutic target for treating lysosomal lipid dyshomeostasis in Alzheimer's disease. Ongoing studies are evaluating whether this metabolic rescue translates to functional recovery.

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Retinal Glial Changes in Alzheimer's Disease: Differential Expression of Glial Markers in Human Post-Mortem Tissue

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PHD YEAR
Year 2

POSTER NO.
72

LOCATION
Foyer ground floor · Fri

KEYWORDS
Alzheimer's Disease | Retina | Glial Activation

BACKGROUND

Neuropathological hallmarks of Alzheimer's disease (AD), including amyloid-β and phosphorylated tau deposition, have been identified in the human retina, highlighting its potential as a biomarker. As cerebral protein accumulation is associated with glial activation, we assessed features of glial activation in the retina of AD patients and non-demented controls.

METHODS

This proof-of-concept study included post-mortem eyes from patients with AD (n=11) and non-demented controls (n=13). All donors were obtained through the Netherlands Brain Bank. Neuropathological diagnosis was made following the NIA-AA criteria. Formalin-fixed paraffin-embedded retinal sections (10 µm) from the superior quadrant were immunostained for GS, GFAP, CD117 and CD68. Protein expression was quantified in the peripheral and central retina using QuPath.

RESULTS

GFAP and GS immunoreactivity tended to be higher in AD in both peripheral and central retina but did not differ significantly from controls. An inverse association between GFAP and GS expression was observed in the central AD retina. CD68 expressions were comparable between groups. CD117-positive cells tended to increase in the central inner nuclear layer and decreased expression in the peripheral retina in AD. In contrast, CD117 immunopositivity in the retinal nerve fiber layer/ganglion cell layer was reduced in both central and peripheral AD retina, independent of age.

CONCLUSIONS

These findings suggest regional and layer-specific alterations in retinal glial markers in AD. Our future experiments will focus on additional glial markers and regional vulnerability in relation to protein accumulation in the retina to further elucidate glial activation in the context of neurodegenerative diseases.

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SARS-CoV-2 Is Associated with Parkinson's Disease-Like Neuropathology in a Non-Human Primate Model

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PHD YEAR
Year 2

POSTER NO.
102

LOCATION
Zaal 24 Woudvleugel · Fri

KEYWORDS
SARS-CoV-2 Parkinson's Disease Non-Human Primate

BACKGROUND

Increasing evidence suggests that viral infections may contribute to neurodegenerative disorders, including a potential link between SARS-CoV-2 and Parkinson's disease (PD) or Alzheimer's disease Neurological symptoms occur in approximately one-third of COVID-19 cases, while 5–20% of infections result in long-term sequelae frequently involving the central nervous system. The emerging epidemiological, experimental, and post-mortem evidence supporting a link between SARS-CoV-2 infection and neurodegenerative processes underscores the need to better understand the mechanisms underlying SARS-CoV-2-associated neurological sequelae.

METHODS

Here, we used a non-human primate (NHP) model to investigate PD-related neuropathological changes following SARS-CoV-2 infection. Neuropathology was assessed at multiple time points post infection (2–52 weeks) to capture both acute and persistent neurological alterations. Immunohistochemistry, immunofluorescence, and cerebrospinal fluid (CSF) proteomics were used to evaluate dopaminergic neuron integrity, neuroinflammation, neurodegeneration, and protein aggregation.

RESULTS

After SARS-CoV-2 infection clear neuropathological alterations are present in the NHP brain. A reduction in dopaminergic neurons was observed in the substantia nigra pars compacta. In addition, microglia and astrocytes displayed changes consistent with increased neuroinflammatory activation. Elevated CSF neurofilament light chain concentrations indicated neuronal injury, while α-synuclein aggregation was detected at multiple post-infection time points.

CONCLUSIONS

Together, these findings demonstrate that SARS-CoV-2 infection is associated with neurodegeneration-associated changes in the NHP brain. This model provides a valuable platform to further investigate the molecular and cellular mechanisms underlying SARS-CoV-2-induced neuropathology and its potential contribution to long-term neurological sequelae.

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Targeting Mutant Huntingtin Exon 1 Protein with Intracellular Antibodies

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PHD YEAR: Year 3
POSTER NO.: 76
LOCATION: Foyer ground floor · Fri
KEYWORDS: Huntington's Disease, Intrabodies, Proteostasis, Degradation

Huntington's disease (HD) is a neurodegenerative disease caused by a mutation in exon 1 of the huntingtin (HTT) gene, leading to an extended polyglutamine tract in the protein. As a result, toxic N-terminal fragments aggregate in the brain. As there is yet no cure for HD, it is critical to pursue efforts to identify and develop therapeutic strategies to prevent or reverse HD phenotype by lowering the levels of mHTT. Here, we focus on targeting mHTT exon 1 protein for degradation through the use of VHH intracellular antibodies (intrabodies). Using an immortalized mouse striatal cell line that expresses untagged mHTT(Q97)-exon1, we established the effect of different intrabodies on the levels of soluble and insoluble mHTT protein. Our results revealed that intrabodies significantly decreased the levels of insoluble mHTT species in both microscopy and biochemical assays. Yet, the intrabodies tested were unable to clear already formed aggregates. Instead, our results suggest that the intrabodies act on the soluble mHTT by stabilizing the protein without causing apparent toxicity. In future studies, various degradation-specific motifs will be linked to the intrabodies with the aim to prevent aggregation and target the solubilized mHTT efficiently towards degradation.

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Tau Aggregation Causes Selective Dendrite Loss in iPSC-Derived Human Neurons

Robin Pelle

PHD YEAR
Year 2

POSTER NO.
105

LOCATION
Zaal 24 Woudvleugel · Fri

KEYWORDS
Alzheimer's Disease · Tau · Neurodegenerative Disorders · iPSC-Derived Neurons

Tauopathies are neurodegenerative disorders characterized by the accumulation of aggregated tau that induces progressive loss of neurites and synapses. However, how aggregated tau leads to neuronal damage and synapse loss remains largely unknown. Here, we investigated the impact of tau aggregates on axonal and dendritic compartments in human induced pluripotent stem cell (iPSC)-derived neurons. To this end, we expressed an aggregate-prone tau construct in human neurons and assessed neurite morphology, synaptic structures, and organelle morphology, trafficking, and function at different stages of tau accumulation. We show that tau pathology induces a progressive and selective loss of dendrites in human neurons, while the axonal compartment remains intact. This coincides with the loss of postsynaptic structures, while presynaptic markers remain present in the preserved axons. The selective dendrite loss is preceded by dysfunction and morphological changes of dendritic mitochondria. Collectively, our data shows that dendrites of human neurons are predominantly vulnerable to tau aggregate-induced damage and highlights mitochondrial deficits as early drivers that precede dendrite loss in tauopathies.

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TDP-43 Aggregate Subtypes in a ALS-FTD Case Consisting of Distinct TDP-43 Fragments

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PHD YEAR: Year 2
POSTER NO.: 101
LOCATION: Zaal 24 Woudvleugel · Fri
KEYWORDS: TDP-43, ALS-FTD, Neurodegeneration

BACKGROUND

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are fatal neurodegenerative diseases that exist on a clinical and pathological spectrum. A key hallmark of ALS-FTD is the abnormal accumulation of TDP-43, which under disease conditions leaves the nucleus and forms cytoplasmic aggregates. TDP-43 aggregates undergo biochemical modifications including hyperphosphorylation and ubiquitination, and appear in morphologically distinct forms containing N- and C-terminal fragments. However, how these fragments relate to aggregate morphology and modification state remains unclear.

METHODS

We used multiplex immunofluorescence on post-mortem brain and spinal cord tissue from a single severe ALS-FTD case (a 72-year-old female) with widespread TDP-43 pathology. By combining markers for different forms of TDP-43 and associated proteins, we mapped co-occurrence patterns across distinct brain regions.

RESULTS

Preliminary double immunofluorescence data reveal heterogeneity in TDP-43 aggregate composition, with inclusions showing variable N- and C-terminal fragment representation, phosphorylation state and ANXA11 co-localisation.

CONCLUSIONS

Studying a single severe ALS-FTD case with widespread pathology allows comprehensive mapping of TDP-43 aggregate heterogeneity, providing a basis for comparison across larger cohorts.

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The Multi-Platform Proteomics for Molecular Subtyping in Neurodegenerative Disease: Integrating Mass Spectrometry, Olink, and NULISAseq Data

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PHD YEAR: Year 2
POSTER NO.: 116
LOCATION: Zaal 25 Woudvleugel · Fri
KEYWORDS: Proteomics, Dementia

BACKGROUND

Alzheimer's disease (AD), Parkinson's disease (PD), and dementia with Lewy bodies (DLB) represent the most prevalent neurodegenerative disorders that cause cognitive and/or motor decline. While these diseases are caused by specific protein aggregates, and characterised by distinct clinical syndromes, they also share underlying pathophysiology.

METHODS

To elucidate molecular mechanisms driving both shared and disease-specific pathological processes, we are currently conducting comprehensive cerebrospinal fluid (CSF) proteomic profiling in more than 1,000 individuals with AD, PD, or DLB, leveraging the European Platform For Neurodegenerative Disease (EPND) Hub. Using a combination of targeted (NULISA, Olink) and untargeted mass spectrometry based proteomic approaches, that capture over 3,000 proteins spanning diverse biological pathways.

RESULTS

The goal of this project is to understand disease heterogeneity in AD, DLB and PD using both hypothesis-driven, as well as data-driven machine learning algorithms. We will present the first analyses on this dataset to highlight AI-based classification of AD, PD and DLB, as well as discovery of molecular subtypes across these disorders.

CONCLUSIONS

Together, these findings will provide a systems-level view of neurodegenerative disease biology and reveal both common and divergent molecular pathways that underly disease heterogeneity. This integrative proteomic and AI-based framework offers a foundation for improved diagnostic stratification and highlights novel therapeutic targets, accelerating the development of more effective treatments for these devastating neurodegenerative diseases.

The Role of Exercise in Brain Lipid Metabolism in Alzheimers Disease

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PHD YEAR
Year 4

TALK
Session 1B

WHEN · WHERE
Thu 10:45–11:45 · Zaal 30

KEYWORDS
Alzheimer Exercise Lipids

BACKGROUND

Lipid metabolism is increasingly recognized as a key driver in early Alzheimer's disease (AD) pathogenesis. Cholesterol accumulation, downstream of genetic AD risk variants, promotes pro-inflammatory states in microglia and astrocytes, and accelerates phosphorylated Tau buildup and amyloid precursor protein (APP) processing to Aβ. Physical activity protects against AD by slowing cognitive decline, and has been shown to reduce pathology and inflammation. However, it is not yet known if, and how, exercise affects brain lipids.

METHODS

5xFAD mice were given either functional or locked running wheels for 4 months. Brain tissue was used to perform lipidomics, transcriptomics, and Western Blot. In addition, mouse serum from a WT cohort that performed forced treadmill running was collected for treatment on human iPSC-derived astrocytes (APOE3/3 and APOE4/4) to identify potential mechanisms related to the observed brain lipid alterations.

RESULTS

5xFAD mice showed increased cholesterol ester (CE) levels compared to WT, which were reversed by exercise. CE levels negatively correlated with the running distance. Transcriptomics and Western Blot data show an AMPK-activated signature in the mouse brain, potentially related to the CE reduction. Exercise serum treatment in astrocytes revealed the same CE reduction, indicating that the effect might come from factors released into the bloodstream. This effect was only present in APOE4 astrocytes, pointing towards a disease-related state that might be resolved by exercise. Preliminary data shows that AMPK inhibition upon exercise serum treatment diminishes the CE reduction, highlighting a potential link with exercise, AMPK and brain lipids.

CONCLUSIONS

Exercise reduces CE levels in 5xFAD mice, and induces AMPK activation in the brain. Ongoing work needs to validate whether AMPK activation upon exercise is directly linked to brain lipid alterations.

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Usefulness of a Multi-Dementia Panel to Track and Predict Functional Decline in an Alzheimer's Disease Clinical Trial

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PHD YEAR
Year 2

POSTER NO.
74

LOCATION
Foyer ground floor · Fri

KEYWORDS
Alzheimer's Disease · Clinical Trials · Multi-Dementia Panel · Cognition

BACKGROUND

Fluid-based biomarkers offer a cost-effective means of assessing treatment effects in disease-modifying therapies, but their utility depends on capturing the diverse pathological pathways linked to functional decline in Alzheimer's disease (AD). Therefore, we developed a Multi-dementia panel, a CSF biomarker test comprising the AD-Diagnostic and AD-Differential Diagnostic panels, which captures the biological heterogeneity of AD and other major dementias. This study evaluates whether these panels can track and predict functional decline in a clinical trial setting.

METHODS

The cohort included CSF AD biomarker positive participants with MCI due to AD (N=64) or AD dementia (N=40; mean age 69 years; 64% female) from the placebo arm of a phase 2 clinical trial (NCT04191486).The AD-Diagnostic (ABL1, SDC4, MMP10, ITGB2, CLEC5A, THBD, SPON2) and AD-Differential Diagnostic (ABL1, THOP1, ENO2, ITGB2, DDC, MMP7, VEGRF3) panels were measured using multiplex proximity extension assays. Spearman correlations evaluated associations between 1.5-year changes in the individual proteins and CDR Sum of Boxes (CDR-SB). Linear mixed-effects models adjusted for age, sex, and APOE ε4 were used to assess the predictive value of these 12 proteins for change in CDR-SB.

RESULTS

Within our biomarker panels, an increase in MMP-10 over 1.5 years demonstrates a moderate positive correlation with functional decline (r=0.30, FDR-adjusted p=0.038), indicating that longitudinal increased CSF levels of this protein are associated with longitudinal worsening in functional performance. Higher baseline MMP-10 concentrations predicted faster subsequent functional decline: each 1 pg/mL higher baseline MMP-10 was associated with a 0.03-point greater annual increase in CDR-SB (p=0.016).

CONCLUSIONS

Increases in CSF MMP-10 concentrations associated with higher scores on the CDR-SB, where higher baseline values are indicative of faster functional decline. The next step is to explore the performance of a panel composite score compared to individual biomarker scores, as well as their correlation/association with other cognitive measures.

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Using Patient-Derived PSEN1-Mutant iPSCs to Study Excitation/Inhibition Imbalance in Alzheimer's Disease

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PHD YEAR
Year 4

TALK
Session 1B

WHEN · WHERE
Thu 10:45–11:45 · Zaal 30

KEYWORDS
iPSCs | E/I Imbalance | Alzheimer's Disease

BACKGROUND

Mutations in the Presenilin-1 (PSEN1) gene lead to early-onset Alzheimer's disease (AD) and are associated with changes in brain oscillations and increased epileptic activity. At the cellular level, these alterations are caused by excitation/inhibition (E/I) imbalance, but the precise contribution of excitatory and inhibitory neurons remains unclear. Our objective is to identify neuron type-specific molecular alterations underlying network dysfunction in neuronal networks derived from patient induced pluripotent stem cells (iPSCs).

METHODS

Using the transcription factors NGN2 or ASCL1/DLX2 respectively, pure populations of excitatory and inhibitory neurons were generated and subsequently studied in either mono- or co-cultures. Proteomics analysis and immunostainings were then performed at 4, 6, 8 and 10 weeks post-induction to identify the molecular changes in PSEN1-mutant neurons relative to control neurons.

RESULTS

Our proteomics measurements revealed robust neuronal maturation over time in both PSEN1-mutant and control lines. Comparison of PSEN1-mutant and control lines revealed a PSEN1-associated molecular signature indicative of mitochondrial dysfunction. Moreover, proteomic alterations seemed more pronounced in PSEN1-mutant inhibitory neurons, while immunostainings showed alterations in inhibitory synapse density in mixed cultures, suggesting that inhibitory rather than excitatory dysfunction drives network alterations in PSEN1-mutant cultures.

CONCLUSIONS

PSEN1 mutations seem to preferentially affect the proteomic composition of inhibitory rather than excitatory neurons, in line with previous studies showing that inhibitory dysfunction may be the driver of AD-related network imbalance. Future experiments in mixed E-I networks will be used to study the specific effects of this dysfunction on network activity and synaptic transmission.

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Divergent Transcriptomic and Functional Aging of Molecularly Defined Neuron Types in Human Brain

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PHD YEAR: Year 4
TALK: Session 4B
WHEN · WHERE: Fri 13:50–15:20 · Woudzicht
KEYWORDS: Human Aging, Electrophysiology, Transcriptomics

BACKGROUND

Human cortical function depends on a balanced network of excitatory and inhibitory neurons. This network destabilizes upon aging, leading to disruption of cortical function and progressive cognitive decline. The contribution to destabilization of distinct cell types within the human cortex is unknown.

METHODS

Predictive classification of transcriptomic labels using a Random Forest based patch-clamp electrophysiological data. Correlations between electrophysiological data and donor age. Transcriptomic analysis of channel genes between young and aged donors.

RESULTS

We show that the 18 molecular neuron types have a unique molecular signature for 248 ion channel genes, which corresponds to unique electrophysiological properties per type. Excitatory neuron types exhibited coordinated age-associated downregulation of numerous ion channel genes in both mean transcriptomic expression and the proportion of neurons expressing the gene. These dynamic transcriptomic shifts are accompanied by marked electrophysiological changes. Inhibitory neurons show age-associated up- and downshifts in transcriptomic intensity and frequency. Despite transcriptomic changes, the electrophysiological properties of inhibitory neurons remain stable.

CONCLUSIONS

Excitatory neurons are affected by healthy aging on a transcriptomic and electrophysiological level, while inhibitory neurons show unstable transcriptomics but stable electrophysiology.

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Identification of a Distinct Microglia Profile in Cognitively Healthy Centenarians with Alzheimer's Disease Neuropathology

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PHD YEAR
Year 3

POSTER NO.
35

LOCATION
Zaal 22 + 23 Woudvleugel · Thu

KEYWORDS
Microglia · Aging · Alzheimer's Disease

BACKGROUND

Microglia maintain brain homeostasis, partly through the removal of cellular debris and accumulated proteins. Their functioning is altered during aging and in patient's with Alzheimer's disease (AD). Interestingly, centenarians participating in the 100-Plus study frequently also show AD-related neuropathology, yet they remain cognitively healthy. We investigated to what extent microglia contributed to the resilience or resistance observed in our centenarians.

METHODS

We investigated microglia activation in post-mortem temporal cortex tissue if 95 healthy aged centenarians from the 100-Plus study and 7 AD patients. We performed immunolabeling with a curated panel of markers of distinct microglia states, namely Iba1(pan-marker), HLA-DR (antigen presenting), CD68 (phagocytic) , CD11c (phagocytic and cell adhesion) and P2RY12 (homeostatic), and compared their load with the spread and local burden of amyloid beta (Aβ) and tau pathology.

RESULTS

We show that centenarians with a high Alzheimer's disease Neuropathological Change (ADNC) score exhibit an increased load of both activation and homeostatic microglial markers compared to centenarians with lower ADNC and AD patients with similar ADNC. We also found a distinct correlation of CD68 with Aβ and tau pathology, and CD11c with tau pathology in the temporal cortex of centenarians.

CONCLUSIONS

These findings suggest that healthy aged centenarians from the 100-Plus study show a balanced profile of microglial activation in the presence of AD-related pathology. Current immunotherapies for AD, such as anti-amyloid antibodies, rely on engaging microglia to clear pathology. Our work suggests that treatments should not only stimulate microglial activation but also focus on microglial homeostasis to ensure a sustainable and effective response.

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Cerebellar Influences on Neocortical Development in Humans and Mice

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PHD YEAR
Year 2

POSTER NO.
13

LOCATION
Foyer ground floor · Thu

KEYWORDS
Cerebellum · Autism · Brain Development

BACKGROUND

Despite a growing body of work showing otherwise, the cerebellum is still often considered to be of limited importance outside of motor and balance pathways. However, early life cerebellar injury is the leading non-genetic predictor of autism diagnosis in children. Despite several papers demonstrating the relationship between these lesions and autism-like behavioural outcomes, a mechanistic and causal explanation is lacking.

METHODS

Using MRI scans from large human cohorts at two time points, cerebellar and cortical volumes are extracted through atlas based parcellation. These volumes are used to build a model of cortical maturation as a function of cerebellar structure volumes and validated in a second large human cohort. In mice, lesions are induced to the cerebellum at different ages. Using deformation-based morphometry on ex vivo MRI data we explored the causal relationship between early life cerebellar lesions and cortical maturation

RESULTS

Cerebellar morphology differentially predicts cortical thickness, depending on both the cerebellar region and gray and white matter density (GMD and WMD). Reversing the model by attempting to predict cerebellar GMD or WMD through thickness of the cortex resulted in lower effect sizes across most associations. We further show that early life lesions in the cerebellar Crus I region in mice result in profound morphological changes throughout the cortex, especially in the temporal association area and somatosensory regions.

CONCLUSIONS

Early cerebellar morphology is a driving factor for cortical maturation providing a possible explanation for the observed relationships between early life cerebellar lesions and autism-like behavioural outcomes.

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Developing a Reliable Rodent phMRI Protocol for Studying Methylphenidate Tolerance

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PHD YEAR	TALK	WHEN · WHERE	KEYWORDS
Year 4	Session 3A	Fri 11:00–12:30 · Zaal 30	MRI · Methylphenidate · Preclinical

BACKGROUND

Methylphenidate is widely prescribed for attention-deficit/hyperactivity disorder. Long-term treatment may induce behavioral tolerance, while the underlying neurobiological mechanisms remain poorly understood. To investigate these mechanisms, we evaluated the feasibility of a protocol to assess the brain's acute response to methylphenidate using pharmacological functional magnetic resonance imaging (phMRI).

METHODS

Male (n=11) and Female (n=15) Wistar rats were scanned at PND25-30 and PND60-65 under a combination of isoflurane and dexmedetomidine anesthesia on a 7T MR Solutions scanner. The 25-minute phMRI scan consisted of a 10-minute baseline acquisition, followed by an intravenous methylphenidate bolus (1.5mg/kg), and 15 minutes of post-bolus imaging. Imaging data was preprocessed using RABIES. ROI-based analyses were performed on the nucleus accumbens, caudoputamen, and prelimbic cortex, in addition whole-brain voxel analysis was conducted.

RESULTS

The ROI-based analyses revealed significant methylphenidate-induced BOLD increases in the prelimbic cortex of and nucleus accumbens in juveniles, but not in adults. The whole-brain voxel analyses found positive BOLD responses in the sensory and associative cortical and subcortical areas in adults, but not in juveniles.

CONCLUSIONS

The protocol successfully detected methylphenidate-induced BOLD responses, demonstrating the feasibility of phMRI in this model. However, age-dependent effects in these results likely reflect differences in data quality and a stronger response to anesthesia in adults compared to juveniles, and inconsistent results between analytical approaches highlight the need for further optimization of acquisition and data analysis before application in longitudinal studies. Updated findings will be presented.

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Development of an N-of-1 Therapeutic Antisense Oligonucleotide for a Unique UNC13A Variant Causing a Neurodevelopmental Disorder

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PHD YEAR
Year 4

TALK
Session 3C

WHEN · WHERE
Fri 11:00–12:30 · Zaal 15

KEYWORDS
Synapse · Rare Neurodevelopmental Disorder · Antisense Oligonucleotides

BACKGROUND

Recently, UNC13A variants have been identified to underlie a rare novel neurodevelopmental disorder (NDD) characterized by developmental delay and seizures. UNC13A is a presynaptic protein involved in regulating vesicle release and gain-of-function mutations lead to increased neurotransmission. We aim to develop a personalized therapy with the use of antisense oligonucleotides (ASO) for an individual with a unique variant in UNC13A and who is currently under care in our institute.

METHODS

Our strategy aims to target either the pathogenic variant or heterozygous single nucleotide polymorphisms (SNPs) to selectively knockdown the pathogenic transcript. ASOs are designed in silico and screened in vitro in a luminescence-based screening assay. Next, toxicity of the ASOs is estimated via multi-electrode arrays, B-cell lymphoma-based assays, and caspase assays for acute neurotoxicity, immunotoxicity, and apoptosis, respectively. Induced pluripotent stem cell (iPS)-derived neurons are used to study the disease phenotype and test our lead ASOs. These cultures have been derived from either patient-derived or genetically engineered iPS.

RESULTS

We have screened around 40 ASOs for knockdown of the UNC13A pathogenic transcript. Out of these, we identified five interesting ASOs: two targeting the variant and three targeting SNPs. These ASOs show no in vitro toxicity. Upon gymnotic administration to iPS-derived neurons, UNC13A appears reduced.

CONCLUSIONS

We are developing a personalized ASO targeting UNC13A to downregulate the pathogenic RNA transcript. This research provides a possible personalized therapy for this individual with NDD. Additionally, the framework we build for development of personalized ASO therapies could be extended to other individuals with a rare NDD.

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Elucidating Disease Mechanisms and Identifying Therapeutic Targets in Three Rare Genetic Developmental Disorders Using Patient-Derived iPSC Models.

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PHD YEAR
Year 2

POSTER NO.
97

LOCATION
Zaal 22 + 23 Woudvleugel · Fri

KEYWORDS
Patient-Derived iPSC Models · Brain Organoids · Rare Genetic Developmental Disorders

BACKGROUND

This project aims to provide insights into disease mechanisms in rare genetic developmental disorders with intellectual disability and to explore novel therapeutic strategies using patient-derived induced pluripotent stem cell (iPSC) models. We focus on Menke-Hennekam syndrome, Marshall-Smith syndrome, and Pitt-Hopkins syndrome. These syndromes come with a high burden of disease, and treatment options are limited to symptomatic treatment.

METHODS

We will establish brain organoids derived from affected individuals to study the molecular and cellular mechanisms underlying neurodevelopmental abnormalities. Transcriptomic analysis will be performed to identify dysregulated genes and affected pathways. We will then validate candidate therapeutic pathways in appropriate iPSC-derived models. Proof-of-concept experiments, including drug repurposing approaches such as clemastine treatment for Pitt-Hopkins syndrome, will assess whether therapeutic modulation of these pathways can improve disease-associated phenotypes, providing a foundation for novel therapeutic approaches. Moreover, we will analyze DNA methylation patterns, in order to establish an episignature for Marshall-Smith syndrome to improve diagnostics, and develop a clinical database for Marshall-Smith syndrome to improve understanding of its clinical spectrum and support revisions of current standards of care. Expected

RESULTS

We expect to identify disease-associated molecular and cellular pathways and candidate therapeutic targets, including potential opportunities for drug repurposing.

CONCLUSIONS

This project aims to advance our understanding of disease mechanisms, identify potential therapeutic targets, and explore repurposed and novel treatment strategies for rare genetic developmental disorders.

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Enhanced GABA Transmission in Kleefstra Patient-Derived Neurons

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PHD YEAR
Year 3

POSTER NO.
22

LOCATION
Foyer top floor · Thu

KEYWORDS
iPSC-Derived Models | Neurodevelopmental Disorders | Patch-Clamp Electrophysiology

BACKGROUND

Kleefstra syndrome is a rare monogenic neurodevelopmental disorder, characterized by intellectual disability and autism spectrum disorder phenotypes. It can be caused by de novo loss of function mutations in the histone methyltransferase gene EHMT1. The EHMT1 protein is important for synaptic scaling and E/I balance. It has been shown that Kleefstra patient network cultures show altered network activity. However, what the underlying cellular mechanisms are, and what the role is of inhibitory cells in the disease phenotype, is yet unknown.

METHODS

In this study, we aimed to investigate the effect of Kleefstra patient mutations on cell-intrinsic synaptic release phenotypes of inhibitory neurons. Three patient derived iPSC lines were induced into inhibitory neurons using PiggyBac Ascl1/Dlx2 and plated onto glia islands in order to get autaptic cultures to measure GABAergic synaptic release, using whole-cell voltage clamp.

RESULTS

We found that Kleefstra patient neurons show enhanced GABA transmission compared to healthy control neurons, as measured by evoked IPSC amplitude and charge. Furthermore, Kleefstra neurons show stronger short-term depression in 10Hz train stimulations and paired pulse stimulations. Spontaneous miniature IPSC frequencies and amplitudes, however, were similar between Kleefstra patient neurons and healthy controls.

CONCLUSIONS

Together, our findings show a clear and consistent effect of EHMT1 patient mutations on GABA release, pointing to an increased presynaptic release probability. Our findings provide important novel insight into the cellular disease mechanisms of Kleefstra syndrome and the contribution of inhibitory neurons on network behavior.

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GRIN2B LoF Elicits Domain-Specific Neuronal Differentiation Impairment

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PHD YEAR
Year 3

POSTER NO.
96

LOCATION
Zaal 22 + 23 Woudvleugel · Fri

KEYWORDS
Neurodevelopment iPSC NMDAR

BACKGROUND

GRIN2B-related disorder (GRIN2B) is a rare neurodevelopmental disorder is caused by de novo mutations to the GRIN2B gene, which encodes the GluN2B subunit of the NMDA receptor (NMDAR). Patients exhibit substantial genotypic and phenotypic heterogeneity, with symptoms including developmental delay, intellectual disability, and EEG abnormalities. GRIN2B loss-of-function (LoF) in neurons is known to compromise neuronal development by disrupting neuronal maturation, synaptogenesis, and plasticity mechanisms. However, the developmental impact of GRIN2B LoF variants across different protein domains remains poorly understood.

METHODS

We generated mixed populations of cortical neurons from iPSC lines previously generated from GRIN2B LoF patients and controls. We measured RNA and protein expression, proliferation rates, morphological changes, and spontaneous neuronal activity during neuronal maturation.

RESULTS

Our results indicate that early neuronal development is stunted in GRIN2B LoF cohort, specifically when the variant locus is within the ligand binding domain. Subsequent neural network activity alterations were observed later in development within this patient sub-subpopulation.

CONCLUSIONS

Domain-specific impairments impair early neuronal differentiation in GRIN2B LoF patient iPSC lines. Despite morphological recovery at later stages in development, neural network activity is subsequently altered in this group, indicating a link between delayed neuronal development, and functional impairments in mature networks.

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Peroxisomes: The Forgotten Organelle

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PHD YEAR
Year 4

TALK
Session 1B

WHEN · WHERE
Thu 10:45–11:45 · Zaal 30

KEYWORDS
iPSCs Zellweger Spectrum Disorder Peroxisomes

The Zellweger Spectrum Disorders (ZSD) are a group of rare neurometabolic disorders caused by biallelic mutations in 12 different PEX genes. These genes code for peroxins which are proteins collectively required for the transport/import of peroxisomal membrane and matrix proteins during peroxisome biogenesis[1]. Peroxisomes are essential for lipid metabolism, and their biogenesis is therefore critical for normal cell function. While patients can present with diverse symptoms, liver dysfunctions and brain abnormalities are the core features[2], as both organs rely heavily on lipid metabolism. Fibroblasts from 5 ZSD patients with biallelic PEX1 mutations were reprogrammed into induced pluripotent stem cells (iPSC). After extensive characterization, control and ZSD iPSCs were differentiated into neurons, astrocytes and hepatocytes. Compared with control cells, ZSD neurons, astrocytes and hepatocytes displayed hallmarks of peroxisomal dysfunction, including reduced processing of peroxisomal 3-ketoacyl-CoA thiolase and cytosolic mislocalization of the peroxisomal enzyme catalase. These findings show that the newly generated ZSD cellular models recapitulate key disease phenotypes and that the thiolase and catalase assays can be used to determine whether a drug is effective in normalizing peroxisomal abnormalities.

REFERENCES

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The Neurodevelopmental Disorder-Associated CAMK2A-p.Thr286Pro Variant Causes Severe Learning Deficits Due to Molecular and Synaptic Hyperactivity

Jaime Borregon Jimenez

PHD YEAR
Year 4

TALK
Session 3C

WHEN · WHERE
Fri 11:00–12:30 · Zaal 15

KEYWORDS
Synaptic Plasticity Neurodevelopmental Disorders Learning Memory

The alpha-isotype of Ca^{2}+/calmodulin-dependent protein kinase 2 (CAMK2A) is the most abundant kinase in the synapse. Due to its molecular properties, it is known to be critical for learning and memory. CAMK2A can translate transient neuronal activation into long-lasting changes in the synapse, resulting in long-term potentiation. In the last decade, individuals with severe intellectual disability have been identified carrying de novo variants in CAMK2A. One of the variants identified is the p.Thr286Pro, shown to render the protein in a constitutive active state. How this variant causes the range of clinical manifestations seen in the patients, including the severe intellectual disability, remains to be studied. Therefore, the Camk2a+/T^{286}P mouse mutant was generated and characterized at the molecular, anatomical, behavioral, and electrophysiological level. In the pure C57Bl6/J background seizures were observer already early on, so mice were tested in hybrid background (C57BL/6J and 129/sv) with different levels of C57Bl6/J. We show that irrespective of the background, learning and plasticity was severely affected, potentially due to occlusion of LTP. In contrast, locomotion and other phenotypes were differentially affected depending on the background, similar to the broad clinical spectrum seen in patients carrying the same variant. Overall, this study of a hyperactive CAMK2A mouse model that seems one of the most affected Camk2a mouse models to date, complements the extended literature on CAMK2A functioning.

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UBE3A-Neighbouring Genes on Chromosome 15q11.2-13.1 Contribute to Angelman Syndrome Phenotype

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PHD YEAR
Year 3

POSTER NO.
37

LOCATION
Zaal 22 + 23 Woudvleugel · Thu

KEYWORDS
Angelman Syndrome
Neurodevelopmental Disorder
Mouse Model

BACKGROUND

Angelman syndrome (AS) is caused by loss of maternally expressed UBE3A. Approximately 70% of individuals with AS carry a large 15q11.2-q13.1 deletion encompassing UBE3A and neighboring non-imprinted genes and show more severe neurodevelopmental impairment and higher epilepsy risk than individuals with non-deletion genotypes. The contribution of these neighboring genes to AS severity remains poorly understood.

METHODS

We combined longitudinal data from 566 AS individuals across five cohorts. Neurodevelopment was assessed using Bayley-III Growth Scale Values and genotype effects were evaluated in epilepsy-free and -affected individuals. To investigate the role of neighboring genes, we generated a mouse model carrying a deletion of all non-imprinted genes in the syntenic region (Atp10a-Tubgcp5; Del7) and crossed it with the AS (Ube3a-E113X) model to generate Del7-AS mice. Following molecular validation, animals underwent behavioral, cognitive, and seizure susceptibility testing.

RESULTS

Deletion AS individuals showed lower developmental scores, higher epilepsy risk, and earlier epilepsy onset than non-deletion AS. Importantly, developmental differences persisted in epilepsy-free individuals, demonstrating that genotype effects precede epilepsy. In mice, the deleted interval showed an approximately 50% reduction in copy number and gene expression. Del7-AS mice were largely indistinguishable from AS mice in standard behavioral assays but displayed exacerbated cognitive deficits and increased seizure susceptibility.

CONCLUSIONS

Clinical and preclinical findings demonstrate that neighboring non-imprinted genes within 15q11.2-q13.1 contribute to AS severity beyond loss of UBE3A alone. Together, these results support a role for neighboring genes as modifiers of neurodevelopmental outcome and epilepsy susceptibility in AS.

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Effects of an Ultra-Rare Developmental and Epileptic Encephalopathy on Neural Migration and Network Formation.

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PHD YEAR
Year 3

POSTER NO.
55

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Developmental and Epileptic Encephalopathy
Neurogenetics
MEA

BACKGROUND

Heterozygous missense variants in RHOBTB2 are causative of RHOBTB2-related neurodevelopmental disorder, characterized by severe developmental and epileptic encephalopathy (DEE), profound intellectual disability (ID) and developmental delay. We identified an individual with DEE, recurrent, intractable epilepsy and developmental delay, harboring a variant of unknown significance (VUS) in RHOBTB2, p.W217R. In this study, we aim to establish the pathogenicity of this VUS.

METHODS

Recombinant expression of RHOBTB2 WT, 2 published pathogenic variants or the VUS was used in all experiments. To assess protein stability and turnover, we overexpressed these constructs in HEK293T cells and inhibited proteasomal degradation (MG132) or translation (cycloheximide) followed by Western blotting. In addition, constructs were delivered by in utero electroporation (IUE) into mouse embryos and neural migration was assessed at P1 and P7. Lastly, lentiviral constructs were transduced in murine primary cortical neurons to study network activity on the multi-electrode array (MEA).

RESULTS

MG132 and CHX treatment showed unaffected protein stability and turnover of the W217R variant compared to RHOBTB2 WT. IUE of RHOBTB2 WT and all RHOBTB2 variants led to a 60% delay in neural migration at P1 compared to empty vector. Interestingly, this delay in migration was resolved at P7 for RHOBTB2 WT and all variants, but persisted for W217R.

CONCLUSIONS

The pathogenicity of this variant in RHOBTB2 was studied at the molecular, cellular and electrophysiological level, showing potentially a gain-of-function effect. Additional molecular and functional assays will help elucidate variant-specific disease mechanisms.

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Epilepsy-Associated Gene AP2M1 Impairs Synaptic Transmission in Human Neurons

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PHD YEAR: Year 3
POSTER NO.: 107
LOCATION: Zaal 24 Woudvleugel · Fri
KEYWORDS: AP2M1, Developmental and Epileptic Encephalopathy, Autaptic iNeuron

BACKGROUND

Developmental and epileptic encephalopathies (DEEs) are rare childhood-onset disorders characterized by epileptic seizures, developmental delay, and severe behavioral or cognitive impairments. The etiology of DEEs remains unknown, but several synaptic transmission genes have been implicated. For instance, a de novo loss-of-function variant in the AP2M1 gene (encoding the mu subunit of the adaptor protein complex 2) has been associated with DEEs. In rodent neurons, AP2M1 loss of function impairs synaptic vesicle reformation, post-synaptic receptor internalization, and reduces dendritic complexity. However, the functional consequences of AP2M1 loss of function at human synapses remain to be elucidated.

METHODS

To investigate the effects of AP2M1 on human synaptic transmission, we performed voltage-clamp recordings and immunocytochemical synapse labelling in autaptic iPSC-derived neurons (iNeurons) treated with AAV-mediated AP2M1-targeting RNAi.

RESULTS

AP2M1 RNAi significantly decreased the proportion of connected GABAergic iNeurons, and reduced the amplitude of evoked and spontaneous events, consistent with a lower readily releasable pool (RRP) size. AP2M1 knockdown glutamatergic iNeurons similarly exhibited lower evoked event amplitudes, but without changes in the RRP size, synaptic density, or the proportion of connected cells. AP2M1 RNAi additionally increased release probability and so promoted paired-pulse depression in glutamatergic iNeurons.

CONCLUSIONS

AP2M1 loss of function impairs both glutamatergic and GABAergic synaptic transmission in human neurons, with greater effects on the latter. Future efforts should focus on the electrophysiological effects of AP2M1 within excitatory/inhibitory neural networks. Such results may reveal the potential influence of AP2M1 on the excitatory/inhibitory balance, providing a basis for the mechanism behind its role in DEEs.

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Investigating Population and Cellular Membrane Dynamics in Hippocampal CA1 Epilepsy Circuits

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PHD YEAR: Year 3
POSTER NO.: 9
LOCATION: Foyer ground floor · Thu
KEYWORDS: Voltage Imaging, Temporal Lobe Epilepsy, Electrical Kindling, Secondary Generalisation

Extracellular field recording techniques may not fully resolve key subthreshold membrane voltage states and single-spike features during seizures and are largely cell-type agnostic. We developed an optical electrophysiology framework integrating genetically encoded voltage indicator (GEVI) imaging with electrophysiology to resolve seizure-related membrane voltage () dynamics. We implemented a scalable, in vivo voltage imaging platform using a conventional widefield microscope and sCMOS camera to image soma-targeted GEVIs. Population photometry () and single-cell imaging () were performed alongside local field potentials (LFPs) in hippocampal CA1 of awake mice during rapid electrical kindling. GEVI photometry resolved intrinsic hippocampal activity with temporal precision comparable to LFPs (e.g., higher theta power during running than rest) and captured population seizure dynamics across epileptogenesis. Early ictal paroxysmal transients time-locked to LFP spike–wave events often progressed to spreading depolarization (SD) waves. Late ictal SDs exhibited significantly greater peak depolarization than baseline (vs ;). Single-cell imaging corroborated these patterns and further showed increased cell-cell synchrony from baseline to early ictal paroxysms in pyramidal (vs) and parvalbumin (PV) neurons (vs ; both). Sustained depolarized with spike suppression from early to late ictal periods (to ;) confirmed depolarization block as a dominant mechanism underlying population SDs. SDs occurred despite ongoing LFP poly-spike activity, indicating dissociation between LFP and underlying voltage states. Diverging spike–LFP coupling for PV (near zero-lag) and pyramidal (biphasic) neurons during ictal states indicates distinct circuit roles in ictal propagation. This multimodal voltage imaging framework reveals seizure-related dynamics inaccessible to LFPs and provides a scalable tool for studying epileptogenesis and seizure propagation.

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Automated Segmentation of Vanishing Whiter Matter Brain Images

White Matter Integrity[1], Volume in Vanishing White Matter[1], Ouwerkerk[1], Pouwels[1], P.J.W.[2], van der Knaap[1], M.S.[1,3]

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PHD YEAR
Year 2

POSTER NO.
104

LOCATION
Zaal 24 Woudvleugel · Fri

KEYWORDS
Vanishing White Matter
Deep Learning Segmentation
Quantitative MRI

BACKGROUND

Vanishing white matter (VWM) is a rare leukodystrophy caused by EIF2B1–5 mutations that lead to progressive neurological decline and premature death. MRI plays a central role in the diagnosis of VWM: the classic pattern consists of diffuse cerebral white matter (WM) abnormalities, with the affected WM gradually undergoing rarefication and cystic degeneration. However, the MRI appearance differs considerably with age at onset and disease stage. To date, MRI-based measures of disease progression are obtained through visual scoring or semi-automated segmentation, both of which require substantial manual input. Widely used automated whole-brain segmentation tools are not designed for extensive pediatric WM pathology, and no VWM-specific alternative currently exists.

METHODS

This study therefore proposes a VWM-specific semi-automated segmentation pipeline that refines standard CSF, gray matter (GM) and WM masks and further subdivides WM into VWM-specific classes: normal-appearing, abnormal but structurally present, rarefied and cystic. These labels subsequently serve as the ground truth to train fully automated deep learning segmentation tool. The model is trained and tested on 109 paired 3D T1 and FLAIR MRIs from 87 patients. Expected results The trained model is expected to outperform standard tools, but performance may drop in predominantly cystic cases and in cases with low GM-WM contrast. WM volume and structural integrity are expected to correlate with clinical measures. Possible implications These measures may be used to monitor disease progression and might serve as surrogate outcome measures in clinical trials. This approach supports quantitative MRI analysis and may be extended to other leukodystrophies and to 2D datasets.

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Cerebrospinal Fluid Proteomics Links Compartmentalized Adaptive Immunity to Broad-Rim Lesion Pathology in Progressive Multiple Sclerosis

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PHD YEAR
Year 4

TALK
Session 3B

WHEN · WHERE
Fri 11:00–12:30 · Woudzicht

KEYWORDS
Multiple Sclerosis · White Matter Lesions · Broad Rim Lesions · T Cells · B Cells · Cerebrospinal Fluid · Proteomics

BACKGROUND

Broad rim lesions (BRLs) represent a novel subtype of white matter lesions associated with accelerated disability accumulation in multiple sclerosis (MS). Their underlying biology remains poorly understood. Objectives/Aims We combined post-mortem immunohistochemistry and cerebrospinal fluid (CSF) proteomics, with validation in an independent MS cohort, to investigate the mechanisms driving BRL pathology.

METHODS

Lesion rim size was correlated with clinical progression, MS severity, and CSF proteomic profiles (> 5400 proteins Olink HT, N=61). Targeted assays for neurofilament light chain (NfL), BCMA, and IgG were performed in a subset of donors (N=18). Relevant lymphocyte cell markers were stained on post-mortem human brain tissue using immunohistochemistry (N=20). Using Boruta-based feature selection followed by ridge-regularized logistic regression, we trained a CSF-proteome classifier to predict BRLs and applied it to an independent post-mortem MS dataset (N=16) and a cohort of living individuals with MS without BRL stratification (N=71).

RESULTS

Donors with histologically defined BRLs showed earlier disability progression, reflected by higher age-related MS severity (ARMSS) scores ($p=0.008$), increased acute axonal damage around BRLs (all $p<0.05$), and elevated CSF NfL levels ($p=0.020$). CSF proteomic profiling in BRL donors revealed enrichment of markers linked to B cell signaling and maturation (CD79B, CD38, MZB1, BCMA), microglial activation (CHIT-1), and T-cell activation (CD27, GZMA) (all $p<0.05$). These changes corresponded to histological evidence of enhanced local perivascular B–T-cell interactions, plasma cell differentiation, and IgG production within BRLs (all $p<0.05$). A preliminary CSF BRL classifier achieved an AUC of 0.856 for differentiating postmortem known BRL donors from those without.

When this classifier was applied to cases with unknown BRL status, cases labeled as potential BRL-donors had the highest ARMSS score (p=0.015). Validation in an independent living cohort is pending.

CONCLUSIONS

These findings identify compartmentalized B cell and T cell interaction and B-cell maturation, as a critical driver of chronic focal white matter inflammation and accelerated disability progression in MS. Strong association between histopathological features of BRLs and soluble biomarkers provides opportunities for guiding personalized treatment decisions in progressive MS.

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Exploring the Protective Role of Blood-Brain Barrier Type I Interferon Expression in Multiple Sclerosis

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5 Netherlands Institute for Neuroscience, Amsterdam, the Netherlands This project is funded by the Dutch MS Research Foundation (23-1211 MS).

PHD YEAR: Year 2
POSTER NO.: 66
LOCATION: Foyer ground floor · Fri
KEYWORDS: Multiple Sclerosis, BBB, IFN-I

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease of the central nervous system with a suspected viral component. Although Type I interferons (IFN-I) orchestrate innate anti-viral defenses, and exogenous IFN-β is a key therapeutic in relapsing-remitting MS, no previous study has investigated a possible endogenous IFN-I response in persons with MS (pwMS). We have identified an IFN-α signature at the blood-brain barrier (BBB) in pwMS. Chronic IFN-α elevation has been established to cause certain autoimmune diseases, raising the question of whether endogenous IFN-I in pwMS is protective or contributory to autoimmunity. We investigated this by immunohistochemistry on a large human MS brain tissue cohort, complemented by mechanistic in vitro modeling. To map IFN-α+ blood vessels (BVs) in MS brain tissue, we developed an image processing pipeline integrating two software packages, DeeperHistReg and BiaPy, into QuPath. Numbers of IFN-α+ BVs were significantly higher in MS tissue compared to controls, with the highest IFN-α+ BV density found around inactive lesions. Interestingly, higher IFN-α+ BV density was positively associated with a longer disease course, indicating a clinically protective effect. Further, IFN-α+ BVs were surrounded by significantly more perivascular CD8+ T cells compared to IFN-α- BVs, but fewer plasma cells. To evaluate these dynamics functionally, we tested recombinant and lentiviral-driven IFN-α6 treatment on hCMEC/D3 monolayers in Transwell assays. IFN-α6 alone did not significantly alter barrier integrity or CD8+ T cell transmigration compared to the standard pro-inflammatory stimulus. In MS brain tissue, however, endogenous IFN-α6 specifically co-localised with pericytes, suggesting its effects may depend on endothelial cell-pericyte communication. In conclusion, local IFN-α expression may serve as an endogenous defense mechanism at the BBB in MS. To substantiate these preliminary findings, future experiments will utilize a more physiological, pre-inflamed in vitro co-culture system, incorporating IFN-α6-overexpressing induced pluripotent stem cell-derived pericytes and brain microvascular endothelial cells.

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Investigating the Role of Astrocyte Endfeet Proteins and Their Interaction with the Blood-Brain-Barrier

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PHD YEAR: Year 2
POSTER NO.: 92
LOCATION: Zaal 22 + 23 Woudvleugel · Fri
KEYWORDS: Astrocyte Endfeet BBB

BACKGROUND

The blood-brain barrier (BBB) consists of endothelial cells, pericytes and astrocyte endfeet and is essential for maintaining homeostasis in the brain. Impaired functioning of the BBB is an important contributor to the progression of neuroinflammatory diseases such as multiple sclerosis (MS). Astrocyte endfeet have recently been implicated as a possible immune target in MS due to the molecular similarity of one of an endfeet protein, GlialCAM to the Epstein-Barr virus. This is a common infection found in almost all MS patients. Investigation of endfeet proteins and could provide valuable insight into the functioning of the BBB in both healthy and pathological circumstances. Previous studies have used rodent cells to investigate these endfeet-endothelial cell interactions, but these models fail to fully replicate the human brain. In this study, we will be developing a fully human induced pluripotent stem-cell (hiPSC) derived model of the BBB on a chip consisting of human brain microvascular endothelial cells (hBMECs), pericytes and astrocytes.

METHODS

A mix of different pro-inflammatory cytokines will be used to mimic the pathological conditions found in MS in order. to investigate their role in MS pathology. Protein targets will be selected based on previously established databases and polarization of these proteins will be tracked using live cell imaging. Selected proteins will be overexpressed or knocked out using CRISPR-cas9 in order to study their role in BBB development and maintenance. A viscous finger patterning model of the BBB will be used to study leukocyte extravasation under flow conditions, providing further insight into the role of astrocyte endfeet in immune cell migration in MS.

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Modelling Acute Episodic Neurological Decline in Vanishing White Matter Using Lipopolysaccharide

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PHD YEAR
Year 2

POSTER NO.
106

LOCATION
Zaal 24 Woudvleugel · Fri

KEYWORDS
Lipopolysaccharide ISR

BACKGROUND

Vanishing white matter (VWM) is a leukodystrophy, characterized by the loss of white matter caused by a genetic defect in the protein complex eIF2B, a central regulator in the integrated stress response (ISR). VWM is showcases chronic progressive neurological decline (CPND), in which patients lose neurological functions and die. Physical stresses, such as infections, activate the ISR upstream of eIF2B, which in VWM may hyperactivate the downstream ISR. Such stresses provoke acute episodes of neurological decline (AEND), in which VWM patients deteriorate rapidly. Sometimes death follows, but often partial or complete recovery occurs. Upon recovery, MRI changes in the pons improve or disappear. CPND and AEND are two separate processes in VWM, each with its own mechanism.

METHODS

VWM mice were injected intraperitoneally with lipopolysaccharide (LPS) (2.5 mg/kg) and assessed for the signs of AEND such as inflammation and accelerated neurological decline. We analyzed ISR related markers, as well as microglial, astrocytic, and myelin changes both on mRNA level, as well as neuropathologically. We compared these changes between AEND affected brain regions compared to CPND affected regions. Wild-type mice were used as additional controls.

RESULTS

We observe inflammation and accelerated neurological decline in VWM mice treated with LPS a day post-treatment compared to VWM saline-treated with a peak on day three post-LPS injection. Moreover, there is an increased expression of ISR-related mRNA markers in LPS-treated VWM mice, compared to saline controls and WT LPS-injected mice. The assessment of astrocyte density, myelin content, microglial activation, and ISR activation suggest regional differences in both VWM and WT after the LPS treatment.

CONCLUSIONS

The present findings highlight the potential of using LPS to model AEND. This model can later be used to find preventative or acute treatment for AEND in patients.

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Optimizing Myelin Water Imaging in MS

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PHD YEAR
Year 2

POSTER NO.
83

LOCATION
Foyer top floor · Fri

KEYWORDS
Demyelination · Multi-Echo Gradient Echo · Multi Compartment Relaxometry

BACKGROUND

Myelin water imaging (MWI) allows in vivo quantification of myelin content using MRI. Multi-echo gradient-echo (MEGRE) sequences with Variable Flip Angles (VFA), combined with diffusion-weighted imaging (DWI), can generate robust, whole-brain myelin water fraction (MWF) maps more efficiently than conventional implementations. We aim to evaluate how spatial resolution and number of flip angles affect MWI quality in a clinical research setting.

METHODS

Fifteen people with MS and ten healthy controls were scanned at 3T (Siemens VIDA). MRI included multi-shell DWI and 3D-MEGRE acquired at 2.0mm and 2.5mm isotropic resolution. Twelve echoes were acquired at five flip angles. Myelin water fraction (MWF) was quantified based on a three-compartment model incorporating T1, T2*, and diffusion information. We determined MWF in normal appearing white matter (NAWM), lesions and corpus callosum. Associations between MWF values across resolutions and VFA schemes were assessed using Bland Altman and ICC-C.

RESULTS

MWF was highest in the corpus callosum (10.2 ± 1.1%), intermediate in NAWM (7.9 ± 0.7%), and lowest in lesions (4.9 ± 0.7%) (values for 2.0mm and FA5). A FA4 MEGRE protocol showed comparable sensitivity to myelin content, while FA3 systematically overestimated MWF and showed greater variability, particularly in lesions. Agreement between spatial resolutions was moderate to good (ICC-C 0.80–0.91), with FA5 and FA4 showing the highest cross-resolution consistency. QC monitoring of fitting results is recommended to strengthen reliability of MWF results.

CONCLUSIONS

MWI duration can be shortened with a FA4 MEGRE protocol. Resolution choice should be guided by study aims, as 2.0mm and2.5 mm were not fully interchangeable.

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Quantitative MRI as Biomarkers for Disease Severity in Hypomyelinating Leukodystrophies

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PHD YEAR
Year 3

POSTER NO.
51

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Leukodystrophies · Myelin · Myelin Water Imaging

BACKGROUND

Hypomyelinating leukodystrophies, including oculodentodigital dysplasia (ODDD), hypomyelination, hypodontia, and hypogonadotropic hypogonadism (4H), hypomyelination with atrophy of the basal ganglia and cerebellum (HABC), and Pelizaeus-Merzbacher disease (PMD), share deficient myelin formation, but differ in the level/region of deficiency, genetic etiology, and clinical severity. We investigated whether quantitative MRI can objectively evaluate myelin deficiency and whether this correlates with clinical severity.

METHODS

Patients with genetically confirmed hypomyelinating leukodystrophies (n=28) and controls (n=26) were scanned at 3T MRI. We obtained Myelin water fraction (MWF), and DTI and NODDI measures. These measures were assessed globally (in cerebral white matter) and will be assessed in separate regions of interest, normalized to age-expected values, using linear mixed models. Spearman correlations were determined with motor function as assessed using GMFC-MLD scores.

RESULTS

All four disease groups showed significantly reduced MWF compared to controls, with lowest values in PMD. FA and NDI were also reduced, except for ODDD. In the PMD group, MWF showed a strong correlation with GMFC-MLD scores (ρ= -0.71, p=0.004).

CONCLUSIONS

Quantitative MRI reflects the biological spectrum of hypomyelination, tracks clinical severity, and differentiates disease-specific neuropathology profiles, supporting its potential as objective neuroimaging biomarkers.

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Targeting the CXCL12/ACKR3 Axis Drives Remyelination in Human MS Lesions ex vivo

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PHD YEAR
Year 4

TALK
Session 3B

WHEN · WHERE
Fri 11:00–12:30 · Woudzicht

KEYWORDS
Remyelination · Human Slice Cultures · Multiple Sclerosis

BACKGROUND

Failure of endogenous oligodendrocyte precursor cell (OPC) recruitment and maturation halts remyelination in multiple sclerosis (MS). This failure is heavily driven by disruptions in the central nervous system's chemical signaling network, in which the CXCL12/CXCR4/ACKR3 axis is emerging as a critical player in directing cell migration and tissue repair. We investigated whether targeting the CXCL12/CXCR4/ACKR3 axis, specifically by blocking the scavenger receptor ACKR3, can overcome impaired remyelination.

METHODS

We evaluated the effect of CXCL12 and the ACKR3 antagonist ACT-1004-1239 using primary rat OPCs (in vitro) and lysophosphatidylcholine (LPC)-demyelinated mouse brain slices (ex vivo),. Using a multidisciplinary approach that included chemotaxis, 3D microfiber wrapping, ELISA, immunofluorescence, and electron microscopy, we investigated the effects of CXCL12 modulation on OPC development and remyelination.

RESULTS

In vitro, CXCL12 directed migration, drove proliferation, led to accelerated differentiation, the formation of myelin sheaths and promoted functional 3D microfiber wrapping. Ex vivo, ACT-1004-1239 blocked ACKR3 scavenging, progressively increasing local CXCL12 levels in both mouse and human slice supernatants. These increased levels promoted structural remyelination.

CONCLUSIONS

We here show that ACKR3 blocking could be a promising strategy for myelin repair in MS.

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The Brain Lipidome Reflects Treatment Effect in Metachromatic Leukodystrophy

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PHD YEAR
Year 2

POSTER NO.
58

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Lipidomics Leukodystrophy Post-Mortem Brain Tissue

BACKGROUND

Metachormatic leukodystrophy (MLD) is an inherited metabolic disorder caused by pathogenic variants in the gene encoding the lysosomal enzyme arylsulfatase A (ASA). ASA deficiency leads to sulfatide accumulation in myelin, resulting in demyelination and neurodegeneration in both the central and peripheral nervous systems. Identification of reliable biomarkers for MLD are essential for monitoring disease activity and evaluating therapy. As myelin consists of over 70% lipid, lipidomic analysis of brain tissue may provide mechanistic insights into disease pathology and facilitate the discovery of novel biomarkers.[1]

METHODS

Lipidomic analysis using UPLC-MS was applied to post-mortem frontal white matter samples from five MLD patients (two untreated, three treated with hematopoietic stem cell transplantation (HSCT)) and four young controls. Lipids were identified based on accurate mass and retention time, then semi-quantified using appropriate internal standards. Data were processed using an in-house R/MATLAB pipeline.[2] Statistical differences between groups were assessed using Student's t-test or one-way ANOVA.

RESULTS

Principal component analysis revealed clear separation between subgroups. Untreated MLD patients showed increased complex glycosphingolipids and sulfatides, and decreased ether lipids. In HSCT-treated patients, these alterations were partially reversed, with near normalisation in the neurologically stable patient.

CONCLUSIONS

Brain lipidomics distinguished controls, untreated MLD, and HSCT-treated patients, showing that HSCT induces partial normalisation of disease associated lipid alterations. Importantly, these changes correlated with the clinical phenotype, indicating that the brain lipidome reflects treatment efficacy in MLD.

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Background Uptake of Monoclonal Antibodies in the Brain

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PHD YEAR
Year 2

POSTER NO.
109

LOCATION
Zaal 25 Woudvleugel · Fri

KEYWORDS
Brain | Monoclonal Antibodies | Immuno-PET

BACKGROUND

Monoclonal antibodies (mAbs) are increasingly used as therapeutic agents in neuro-oncology and neurodegenerative disease. Despite their growing clinical relevance, their ability to penetrate the brain remains poorly understood due to the restrictive nature of the blood–brain barrier (BBB). PET imaging with Zirconium-89 (^{89}Zr)-labeled mAbs allows for quantification of antibody uptake in organs and tumors. This study aims to quantify the baseline, non-specific uptake of ^{89}Zr-labeled mAbs in brain tissue. Additionally, the influence of target expression, BBB disruption, lesion viability, and dosing on antibody uptake was investigated.

METHODS

Retrospective positron emission tomography/computed tomography (PET/CT) data from three clinical trials with ^{89}Zr-labeled mAbs were analyzed. Ki values, representing irreversible tracer uptake, were derived using Patlak analysis from scans ≥1-day post-injection. Brain tissue and metastases were delineated manually, and Ki values were compared across cohorts with no target expression, target expression, and brain metastases. Interobserver reliability was assessed, and statistical comparisons were performed using Kruskal-Wallis and Wilcoxon tests.

RESULTS

Uptake in normal brain tissue was assessed in 18 patients, two of whom had post-treatment brain metastases that were included in the analysis. Ki in target-negative brain tissue was low but measurable (median: 2.0×10^{-5} $\mu L \cdot g^{-1} \cdot h^{-1}$, IQR: 1.5 – 3.2), indicating baseline non-specific uptake. Ki was significantly higher in target-positive brain tissue (median: 3.9×10^{-5} $\mu L \cdot g^{-1} \cdot h^{-1}$, IQR: 2.5 - 4.6), and substantially elevated in post-treatment brain metastases (median: 120×10^{-5} $\mu L \cdot g^{-1} \cdot h^{-1}$, IQR: 115 – 180). Notably, uptake was particularly high in post-treatment lesions with viable tumor tissue (median: 180×10^{-5} $\mu L \cdot g^{-1} \cdot h^{-1}$, n =2), compared to post-treatment lesions with therapy-related imaging changes (52.1×10^{-5} $\mu L \cdot g^{-1} \cdot h^{-1}$). In a subset of five patients with two injections with different doses of non-labeled mAb, three showed decreased Ki at higher mass doses.

CONCLUSIONS

Irreversible brain uptake of mAbs can be quantified using Patlak-derived Ki values, even at low levels. The data establish a baseline for non-specific brain uptake. The uptake is significantly higher in the presence of target expression and even higher in brain metastases, likely due to BBB disruption. These findings support the use of PET imaging with Patlak analysis as a non-invasive method to evaluate CNS target engagement and drug delivery in early-phase clinical trials.

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Towards Functional Understanding of Malignant Neuron-Glioblastoma Synaptic Crosstalk

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PHD YEAR: Year 2
POSTER NO.: 95
LOCATION: Zaal 22 + 23 Woudvleugel · Fri
KEYWORDS: Neurogliomal Synapses, Glioblastoma, Live Cell Calcium Imaging

BACKGROUND

Glioblastoma (GBM) is the most aggressive primary adult brain tumor, characterized by rapid growth, invasion, therapy resistance, and a median survival of ~15 months. Recent studies reveal that GBM cells form functional ”neurogliomal synapses” with neurons. Synaptic activity drives calcium (Ca^{2+}) influx into tumor cells, promoting proliferation and progression. The main goal of this research is to disrupt neurogliomal synaptic transmission to reduce tumor survival by identifying key synaptic regulators through functional screening.

METHODS

Human skin fibroblasts were reprogrammed into induced pluripotent stem cells (iPSCs) and differentiated into NGN2 cortical-like glutamatergic neurons. These neurons were co-cultured with rat glia and patient-derived GBM cells. Neurons and tumor cells were separately transduced with lentiviruses expressing genetically encoded calcium indicators—jRGECO6 (red) and GCaMP6 (green), respectively. Functional connectivity was evaluated using dual-color live-cell calcium imaging (LCI) under electrical and chemical stimulation, alongside immunocytochemical validation of synaptic and tumor markers.

RESULTS

We established a human in vitro model of neurogliomal synapses, revealing marked intra- and inter-line cellular heterogeneity. Quantitative LCI analysis under electrical and chemical triggers demonstrated that tumor network functional responsiveness varies significantly across patient-derived cell lines, with the S24 line exhibiting the highest functional engagement (~40%).

CONCLUSIONS

This human co-culture platform confirms line-dependent functional heterogeneity in neuron–tumor connectivity. The hyper-responsive S24 line provides a validated model for high-throughput arrayed screening. Combining Channelrhodopsin-2 (ChR2) neuronal optogenetics with tumor-specific Ca^{2+} reporters and CRISPR-knockdowns enables systematic identification and disruption of key synaptic regulators driving tumor progression.

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Lipid Nanoparticles with Enhanced Endosomal Escape Improve mRNA Delivery to Retinal Cells

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PHD YEAR
Year 3

POSTER NO.
98

LOCATION
Zaal 24 Woudvleugel · Fri

KEYWORDS
Gene Therapy · Lipid Nanoparticles · Inherited Retinal Degeneration

BACKGROUND

Adeno-associated viruses (AAVs) are commonly used to deliver gene therapy for inherited retinal diseases, but there are safety concerns regarding their viral origin. Lipid nanoparticles (LNPs) are alternative non-viral delivery vesicles for gene therapy. The major bottleneck of LNP-mediated nucleic acid delivery is inefficient endosomal escape. As a result, high doses are often required for effective retinal transfection. To address this, we compared a widely used gold standard LNP (inspired by the clinical Onpattro formulation; LNP1) to an LNP with enhanced endosomal escape (LNP2), aiming to improve delivery efficiency to retinal cells.

METHODS

We created LNPs containing eGFP-encoding mRNA, with or without a fluorescent label (DiD) to track the particle cellular uptake. LNPs were screened in two retinal primary cell lines, and cellular uptake and transfection efficiency were quantified by fluorescence microscopy and flow cytometry analysis. We subretinally injected Brown Norway rats with LNP (100, 200, and 300 ng of mRNA per eye) and terminated them 24 h post-injection. Eyes and major organs were collected for transfection and biodistribution analyses.

RESULTS

LNP2 outperformed LNP1 in transfection efficiency, despite similar cellular uptake levels. Additionally, at high doses, LNP2 exhibited lower cytotoxicity than LNP1. Improved retinal transfection was also observed in vivo with LNP2 compared to LNP1, though further analysis is ongoing to determine cellular specificity and biodistribution.

CONCLUSIONS

LNP2 achieved high transfection efficiency in the retina at lower doses than LNP1. Future studies will focus on determining the long-term safety and efficacy of this formulation for gene-editing applications.

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Clearing the Air: Smoking and Neurobiological Changes Across the Early Stages of Psychosis

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PHD YEAR
Year 4

TALK
Session 4C

WHEN · WHERE
Fri 13:50–15:20 · Zaal 15 (45 places)

KEYWORDS
Tobacco Smoking · Psychosis · Magnetic Resonance Imaging

Tobacco use is alarmingly prevalent among patients with schizophrenia and poses a serious health concern as it is linked to increased mortality, higher rates of psychotic relapse, more severe symptoms, and reduced quality of life. While the underlying mechanisms of this co-occurrence remain unclear, it is likely that shared neurobiological and genetic vulnerabilities play a pivotal role. In this talk, I'll give a layman's overview of my PhD thesis (to be presented at my public PhD defence), in which I used magnetic resonance imaging (MRI), a powerful tool for looking at the brain's structure and function, to investigate this link. Across 10 studies using various MRI techniques (including structural MRI, functional MRI, diffusion tensor imaging [DTI], neuromelanin-MRI, and magnetic resonance spectroscopy [MRS]), I examined the brains of people at different early stages of psychosis: individuals at clinical high-risk for psychosis, and first-episode psychosis patients (FEP). I'll share what these studies reveal about how smoking may be connected to the brain changes seen in early psychosis, and what this could mean for patients going forward.

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Cross-Disorder Convergence of Cortical Thickness Alterations Across Neuropsychiatric Conditions

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PHD YEAR
Year 3

POSTER NO.
77

LOCATION
Foyer ground floor · Fri

KEYWORDS
Mega-Analysis | MRI | Cortical Thickness | Cross-Disorder | Shared Vulnerability | Psychiatry

BACKGROUND

Neuropsychiatric disorders frequently show overlapping cortical abnormalities, but the extent to which these patterns converge across diagnoses remains unclear at high spatial resolution. We examined shared and disorder-specific cortical thickness (CT) alterations across ten neuropsychiatric conditions.

METHODS

T1-weighted MRI data from 14,704 participants (7,366 patients, 7,338 controls) across 39 datasets were analyzed in a vertex-wise mega-analysis. Including 10 different conditions: attention-deficit/hyperactivity disorder (ADHD), anxiety disorders (ANX), autism spectrum disorder (ASD), bipolar disorder (BD), major depressive disorder (MDD), insomnia (INS), obsessive-compulsive disorder (OCD), schizoaffective disorder (SCA), schizophrenia (SCZ), and substance use disorder (SUD). Disorder-specific CT effect-size maps were compared using pairwise spatial correlations, hierarchical clustering, and principal component analysis. Shared cortical involvement was characterized across the disorders showing the strongest convergence and related to cortical networks, normative receptor-density maps, and meta-analytic cognitive activation maps. Matched analyses of cortical surface area and volume tested whether the cross-disorder organization extended across morphometric measures.

RESULTS

Significant CT alterations were observed in all ten disorders (Cohen's d=-0.62 to 0.40). The strongest convergence occurred among BD, MDD, SCA, SCZ, and SUD (mean r=0.36), with additional correspondence between ADHD and ASD. Shared involvement across the five convergent disorders was predominantly characterized by cortical thinning and was strongest in frontal, temporal, and cingulate cortex, and within limbic and default-mode networks. This pattern showed spatial associations with several normative neurotransmitter receptor distributions and with cognitive maps related to emotion, social function, and executive/cognitive control. Cross-disorder CT similarity corresponded partly with cortical volume but not with surface area.

CONCLUSIONS

CT alterations converge across diagnostic boundaries, with the strongest shared pattern among bipolar disorder, major depressive disorder, schizoaffective disorder, schizophrenia, and substance use disorder. These findings map shared cortical vulnerability across neuropsychiatric conditions.

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Emotion Dynamics in Insomnia: An Experience Sampling Dynamic Time Warp Study

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PHD YEAR
Year 2

POSTER NO.
80

LOCATION
Foyer top floor · Fri

KEYWORDS
Insomnia | Ecological Momentary Assessment | Dynamic Time Warping

BACKGROUND

Insomnia is a key risk factor for the development of mental health disorders. One proposed mechanism underlying this vulnerability is that poor sleep quality disrupts overnight emotional processing. This study investigated the temporal dynamics of emotions in individuals with insomnia and normal sleepers.

METHODS

Using ecological momentary assessment (EMA), we assessed the dynamics of momentary well-being across affective, physical, and cognitive domains. 171 individuals with insomnia and 38 controls completed EMA 8 times a day for 9 consecutive days. The temporal dynamics of emotions were analysed with dynamic time warp (DTW) analyses. DTW analyses were conducted at the group-level and were visualized in symptom networks.

RESULTS

Participants had a mean age of 48.8 years (range: 20–69), and 71% were women. Feeling sleepy appeared to be the driver in the emotion dynamic network of individuals with insomnia, as this item emerged as a prominent lead (p=0.003). This differed markedly from the normal sleepers' network (p=0.01), in which not feeling satisfied was the emotion most often preceding other items that approached significance (p=0.07). Moreover, a strongly interconnected hyperarousal cluster was found in the network of individuals with insomnia, possibly reflecting the chronic hyperarousal state that characterizes insomnia disorder. Within this hyperarousal cluster, fluctuations in the inability to concentrate preceded fluctuations in perceived stress (p=0.002).

CONCLUSIONS

The temporal dynamics of emotional states differ markedly between individuals with and without insomnia, suggesting a fundamentally different pattern in the perception of sleepiness. Chronic hyperarousal may partly account for this pattern, with implications for treatments targeting arousal regulation.

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Post-Treatment Sleep Shapes Treatment Session Outcome in Post-Traumatic Stress Disorder

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PHD YEAR
Year 3

POSTER NO.
94

LOCATION
Zaal 22 + 23 Woudvleugel · Fri

KEYWORDS
Posttraumatic Stress Disorder · Sleep · Treatment

BACKGROUND

During exposure-based therapy for posttraumatic stress disorder (PTSD), traumatic memories are neutralized by reactivating and re-encoding them with reduced fear and arousal. Sleep is essential for the integration of the altered memories into long-term memory networks through memory consolidation. In this study, we aimed to identify the role of sleep in ongoing PTSD treatment by assessing the day-to-day interrelatedness between treatment session outcome and different subjective and objective sleep parameters during a standard 5-day inpatient treatment program for PTSD.

METHODS

Sleep was measured using sleep diaries and a 2-channel wearable EEG-device (ZMax). At the start and end of each treatment day and the following morning, patients rated symptoms related to the treated memory using the Index Trauma Memory Interview. The Overnight Retention (OR) per treated memory was calculated to quantify the retention of the daytime treatment effect overnight. Linear mixed models were used to investigate the relation between the OR and sleep.

RESULTS

Data of 57 patients were used in analyses. The ORs were mostly negative, indicating an overnight loss of daytime treatment effect. The OR was positively associated with spindle density during NREM2 sleep (β=5.10, p=0.024), and reported sleep efficiency (β=0.59, p=0.028).

CONCLUSIONS

Overnight retention of treatment session outcome in PTSD was associated with sleep diary-derived sleep efficiency and EEG-derived sleep spindle density. Higher spindle density and sleep efficiency might indicate more pronounced adaptive memory processing of the therapeutically-altered traumatic memories.
Post-treatment sleeps thus plays a role in shaping treatment response in PTSD, providing the rationale for future sleep-based approaches to augment day-time treatment effects in PTSD.

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Resolving Distress Overnight: The Role of Noradrenaline in Sleep

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PHD YEAR
Year 3

POSTER NO.
49

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Sleep Noradrenaline Stress

Anxiety- and stress-related disorders (ASRD) and insomnia disorder (ID) collectively account for a large proportion of neuropsychiatric burden and are characterized by chronic distress and hyperarousal. Growing evidence suggests that noradrenergic activity during rapid eye movement (REM) sleep is key in resolving emotional distress overnight. During REM sleep, the brain's main source of noradrenaline - the locus coeruleus - becomes inactive, facilitating emotional regulation and synaptic plasticity. Disruptions to this process may impair overnight emotional regulation, worsening distress and contributing to the chronicity of ASRD and ID. We investigated whether modulating noradrenergic activity during REM sleep influenced the overnight resolution of emotional distress related to recent memories. 59 participants with varying levels of insomnia and anxiety symptoms completed five overnight lab visits, receiving a placebo or a medication that either upregulates (Atomoxetine) or downregulates (Nebivolol, Clonidine, and Daridorexant) noradrenergic activity before sleep. To test how these pharmacological manipulations affected overnight emotional regulation, we assessed emotional distress before and after sleep using a karaoke task, in which participants listened to recordings of their off-tune solo singing. Subjective distress ratings and physiological measures were collected to quantify emotional distress. High-density electroencephalography was recorded during sleep to investigate whether REM sleep features mediated the effects of noradrenergic modulation on emotion regulation. I will present preliminary findings on how noradrenergic signaling during REM sleep influences emotional regulation and discuss potential implications for treating ASRD and ID.

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Where Are You Feeling?

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PHD YEAR
Year 2

POSTER NO.
21

LOCATION
Foyer top floor · Thu

KEYWORDS
Empathy | Emotional Granularity | Dark Traits

BACKGROUND

Emotional granularity refers to the ability to differentiate between emotional states, and has been shown to predict well-being and resilience in adolescence [1,2]. This capacity is thought to support empathy [3], and appears to be reduced in people with antisocial tendencies [4]. We investigated how emotional and bodily experiences of an emotionally evocative movie fragment (The Champ) relate to empathic and dark personality traits. Because scenes were selected to elicit distinct emotional states, we expected participants' responses to vary meaningfully across scenes, and hypothesized that this variability would increase with empathy and decrease with psychopathy.

METHODS

As a first step toward an fMRI study in youth at risk for antisocial behavior, we conducted an online pilot study in a healthy adult sample (N = 100, ages 18-30). For each participant, we calculated Spearman correlations between pairs of scenes' emotion and bodily sensation ratings, yielding within-subject similarity matrices. Granularity was defined as 1 minus the mean unique pairwise correlation, with higher scores indicating greater differentiation.

RESULTS

Bodily and emotional granularity were only weakly correlated, suggesting they capture partially distinct aspects of affective differentiation. The tendency to identify with fictional characters predicted higher emotional granularity, while narcissism predicted greater bodily granularity. Psychopathy was unrelated to either measure, possibly reflecting low psychopathy scores in this sample.

CONCLUSIONS

Emotional and bodily granularity appear to reflect distinct dimensions of affective differentiation with different personality correlates. We will next examine whether these individual differences relate to neural synchronization during film viewing (ISC) in youth at risk for antisocial behavior.

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Age-Related Effects of Alcohol and Cannabis Exposure in Rats: An Overview of My PhD Trajectory

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PHD YEAR: Year 4
TALK: Session 1A
WHEN · WHERE: Thu 10:45–11:45 · Woudzicht (108)
KEYWORDS: Alcohol, Cannabis, Animal Models, Neurobiology, Behaviour, Cognition

Vulnerability and resilience to addiction are strongly age-dependent. Adolescence is characterised by heightened engagement in risk-taking and novelty-seeking behaviours, including experimentation with drugs of abuse. Despite this increased exposure, most adolescent-onset substance use does not develop into a lasting disorder. However, in the subset of cases where adolescent-onset addiction persists into adulthood, it tends to follow a more severe and treatment-resistant course than addiction that develops later in life. This apparent paradox, greater exposure and risk-taking during adolescence, yet greater resilience overall, coupled with poorer outcomes in the minority who do not resolve, formed the central question guiding my PhD research. To investigate the neurobiological basis of this age-dependent vulnerability, I employed a preclinical rat model, using alcohol and cannabis as the substances of interest given their high prevalence of use among adolescence. As part of this work, I designed and constructed custom cannabis vapour exposure chambers to allow for controlled, standardised drug administration. In separated studies, rats were exposed to either alcohol or cannabis during adolescence or adulthood, allowing for direct comparison of the behavioural and neurobiological consequences of drug exposure across these two developmental windows. Behavioural outcomes, including Pavlovian approach, cognitive impulsivity, and cognitive flexibility, and cognitive inhibition, were assessed, alongside neurobiological measures encompassing proteomics, MR imaging and morphological assessment using Golgi staining. In this presentation, I will reflect on my PhD trajectory as a whole: the conceptual and technical challenges involved in establishing this model system, the key behavioural and neurobiological findings that emerged, and how these results contribute to our broader understanding of why the adolescent brain is both particularly vulnerable and particularly resilient to the long-term effects of drug exposure.

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Dissecting the Downstream Connections of Prelimbic Alcohol- and Sucrose Self-Administration Ensembles

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PHD YEAR: Year 3
POSTER NO.: 75
LOCATION: Foyer ground floor · Fri
KEYWORDS: Alcohol, Ensembles, Connectivity

BACKGROUND

Alcohol Use Disorder (AUD) is a chronic brain disease marked by continued alcohol use and a long-lasting vulnerability to relapse. Triggers for relapse include learned associations with the rewarding effects of alcohol, such as specific environments (e.g., bars) or visual cues (like bottles or advertisements). These associations can cause relapse even long after abstinence, suggesting they are supported by lasting neurobiological changes. Our earlier work (Visser et al., 2020, Sci Adv) showed that alcohol-associated memories are stored in small groups of neurons – called ensembles – in the prefrontal cortex (PFC), and that these neurons drive relapse behaviour. In contrast, similar sucrose-associated ensembles were not necessary for relapse. The difference in relevance might lie in the connections these ensembles have to other areas in the brain, but this remains as of yet unknown.

METHODS

To uncover this, we investigated prelimbic neurons active during cue-paired alcohol or sucrose self-administration and traced their projections throughout the brain. Furhtermore, we assessed the relevance of this prelimbic ensemble for cue-induced reinstatement by measuring cFos expression throughout the brain.

RESULTS

We found that alcohol and sucrose self-administration recruit PL ensembles of similar size, but that alcohol-related ensembles are more strongly reactivated following cue-induced reinstatement. This is accompanied by differences in downstream connections, with alcohol ensembles projecting more strongly to.. and sucrose more strongly to.. Rest TBD !

CONCLUSIONS

TBD

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05

THEME

Integrative Systems

Neuroimmunology p. 150

Stress and the Brain p. 161

Water & Energy balance p. 163

Biological Rhythms and Sleep p. 164

Early Life Nutritional Programming of Neuroinflammation: The Impact of Dietary ω6/ω3 Fatty Acids Ratios on Microglia

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PHD YEAR
Year 4

TALK
Session 3C

WHEN · WHERE
Fri 11:00–12:30 · Zaal 15

KEYWORDS
Omega-3 PUFAs | Early Life | Neuroinflammation

BACKGROUND

Early life is a critical window in which diet may have lasting effects on brain development, neuroimmune function, and lipid metabolism. Ω-3 and ω-6 polyunsaturated fatty acids (PUFAs), including their derivatives, regulate microglial function and inflammatory responses. We previously showed that early dietary modulation of the ω6:ω3 PUFA ratio protects against cognitive decline and persistently alters microglia and brain lipids following early-life stress (ELS). This is relevant to Alzheimer's disease (AD), in which neuroinflammation and lipid dysregulation may promote disease progression. Here, we examined whether early-life ω3 PUFA enrichment durably affects microglia, amyloid-β pathology, and brain lipid profiles in mouse models of ELS and AD.

METHODS

Mice received a standard-like ω6:ω3 diet (15:1; STL) or an ω3-enriched diet (1:1; ENR) from postnatal day 2 to 42. I) Long-term effects were assessed in wild-type mice exposed to ELS from postnatal day 2 to 9 and examined at postnatal day 60, and ii) in APPswe/PS1dE9 mice examined at approximately 6 months. We assessed microglial morphology, activation-related markers, and hippocampal PUFA and oxylipin profiles. In APP/PS1 mice, amyloid-β plaque load and ex vivo microglial phagocytosis were additionally evaluated.

RESULTS

In wild-type mice, ELS induced persistent hippocampal microglial morphological changes in males. In females, early ω3 enrichment altered microglial complexity independently of ELS. ELS alone did not affect hippocampal free PUFA or oxylipin concentrations, although dietary responses differed by ELS exposure. In APP/PS1 mice, early ω3 enrichment reduced amyloid-β plaque load in the hippocampus and entorhinal cortex, attenuated disease-associated microglial morphological changes, and enhanced microglial amyloid-β, but not synaptosome, phagocytosis.

CONCLUSIONS

Early-life ω3 enrichment may durably modulate microglial function and amyloid pathology, supporting early nutritional targeting of microglia–lipid interactions to reduce vulnerability to AD-related neuroinflammation.

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Increased 15-HETE in Multiple Sclerosis Lesions and the Effect on the Microglial State in iPSC-Derived Human Microglia

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PHD YEAR: Year 3
POSTER NO.: 73
LOCATION: Foyer ground floor · Fri
KEYWORDS: Lipid Mediators · Multiple Sclerosis · Microglia

BACKGROUND

A dysregulated bioactive lipid mediator (LM) profile may contribute to the chronic neuro-inflammatory nature of Multiple Sclerosis (MS). In particular, we have previously reported elevated plasma levels of the arachidonic acid (AA)-derivative 15-HETE , which correlated with reduced brain and increased lesion volumes in people with progressive MS (pwPMS). Yet, local 15-HETE levels within the MS brain and the putative effect of 15-HETE on neighboring central nervous system (CNS) cells remain elusive.

METHODS

The distribution of 15-HETE in white matter (WM) MS brain tissue and non-neurological controls was examined using mass spectrometry imaging analyses. As 15-HETE can exist in two stereoisomers synthesized by distinct enzymes, spatial transcriptomic was used to determine WM lesion-specific expression. The effect of ALOX15B-derived 15(S)-HETE was subsequently tested on IFNy/LPS-treated human iPSC-derived microglia (iMicroglia) with bulk RNA sequencing.

RESULTS

With a trend of overall increased 15-HETE in the WM of pwPMS, a significant increase was determined in the core of the lesions. Similarly, an increase of ALOX15B was mainly allocated to the core of WM lesions. On IFNY/LPS-reactive iMicroglia, differential gene expression revealed a decrease of cytokine production (SOCS1/3/7, TGFB2), increase of disease-associated microglial markers (Perilipin-2, FABP4, CD9) and lipid metabolism (PTGS2, ACSL1/4/5) by 15(S)-HETE.

CONCLUSIONS

With ALOX15B expression similarly being increased in WM lesions and microglia, we additionally reveal a disease-associated potential of ALOX15B-derived 15(S)-HETE on the microglial state in vitro.

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Natural Killer Cells Acquire an Activated and Migratory Phenotype in a Unique Same-Birthyear Cohort of People with Multiple Sclerosis

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PHD YEAR: Year 4 | POSTER NO. | LOCATION | KEYWORDS

BACKGROUND

Multiple sclerosis (MS) is characterized by immune cell infiltration into the central nervous system. We have previously demonstrated that natural killer cells (NK cells), specifically CD56bright NK cells, accumulate in periventricular brain areas in MS, displaying a migratory and activated phenotype[1]. Given the immunomodulatory properties of CD56bright NK cells, we hypothesized that their protective capacities are lost in the course of disease. This study aimed to characterize NK cells in relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) within a unique cohort of individuals born in the same year, eliminating age as a confounding factor.

METHODS

We performed a 37-marker mass cytometry by time-of-flight (CyTOF) analysis on peripheral blood mononuclear cells from 50 healthy controls, 48 RRMS patients, and 24 PPMS patients from the Project Y cohort of the MS Center Amsterdam[2]. This cohort consisted of untreated patients born in 1966 and age- and sex-matched healthy controls.

RESULTS

The proportion of NK cell subsets was similar between groups, however, their phenotype was affected in RRMS and PPMS compared to healthy controls. In RRMS, NK cells showed upregulated expression of cytotoxic and inflammatory proteins. Among these proteins, DNAM-1 expression correlated positively with the time passed since the previous relapse. In PPMS, all NK cell subtypes showed increased expression of CD16 (FcγRIIIa), suggesting a role in antibody-dependent cellular cytotoxicity (ADCC), possibly contributing to myelin damage. Furthermore, CD56bright NK cells exhibited increased expression of the immunoregulatory protein NKp46 and migratory protein CD49d. Both DNAM-1 and NKp46 are involved in autologous T cell-killing, indicating possible alterations in the NK-T cell interaction in MS. This was further supported by the upregulation of the NK cell-inhibitory ligand HLA-E on $CD4^+$ T cells in MS. Exploring the relationship between disease duration and NK cell phenotype independent of age revealed a negative correlation with HLA-E expression on CD56dim NK cells in RRMS, and a positive correlation with inhibitory receptor NKG2A on this subset in PPMS. CONCLUSIONS/ACKNOWLEDGEMENTS Our data show that NK cells in MS acquire an activated and migratory phenotype, with altered expression of proteins related to T cell suppression and ADCC. Several of these proteins correlate with disease duration, suggesting that NK cells may play a yet unidentified role in disease progression. Currently, in vitro experiments are being conducted to validate our findings on a functional level, allowing for a detailed understanding of the role of NK cells in MS. This work is supported by Stichting MS Research.

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Oxylipin Biosynthesis by Foamy Macrophages in Multiple Sclerosis Lesions

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PHD YEAR
Year 3

POSTER NO.
59

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Foamy Myeloid Cells · Myelin · Oxylipins

BACKGROUND

Multiple Sclerosis (MS) is a chronic, progressive disease of the central nervous system (CNS), characterized by immune-mediated neuroinflammation and neurodegeneration. The disease is defined by the formation of CNS lesions, some of which contain foamy myeloid cells with intracellular myelin debris, reflecting active demyelination and phagocytic activity. Recent evidence indicates that lesions containing foamy cells are enriched in oxidized metabolites derived from free fatty acids (oxylipins), suggesting that enhanced lipid metabolism within these cells may contribute to neuroinflammatory signaling and disease modulation. In this study, we hypothesize that foamy myeloid cells biosynthesize increased levels of oxylipins due to the enhanced availability of substrates derived from phagocytosed myelin, which is rich in polyunsaturated fatty acids-containing phospholipids.

METHODS

To test this hypothesis, human monocyte-derived macrophages were exposed to human myelin (100 µg/ml) for 72 hours to induce a foamy phenotype, after which the oxylipin profile was analyzed using liquid chromatography–mass spectrometry (LC-MS/MS). Moreover, expression of inflammatory and lipid-associated genes was determined by quantitative PCR. To assess whether oxylipin biosynthesis is mediated by enzymatic pathways, pharmacological inhibitors targeting key lipid mediator biosynthesizing enzymes were applied to the foamy myeloid cells.

RESULTS

In this study, we established an in vitro model to investigate foamy monocyte-derived macrophages, resulting in the development of a foamy phenotype characterized by intracellular lipid accumulation. Myelin-treated macrophages showed increased expression of genes associated with lipid droplet formation (PLIN2), cholesterol efflux (ABCA1), lysosomal degradation of phagocytosed material (CTSL), and inflammatory lipid mediator synthesis (PTGS2) as well as macrophage activation (SPP1). Preliminary LC–MS/MS analysis indicates that myelin uptake alters the oxylipin profile of foamy macrophages, suggesting that lipid loading may influence oxylipin production. Ongoing analyses aims to further characterize these changes and to determine whether oxylipin biosynthesis is mediated by specific enzymatic pathways.

CONCLUSIONS

Together, this study aims to define the oxylipin profile of foamy myeloid cells and determine whether myelin uptake drives oxylipin biosynthesis. Understanding how foamy macrophages contribute to lipid-mediated neuroinflammation may provide new insights into mechanisms underlying lesion progression in MS.

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Region- and Age-Dependent Microglia Heterogeneity in the Healthy Human Brain

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PHD YEAR
Year 2

POSTER NO.
42

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Microglia · Heterogeneity · Spatiotemporal · Healthy · Development · Aging

Microglia are the resident innate immune cells of the central nervous system. Their functions span immune surveillance, maintenance of homeostasis, and synaptic remodeling. To fulfill their diverse roles, microglia display remarkable heterogeneity. Omics-based studies have identified a spectrum of microglial states, including development-, and white matter-related and disease-associated phenotypes. Beyond transcriptional diversity, microglia vary morphologically from homeostatic to reactive and dystrophic states: the latter two often appear in inflamed neurodegenerative environments. While most research has focused on microglia in pathology, their physiological diversity across brain regions and ages remains understudied. Here, we investigated the effects of brain region and age on microglial characteristics in the healthy human brain. Proteomic analysis was performed on frontal lobe (FL) white matter (WM), grey matter (GM), and cerebellar (CB) WM from four non-neurological adult donors aged 21–35 years. They are part of a larger cohort of 19 donors spanning from neonates to centenarians, all devoid of neuropathology. In this cohort, region- and age-related microglial expression patterns were characterized using immunohistochemistry (IHC). Proteomic analyses in the four donors identified four candidate microglial proteins (C3, SRGAP2, CYFIP1 and CAPG), which were further investigated with IHC in the 19 donors. IHC analysis revealed highest IBA1+ cell density in the FL and CB during early development and childhood, and lower in adults and centenarians. Within the cortical layers, IBA1+ cell density is highest in layer I during early development, whereas in children and adults the highest density shifts to layer VI. Collectively, these findings advance our understanding of region- and age-dependent microglial heterogeneity in the healthy human brain, providing a crucial baseline for interpreting disease-related changes.

Spatial Transcriptomic Profiling of Microglial Heterogeneity in APOE4-KI Mouse Brains

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PHD YEAR
Year 3

POSTER NO.
12

LOCATION
Foyer ground floor · Thu

KEYWORDS
Microglia APOE4 Transcriptomics

Microglia, the brain's resident immune cells, play a key role in the neuroimmune changes associated with neurodegenerative disorders. These changes include microglial activation, impaired phagocytosis and recruitment of peripheral immune cells[1, 2]. However, microglial heterogeneity throughout the brain makes it difficult to study distinct microglial states. Importantly, the spatial tissue organization in which microglia reside is a critical aspect that defines the function of specific microglial states[3, 4]. ApoE4 is the most important known genetic risk factor for developing late-onset Alzheimer's disease (AD) and is associated with dysfunctional microglia[5-8]. However, it remains unclear whether and how dysfunctional microglia drive neuroimmune changes observed in AD patients carrying the ApoE4 genotype, such as modulation of the blood-brain barrier and adaptive immune cell recruitment. To investigate these neuroimmune changes, we performed immunohistochemistry on APOE3 and APOE4 knock-in mice. We found that CD8+ T cells infiltrate the white matter of middle-aged (10-12 month old) APOE4-KI mice. Additionally, microglia of adult (6 month old) APOE4-KI mice show increased HLA-DR expression in the corpus callosum. This indicates heightened microglial activation preceding the increased CD8+ T cell infiltration. To address this, we applied Xenium spatial transcriptomics to brain slices of 6-month-old female APOE3 (n=3) and APOE4 (n=3) knock-in mice using a pan-tissue panel targeting ~5,000 genes supplemented with 50 custom immune-related probes. This approach enables the in situ definition of microglial and macrophage subpopulations across brain compartments and their spatial relationships with neighboring neurons, glia, and infiltrating immune cells. Preliminary analyses confirmed robust transcript capture and reliable cell detection, with integrated clustering revealing distinct cell populations and region-specific spatial patterns. We have now established an integrated analysis pipeline for cell-type annotation and characterization. Microglial populations have been identified and further subclustered to resolve distinct immune states, with ongoing analyses comparing these populations between APOE3 and APOE4 conditions and across brain regions. Together, these analyses will provide a comprehensive spatial map of microglial and macrophage diversity in APOE3 versus APOE4 brains, with the goal of determining how APOE4 reshapes immune states across brain niches and contributes to regional vulnerability to AD.

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Targeting Microglial Glucocorticoid Receptors to Mitigate Alzheimer's Pathology

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PHD YEAR
Year 3

POSTER NO.
2

LOCATION
Foyer ground floor · Thu

KEYWORDS
Alzheimer's Disease · Microglia · Glucocorticoid Receptors · LPS · snRNAseq

Exposure to chronic stress or early life stress has been associated with an increased risk for developing Alzheimer's disease (AD) (Ávila-Villanueva et al. 2020, Brosens et al. 2023, Hoeijmakers et al. 2017, Lesuis et al. 2018; Lucassen et al., 2025). Experimental and clinical evidence suggests that stress can accelerate AD-related pathology and exacerbate cognitive decline (Lesuis et al., 2018). Moreover, patients with AD frequently exhibit elevated cortisol levels (Csernansky et al., 2006, Ouanes & Popp, 2019), which has been associated with increased supporting a potential role for glucocorticoid signalling in disease progression. Consequently, modulation of stress hormone receptor signalling has emerged as a potential therapeutic strategy to attenuate AD pathology (Canet et al. 2025, Lesuis et al. 2018). Microglia may play a central role in mediating the effects of stress on AD pathology. Microglia are highly responsive to stress and play essential roles in mediating disease-associated processes (Qin et al. 2023). In AD, microglial dysfunction has been implicated in disease progression through impaired phagocytic capacity, aberrant synaptic pruning, and dysregulated neuroinflammatory responses (Azmal et al. 2025, Miao et al. 2023). In this study, our long-term objective is to determine whether and how microglial glucocorticoid receptor (GR) signalling contributes to AD pathology. As an initial step toward this goal, we investigate the role of microglial GR in the response to an immune challenge to establish its function under both physiological and inflammatory conditions. To study this, we use a transgenic mouse model that allows tamoxifen inducible GR depletion in microglia. Under baseline and immune challenged conditions (via i.p. LPS injections), we study the role of microglial GR in 1) immune-induced changes in microglial morphology, using an advanced morphometrics pipeline (Weering et al. 2023), 2) phagocytosis function, 3) the molecular response of microglia and other cell types using single-nucleus RNA sequencing.

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Uncovering the Molecular Drivers of BBB Impairment in Multiple Sclerosis

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PHD YEAR
Year 4

TALK
Session 3B

WHEN · WHERE
Fri 11:00–12:30 · Woudzicht

KEYWORDS
Blood Brain Barrier Single Nucleus RNA Sequencing Multiple Scl

BACKGROUND

The proper functioning of the blood-brain barrier (BBB) is crucial for the optimal performance of our brain. The BBB protects our brain against unwanted invaders (harmful proteins, pathogens) and activated immune cells. In multiple sclerosis (MS), BBB function is compromised, allowing auto-reactive immune cells to migrate into the brain and attack the myelin layer and nerve cells, leading to neuroinflammation and neurodegeneration. Reinstating BBB function may therefore be a novel target for treatment, but to date we lack essential insights into the underlying mechanisms of BBB impairment. Therefore, this study aims to uncover molecular changes in the neurovascular unit that contribute to BBB dysfunction in MS.

METHODS

To gain such essential insights, we will perform single-nucleus RNA-sequencing (snRNAseq) analysis on postmortem brains of MS patients [1]. Using this transcriptomic approach, we conducted differential gene expression analysis and Weighted Gene Co-expression Network Analysis (WGCNA) on vascular and BBB-supporting cell types in order to identify key genes affected in the neurovascular unit of MS cases.

RESULTS

We identified 94 differentially expressed genes (DEGs) in the gray matter capillaries of MS patients. Among these, the early response gene APOLD1 was significantly upregulated. To assess its functional role in BBB function, we will conduct overexpression and knockdown experiments in human induced pluripotent stem cell (hiPSC)-derived brain microvascular endothelial cells.

CONCLUSIONS

Our findings highlight novel gene targets involved in BBB impairment in MS. Functional characterization of APOLD1 may reveal new insights into the molecular mechanisms driving BBB dysfunction in MS. (242 words)

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From Mouse Models to Human Blood: Early Life Stress Induced Mitochondrial Dysfunction as a Translational Marker of Alzheimer's Disease

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PHD YEAR
Year 2

POSTER NO.
111

LOCATION
Zaal 25 Woudvleugel · Fri

KEYWORDS
Alzheimer's · Early-Life Stress · Diet

BACKGROUND

Alzheimer's disease (AD) is a prevalent age-related neurological disorder, characterized by progressive cognitive decline and accumulation of neuropathological hallmarks across brain regions. Among risk factors, early-life stress (ES) exacerbates AD deficits and alters glial cell function in AD mouse models of amyloid overexpression. Mitochondrial dysfunction is a hallmark of AD pathogenesis, with poorly understood cellular origins and relation to ES. Prior work from our lab showed that ES in wild-type mice disrupts mitochondrial integrity and induces synaptic proteome alterations in the hippocampus resembling early-stage AD (APP/PS1) mice. In advanced AD stages, ES further dysregulated proteins related to astrocytes and fatty acid metabolism. We hypothesize that ES drives early mitochondrial dysfunction contributing to lipid dyshomeostasis, neuroinflammation, and synaptic dysfunction in AD.

METHODS

We examine the impact of ES on mitochondrial biology in synapses, glial cells, and blood cells of wild-type and AD model mice across pathological stages. We investigate whether nutritional supplementation targeting mitochondrial function can prevent or reduce AD deficits with/without ES. We aim to translate findings to humans using the Dutch famine birth cohort, where prenatal famine exposure is linked to premature brain aging by studying peripheral mitochondrial measures in blood at age 75.

RESULTS

Preliminary proteomic analyses show that ES disrupts synaptic mitochondrial integrity in wild-type mice as early as postnatal day 9. Processing of blood samples from the Dutch famine birth cohort is ongoing to assess peripheral mitochondrial markers.

CONCLUSIONS

These findings suggest that ES induces early and lasting mitochondrial alterations that may increase vulnerability to Alzheimer's disease.

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The Effects of Oral Tributyrin Supplementation in a Murine, Double-Hit Model of Depression

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PHD YEAR
Year 4

TALK
Session 1A

WHEN · WHERE
Thu 10:45–11:45 · Woudzicht (108)

KEYWORDS
Early Life Adversity Depression Tributyrin

BACKGROUND

Current treatments for depression alleviate less than half of the disease burden, highlighting the need for novel therapeutic strategies. Nutritional psychiatry is an emerging field, with growing evidence that microbially derived butyrate contributes to beneficial effects of dietary, prebiotic, probiotic, and synbiotic interventions. Direct butyrate administration may therefore alleviate depressive symptoms. Given the sex bias in depression, the importance of early-life stress (ELS) as a risk factor, and adolescence as a sensitive period for symptom emergence, we investigate whether tributyrin supplementation counteracts behavioral effects of stress exposure in male and female mice.

METHODS

C57BL/6J mice of both sexes were exposed to ELS using the limited bedding and nesting paradigm (P2–P9), followed by three weeks of chronic unpredictable mild stress (CUMS) during adolescence (P28–P48). During the final two weeks of CUMS (P36–P48), mice received a diet supplemented with 0.1% tributyrin. Primary outcomes include anxiety-like behavior, self-care, and anhedonia. Secondary outcomes investigate mechanisms along the microbiota–gut–brain axis, including gut-derived metabolites, endocrine stress responses, inflammation, intestinal barrier integrity, and brain-related measures. Outcomes are assessed immediately after intervention and one month later to evaluate short- and long-term effects.

RESULTS

Pilot testing confirmed that mice readily consumed both diets and maintained normal weight gain. Experiments and analyses are ongoing. We hypothesize that tributyrin exerts antidepressant-like effects through restoration of gut barrier integrity, reduced systemic and neuroinflammation, epigenetic modulation, and increased neurotrophic factors. This study runs alongside a clinical trial of oral tributyrin in major depressive disorder, enhancing its translational relevance.

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Cellular Budget Cuts: Stability of Action Potential Kinetics Under ATP Limitation

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PHD YEAR
Year 2

POSTER NO.
54

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Energy Metabolism · Human Neuron · Electrophysiology

BACKGROUND

Human cognition is associated with the evolutionary expansion of supragranular cortical layer 2/3 (L2/3), a central hub for cortico-cortical integration. Large human L2/3 pyramidal neurons encode inputs at high temporal bandwidth and maintain fast and stable action potential (AP) kinetics during sustained high-frequency activity. However, such firing patterns impose substantial metabolic demands, and how large human L2/3 pyramidal neurons meet these demands remains unclear.

METHODS

We combine patch-clamp electrophysiology with pharmacological manipulation of metabolic pathways to investigate how AP kinetics are sustained during burst activity across the cortical column. Using low [ATP]i whole-cell patch clamp and perforated-patch recordings in acute cortical slices, we will determine how intracellular ATP availability and different energy substrates affect AP waveform stability during sustained firing. We hypothesize that the ion channel properties enabling high-frequency activity in human neurons place substantial demands on the cellular energy budget, potentially reducing the metabolic reserve and increasing vulnerability to disruptions of cellular energy homeostasis. We expect this vulnerability to vary with cortical depth, with large neurons in deeper supragranular cortex having the greatest ATP dependence and ATP-generating capacity. ATP restriction should therefore preferentially affect smaller superficial neurons, whereas metabolic inhibition should more strongly affect larger deeper neurons.

RESULTS

Expected at ONWAR Meeting 2026

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Brain Morphology in Central Disorders of Hypersomnolence: First Results from the Global Multi-Site Neuroimaging Consortium NICHY

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PHD YEAR
Year 2

POSTER NO.
38

LOCATION
Zaal 22 + 23 Woudvleugel · Thu

KEYWORDS
MRI · Hypersomnolence · Consortium

BACKGROUND

Central disorders of hypersomnolence are characterised by excessive daytime sleepiness. The neural correlates of narcolepsy type 1 (NT1) and type 2 (NT2), and idiopathic hypersomnia (IH) remain elusive, with few cross-disorder comparisons and conflicting results, due to small samples and inconsistent methodologies. The NICHY (NeuroImaging in Central disorders of HYpersomnolence) consortium aims to overcome these inconsistencies by pooling datasets. Here, we present preliminary findings from the consortium's brain morphology analysis.

METHODS

T1-weighted MRI scans and clinical data were collected from four sites with matched samples of 42 NT1, 21 NT2, 42 IH, and 46 healthy controls (HC). Cortical thickness (nROIs=68) and subcortical volumes (nROIs=64) were evaluated using FreeSurfer. We applied ComBat harmonisation, and statistical models were corrected for age, sex, and intracranial volume. Multiple comparisons were FDR-corrected.

RESULTS

We identified a smaller left amygdala in NT1 and IH compared to HC and thinner cortices in NT1 compared to HC. NT2 compared to HC did not show significant differences. NT1 compared to NT2 showed thinner cortex in the frontal and temporal lobes. The left anterior-superior hypothalamus was larger in NT1 and NT2 compared to IH, and right frontal regions were thinner in NT1 versus IH.

CONCLUSIONS

This first NICHY analysis shows successful harmonised data processing across sites. Overall, we identified widespread lower cortical thickness in NT1 compared to NT2, IH, controls, and, counterintuitively, a larger hypothalamic subregion in NT1 and NT2 compared to IH. This preliminary analysis shapes future large-scale analyses, enabling further exploration of morphometry in relation to clinical measures.

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Characterizing Hyperarousal in Insomnia: A Multidimensional Approach

Roxanne Bongers

PHD YEAR: Year 3
POSTER NO.: 33
LOCATION: Zaal 22 + 23 Woudvleugel · Thu
KEYWORDS: Insomnia, Hyperarousal, Distress

Hyperarousal is a core component in most insomnia models, proposing that individuals with insomnia show elevated cognitive, emotional, and physiological arousal, both at baseline and in response to stress. This study investigated how daytime hyperarousal manifests in insomnia across multiple domains: trait hyperarousal, and subjective and objective responses during stress induction. Twenty individuals with insomnia and eighteen healthy controls (26 females; Mage = 42) participated in five laboratory sessions. Each session comprised a stress induction in which participants listened to their own out-of-tune singing. Heart rate (ECG), electrodermal activity (EDA), blushing (PPG), and subjective arousal (VAS 0–100) were assessed. Trait hyperarousal was measured using the newly developed Trait Hyperarousal Dimension Questionnaire (THDQ). Individuals with insomnia scored higher on six of seven THDQ dimensions compared to health controls, namely: anxious, somatic, sensitive, sleep-related, sudomotor, and irritable. During stress induction, insomniacs showed larger increases in heart rate, blushing response, and skin conductance level and response amplitude. Subjective arousal during stress did not differ between groups. These findings suggest that insomnia is characterized by elevated trait hyperarousal and autonomic stress reactivity. Our multidimensional approach could help explain how hyperarousal may serve as a transdiagnostic mechanism linking insomnia to anxiety and depression.

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Sleep Stage-Dependent BOLD-CSF Coupling in Central Disorders of Hypersomnolence: An fMRI-EEG Study

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PHD YEAR
Year 4

TALK
Session 4C

WHEN · WHERE
Fri 13:50–15:20 · Zaal 15 (45 places)

KEYWORDS
MRI-Brain Clearance-Sleep

BACKGROUND

Brain clearance during sleep is an active research area, but direct measurement remains challenging. BOLD-CSF coupling, the temporal relationship between fMRI signal fluctuations in brain tissue (BOLD) and ventricular cerebrospinal fluid (CSF), has been proposed as a non-invasive marker of brain clearance. People with central disorders of hypersomnolence, including narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH), experience excessive daytime sleepiness and fall asleep easily, making them suited for in-scanner sleep studies. We examined how BOLD-CSF coupling varies across sleep stages and whether it differs between people with a central disorder of hypersomnolence and healthy controls.

METHODS

97 participants (24 NT1, 18 NT2, 35 IH, 20 healthy controls) underwent simultaneous EEG-fMRI during a 30-minute nap opportunity across two sites. EEG was cleaned and scored by trained scorers in pairs using AASM criteria. BOLD and CSF signals were processed with standardised pipelines; coupling was quantified using cross-correlation on sleep-stage segments of at least 120 seconds. Group and stage differences were assessed with linear mixed-effects models, controlling for site.

RESULTS

Of 97 participants, 71 slept, contributing 632 segments across wake (n=82), N1 (n=25), N2 (n=68), and REM (n=26). BOLD-CSF coupling was significantly higher during N2 than wakefulness ($p<.001$), with no differences versus N1, N3, or REM. No group differences emerged across diagnoses.

CONCLUSIONS

BOLD-CSF coupling was strongest during N2 relative to wakefulness, with no diagnostic group differences. While clearance research has emphasised N3 slow waves, our findings suggest N2 may play a role too, and that sleep generally strengthens brain-CSF coordination.

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06

THEME

Novel Methods and Technology Development

Molecular, Biochemical, and Genetic Techniques p. 170

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Data Analysis and Statistics p. 187

Establishment of an in vitro Transwell Assay for Assessment of TfR-1 Mediated Transcytosis of Immuno-PET Brain-Shuttle Compounds

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PHD YEAR
Year 2
POSTER NO.
88
LOCATION
Zaal 22 + 23 Woudvleugel · Fri
KEYWORDS
Blood-Brain Barrier | Transwell Assay | TEER

BACKGROUND

Transport of monoclonal antibodies (mAbs) into the brain is limited by the blood-brain barrier (BBB). The BBB can be overcome by attaching a shuttle to the mAb, enabling receptor-mediated transcytosis through binding to Transferrin receptor 1 (TfR-1). Established in vitro methods are missing to evaluate immuno-PET brain-shuttle compounds, which is explored in this work.

METHODS

The transwell model was optimised by testing different coating conditions: no coating, collagen coating (C), and collagen:fibronectin=1 :1 (CF) coating. 6.6 x 10^4 mouse endothelial brain cells (bEnd.3) were seeded onto the inserts (N=3), and were cultured at 37 °C and 5% CO2 for 2 days before evaluating the integrity of the monolayer by transendothelial electrical resistance (TEER) (t=0 hours), and ^{89}Zr-DFO-rituximab permeability (t=0,1, 2, 4, 6, and 72 hours). Statistical analyses were performed using GraphPad Prism v10.6.0.

RESULTS

Table 1 provides an overview of the TEER and rituximab permeability results. The differences are statistically insignificant (P=0.88).

Table 1 – TEER values and rituximab permeability.

		Rituximab permeability (%)					
Coating	**TEER (Ωcm²)**	**0 h**	**1 h**	**2 h**	**4 h**	**6 h**	**72 h**
No coating	22.1 ± 14.2	0.3	1.1	0.9	1.7	2.2	20.6
C	25.5 ± 6.2	0.0	0.6	0.3	1.2	1.7	18.6
CF	25.2 ± 12.1	0.2	0.3	0.2	0.8	1.1	12.3

CONCLUSIONS

The similar TEER values suggest that coating conditions do not significantly impact the monolayer integrity. Furthermore, rituximab permeability suggest good monolayer tightness for at least 6 hours. Further validation with dyes, and permeability measurements of ^{89}Zr-labelled brain shuttles are needed.

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Blood-Based Protein Biomarker Candidates as Surrogates of B-Cell Count in Anti-

Florence van der Zee[1], Inge Verberk[1], Mark Wessels[1,2], Zoe van Lierop[1,2], Isabel[1], Houtkamp[1,3], Tradite Neziraj[4,5,6], Vasiliki Pantazou[7,8], Amandine Mathias[7,8], Elisabeth[1], Pössnecker[4,5,6], Caroline Pot[7,8], Renaud Du Pasquier[7,8], Anne-Katrin Pröbstel[4,6,9,10], Joep[1], Killestein[2], Zoé van Kempen[2], Charlotte Teunissen[1], Adrian-Minh Schumacher[1,2]

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PHD YEAR
Year 2

POSTER NO.
114

LOCATION
Zaal 25 Woudvleugel · Fri

KEYWORDS
Multiple Sclerosis · Biomarkers · B-Cell

BACKGROUND

Highly effective anti-CD20 disease-modifying therapies are widely used to treat people with MS (pwMS), with some administering treatment at home. Duration of treatment effect varies greatly between pwMS, requiring careful monitoring of B-cell depletion to enable extended interval dosing. Traditional B-cell monitoring by flow cytometry requires intact cells and is therefore not suitable for remote sampling or testing, whereas next-generation immunoassays could fulfill this need. Objective Identify robust blood-based protein markers for remote B-cell count monitoring.

METHODS

Ocrelizumab-treated pwMS of whom longitudinal Proximity Extension Assay (PEA) based proteomics results and time-matched CD19+ B-cell counts were available were included from two different cohorts (discovery: n=30, Olink Explore HT, validation: n=77, Olink Explore 1536, combined 248 serum samples). One baseline (pre-treatment) and up to 3 follow-up samples (on treatment) collected within 24 months were available. Candidate proteins were selected based on significant and largest fold-change from baseline to follow-up. Correlation between candidate protein levels with flow cytometric CD19+ B-cell count was assessed. Lastly, stability of candidate proteins at room temperature with delayed processing was evaluated in a rich PEA-based pre-analytics resource.

RESULTS

In the discovery cohort, 28 candidate proteins were identified based on fold-change from pre- to post-treatment within each individual. 16 showed significant correlation with CD19+ B-cell count (Spearman's ρ=0.38-0.89, p.adj<0.001). The strongest correlations were observed for the serum proteins CD20 (MS4A1) and CD22 (ρ=0.89 p>0.001 and ρ=0.85, p>0.001 respectively). 9 out of 16 proteins that were measured on both Olink panels correlated significantly with B-cell count (ρ=0.36– 0.84, p>0.001). The strong correlation for CD22 was replicated (ρ=0.83, p>0.001). CD20 (MS4A1) is not part of Olink Explore 1536. PEA-based pre-analytics showed

CD22 was stably measurable for up to 72 hours at room temperature, while CD20 (MS4A1) was stable for up to 24 hours.

CONCLUSIONS

We identified 16 serum protein candidates that significantly correlated with B-cell count, with CD20 and CD22 showing strongest correlation. The prolonged stability at room temperature supports their potential for at-home monitoring or testing, pending further validation with clinical immunoassays in patient cohorts.

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Development and Validation of Proximity Extension Assay-Based Classification Models for Alzheimer's Disease Molecular Subtypes

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PHD YEAR
Year 4

TALK
Session 4B

WHEN · WHERE
Fri 13:50–15:20 · Woudzicht

KEYWORDS
Alzheimer's Disease · Proteomics · Machine Learning

BACKGROUND

Recent cerebrospinal fluid (CSF) mass spectrometry (MS) proteomics studies have identified five distinct molecular subtypes of Alzheimer's disease (AD). Here, we used Proximity Extension Assay (PEA) proteomics to assess its ability to classify AD subtypes.

METHODS

We selected individuals from the Amsterdam Dementia Cohort. The discovery cohort (n=207) consisted of controls and all five subtypes. We performed CSF proteomics using PEA, and trained 5 binary random forest classifiers using synthetic minority oversampling. Model performance was evaluated using repeated cross-validation with 100 iterations of a 70/30 train-test split.

RESULTS

For subtypes 1 (neuronal hyper-plasticity), 2 (innate immune activation), 3 (RNA metabolism dysregulation) and 5 (blood-brain barrier dysfunction), PEA proteomic effect sizes between the control group and the subtypes displayed strong correlations with previously measured MS proteomics. For S4 (choroid plexus dysfunction), we observed lower levels of most detected proteins and weaker correlations with previous MS findings compared to other subtypes. Classification models performed well in the discovery cohort for S1, S2, S4, and S5 with average areas under the receiver operating characteristic curve (ROC-AUCs) of 0.90, 0.88, 0.92, and 0.93, respectively, and moderately for S3 (ROC-AUC=0.72).

CONCLUSIONS

CSF PEA proteomics of AD subtypes was in line with previous MS-based measurements, underscoring its value in bridging discovery proteomics and targeted biomarker validation. Using this method we trained classification models capable of detecting AD subtype 1, 2 and 5 with high accuracy. These subtype models hold promise for large scale validation in the clinic and in treatment development programs.

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Genome-Wide Association Study of Brain Volume

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PHD YEAR
Year 2
POSTER NO.
65
LOCATION
Foyer ground floor · Fri
KEYWORDS
GWAS Genomics Bioinformatics

BACKGROUND

Total Brain Volume (BV) is a highly heritable phenotype that is implicated in a range of neuropsychiatric and neurodevelopmental disorders. Thus, we performed the largest meta genome-wide association study (GWAS) of BV to date.

METHODS

We used patients with MRI data from the UKB and meta-analysed these results with a GWAS on intercranial volume from the CHARGE ENIGMA cohort and from a GWAS on head circumference. We used LDAK-KVIK to perform the GWAS. We also looked at the genetic correlations between BV and other neurological traits using LD-score regression. Finally, we prioritized genes of interest using FLAMES.

RESULTS

We identified 222 independent genome-side significant loci and estimated a SNP-heritability of 31%. We prioritised 141 high-confidence genes, which were significantly enriched for genes causing monogenic neurodevelopmental disorders. We also demonstrated genetic correlations between BV and four brain-related traits: ADHD, MDD, Parkinson's disease and migraine.

CONCLUSIONS

Together these findings significantly expand the catalogue of BV-associated loci, illuminate shared biology between normal brain-size variation and severe developmental disorders and provide a valuable resource for future functional investigations.

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Multi-Omics Analysis Reveals Mechanisms of Blood-Brain Barrier Alterations in Dementia

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PHD YEAR
Year 4

POSTER NO.

LOCATION

KEYWORDS
Multi-Omics Blood-Brain Barrier Dementia

BACKGROUND

Dementia is a clinical condition caused by a variety of underlying pathologies. Despite recent advances in diagnostic biomarkers, disease mechanisms of the most common dementias remain unknown. Neuroinflammation, together with blood-brain barrier (BBB) dysfunction, are recognized as key players in the early pathological processes. Understanding the common and unique pathways leading to BBB dysfunction in dementia can reveal critical aspects of vascular contributions to cognitive decline and identify targets to mitigate neuroinflammation and improve brain health.

METHODS

First, we accumulated 30+ studies on untargeted proteomics of blood samples of dementia patients to further characterize the landscape of the clinical AD proteome. Then, to study the BBB in detail, we isolated and characterized capillaries from post-mortem human brain cortex tissue of different dementias. The isolated vessels were subjected to proteomic analysis. In addition, we performed single-nucleus RNA sequencing on the same post-mortem human tissue, where we enriched for vascular and glial cells by depleting the nuclei of neurons and oligodendrocytes. These markers were further characterized in vitro.

RESULTS

The clinical screening identified an early-stage systemic signalling in dementia that linked to angiogenesis and immunity. The postmortem analysis highlighted EMT, Aniogenesis and metabolic effects across different types of dementia.

CONCLUSIONS

Here we provide a comprehensive analysis of the BBB in dementia, discovering a number of specific but also shared pathways altered that can be further investigated for treatment interventions and biomarker research. This research focuses particularly on changes in blood vessel architecture and metabolic changes.

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Submitted Explore SNP Effects on the Longitudinal Features of Substance Use

Zeli Chen

PHD YEAR
Year 4

TALK
Session 1A

WHEN · WHERE
Thu 10:45–11:45 · Woudzicht (108)

KEYWORDS

BACKGROUND

Substance use behavior exhibits dynamic trajectories across adulthood driven by a complex interplay of genetic and environmental factors. While large biobank scale genome-wide association studies (GWAS) have identified genetic risk loci associated with substance use, those studies are predominantly driven by cross-sectional designs. Longitudinal datasets are primarily explored with linear mixed models (LMM) summarizing population-level trends, while few studies have addressed the role of genetic effects on individual variability across time. Here we propose to use a latent growth curve (LGC) model to explore the genetic architecture of personal trajectory on substance use.

METHODS

We utilized longitudinal data from the UK Biobank, a population-based sample of UK adults. Self-report questionnaires from in-person assessment visits and online mental health follow-up questionnaires were used to obtain repeated measures of substance use behaviors across time. As an initial phenotype, we examined standardized monthly drinking frequency, including only subjects with at least 2 time points (N = 237,104), with ages ranging from 38 to 87. Longitudinal trajectories were first modeled using LGC models in OpenMx, the resulting model structure will be extended to the genomic level using GWSEM to estimate individual SNP effects on the latent growth factors.

RESULTS

Phenotypic modeling best supported a quadratic LGC model. The mean intercept was 8.84 (SE = 0.03), with a mean linear slope of 3.37 (SE = 0.08) and a mean quadratic effect of -1.52 (SE = 0.05), indicating an average drinking level of 8.84 times per month and an initial increase followed by decline. Considerable variance was observed for the intercept (σ^2 = 33.26), linear slope (σ^2 = 4.98), and quadratic slope (σ^2 = 0.07), which indicates substantial individual differences in trajectories that may be relevant for investigating genetic effects. Sex was also significantly associated with the LGC trajectories, with males having higher initial drinking levels, steeper slope and faster decline across time. We intend to run GWAS analysis with the extracted factor and extend the analysis to other phenotypes involving tabacco use and recreational drugs.

CONCLUSIONS

Our results suggest that there's substantial heterogeneity in individual drinking trajectories, which supports the necessity of moving beyond cross-sectional design to study the genetic effects on individual variability of drinking behaviors. As suggested by other recent studies of substance use genetics, a deeper consideration of between- and within-person heterogeneity is critical to advancing future precision medicine applications.

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An Analysis Pipeline for Single Molecule Imaging of Endogenous Synaptic Proteins in Brain Tissue

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PHD YEAR
Year 2

POSTER NO.
110

LOCATION
Zaal 25 Woudvleugel · Fri

KEYWORDS
Synapse Identity · Organotypic Slices · Super-Resolution Microscopy

BACKGROUND

The number and dynamic nanoscale organization of AMPA receptors (AMPARs) defines synaptic transmission efficacy and is regulated by activity-dependent plasticity mechanisms and transsynaptic complexes. These complexes ensure alignment of release sites with AMPAR nanodomains. Visualizing receptor trafficking and clustering of endogenous receptors in intact synaptic networks remains a key challenge for understanding how organizational diversity defines synapse-type-specific function.

METHODS

Genetic knock-in of small epitope tags enables labelling of synaptic proteins such as AMPARs and cell-adhesion molecules with small imaging probes. These probes are ideal for live labelling of cell-surface proteins in tissue, including dense structures like the synaptic cleft. Trough lattice light-sheet-based Single Molecule Localization Microscopy (SMLM), Single Particle Tracking (SPT) was performed in live brain slices. Adaptive optics enabled 3D-SPT of molecular dynamics throughout dendritic spines in a single acquisition.

RESULTS

Characterization of the diffusive behaviour of AMPARs and the transsynaptic adhesion molecule neuroligin-1 (NLG1) revealed distinct molecular dynamics across subcellular compartments. In dendritic spines and shafts, AMPARs exhibited higher mobility than NLG1. Morphological analysis identified four major spine classes. Integrating molecular dynamics with morphology revealed spine-type-dependent differences in receptor mobility.

CONCLUSIONS

AMPARs and NLG1 exhibit distinct molecular dynamics within intact neural networks. NLG1 displays reduced mobility compared to AMPARs, consistent with a transsynaptic anchoring role, whereas AMPARs remain dynamic and undergo diffusional trapping within synaptic compartments. Furthermore, AMPAR mobility differs across spine types and may reflect spine maturation, where mature spines trend toward a larger trapped receptor fraction. Together, these findings highlight differential regulation of receptor and adhesion molecule dynamics and their contribution to synaptic identity.

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Towards Investigating Molecular Pathways Involved in Hippocampal Synaptic Potentiation Using Advanced Optical Tools

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PHD YEAR
Year 2

POSTER NO.
68

LOCATION
Foyer ground floor · Fri

KEYWORDS
Microscopy Biosensors Optogenetics

BACKGROUND

Complex biological processes arise from cellular mechanisms involving secondary messengers such as cyclic AMP and Phosphatidylinositol (3,4,5)-trisphosphate), protein kinases and small GTPases (such as Ras). These signaling molecules are essential in regulating the molecular machinery necessary to enable neurological phenomena such as memory formation and retrieval, which rely on synaptic potentiation mechanisms that take place within hippocampal synapses.

METHODS

HeLa and U2OS cells were transiently transfected with biosensors and optogenetic systems and imaged before and after treatments inducing changes in the levels of specific signaling molecules.

RESULTS

We report on our progress in developing a biosensor with specifications optimized for the quantitative measurement of cAMP within neuronal synapses (a red single FP lifetime-based cAMP biosensor) as well as preliminary results involving manipulation and imaging of protein kinase and small GTPase activity within model cell lines.

CONCLUSIONS

Once these tools have been further improved and characterized, we aim express them in hippocampal neurons (both as dissociated neurons and within brain slices) to investigate a GluA3-dependent synaptic plasticity molecular pathway which we hypothesize to involve cAMP and PIP3 as key signaling molecules.

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A Proof-of-Concept Automated Platform for Synaptic Assays on HD-MEAs

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PHD YEAR
Year 3

POSTER NO.
1

LOCATION
Foyer ground floor · Thu

KEYWORDS
High-Density Microelectrode Arrays (HD-MEAs)
Synaptic Transmission
Microfluidics

BACKGROUND

Monogenic neurodevelopmental disorders (mNDDs) often lack effective treatments due to their complexity and the limitations of current drug-screening techniques. Traditional methods such as patch-clamp electrophysiology and low-density microelectrode arrays are time-consuming or fail to capture network-level neuronal behavior essential for understanding synaptic dysfunction. Within the context of the BRAINmodel consortium, we aim to advance the development of a high-throughput drug-screening platform for patient-specific induced pluripotent stem cell (iPSC)-derived neurons on high-density microelectrode arrays (HD-MEAs) to evaluate disease dynamics and identify off-label therapeutic candidates for mNDD patients.

METHODS

The proposed platform integrates four components to enable high-resolution electrophysiological screening: i) PDMS single-pair neuron microstructures, which enable directional neuronal connectivity and isolate individual iPSC-derived neuronal pairs cultured on top of HD-MEAs to measure synaptic transmission, ii) a custom incubator chamber which provides precise environmental control and stability during extended electrophysiological recordings, iii) a custom water-compartment lid to prevent media evaporation, designed with two inlet and one outlet syringe for fluidic access, and iv) a custom automated perfusion system designed in collaboration with Bronkhorst High Tech, enabling hands-free compound administration and media replacement.

RESULTS

This ongoing project uses the platform to precisely quantify baseline synaptic transmission and neuronal excitability. Once these baseline parameters are established, the platform can be used to induce specific phenotypes in excitatory neurons cultured within the microstructures.

CONCLUSIONS

Ultimately, by systematically screening compounds to test if they can rescue these induced phenotypes, the platform aims to provide a robust, scalable framework for validating disease mechanisms and accelerating personalized drug treatments.

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Validation of a THC-Vapor Exposure Set-up in Mice

Effects on temperature[1], locomotor activity[1], blood metabolite levels[1], Elisabeth M. Bouwman[1,2], Susanne E.M Hazenberg[1,2], Roos van der Laan[1], Paul J. Lucassen[1,2], Rixt van der Veen[1,2]

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PHD YEAR
Year 3

POSTER NO.
52

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Cannabis THC Mouse

BACKGROUND

Chronic and heavy use of cannabis and its main psychoactive compound Δ9-tetrahydrocannabinol (THC) is a growing problem among adolescents. We do not fully understood yet what the long-term effects of THC exposure during this sensitive developmental period are and what factors might play a role in the sensitivity to these drugs. Exposing rodents to cannabis compounds in a controlled setting enables in-depth investigation of the neurobiological, physiological and behavioural effects of adolescent cannabis exposure. In this field, more and more studies are moving from injection protocols to vapor exposure, which is of more translational value. Here, we validate the efficacy of our novel in-house vapor set-up by exposing both adult and adolescent mice to an increasing dosage of THC vape.

METHODS

We exposed adult male and female mice to THC vape once per day for a period of 3 weeks. The dose was increased in three steps. Temperature and locomotor activity were measured after vapor exposure. Finally, blood was collected, in which we are currently measuring the levels of THC and its metabolites using mass spectrometry.

RESULTS

We found that mice exposed to cannabis had a significantly lower body temperature and reduced locomotor activity compared to the vehicle group. This effect was stronger when exposed to a higher dosage.

CONCLUSIONS

Our data show that exposing mice to THC vape induces hypothermia and hypolocomotion, indicating successful administration of THC. This shows that the vapor-based set-up can alter physiology and behaviour in mice. We will continue to use this set-up in follow-up experiments with adolescent mice.

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Distance Based Spatial Clustering Enhances Disease Gene Discovery in ALS

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PHD YEAR
Year 2

POSTER NO.
56

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Amyotrophic Lateral Sclerosis
Rare Genetic Variants
Clustering

BACKGROUND

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease. For most patients, no genetic cause has been identified yet. It is assumed that rare genetic variants play an important role to explain ALS risk. Conventional single variant analyses cannot be used to identify these variants. Instead, variants that occur within the same gene are typically aggregated for gene burden analyses. However, these traditional analyses might overlook genes for which pathogenic variants occur within specific regions (hotspots) rather than across the entire gene.

METHODS

Missense variants were obtained from the project MinE exome sequencing dataset previously described by Hop et al. (2026), which includes 13K ALS patients and 70K controls. These variants were aggregated, into units for burden testing, using one- and three-dimensional spatial clustering methods. Cauchy aggregation was applied to the resulting association signals to obtain a single score for each gene.

RESULTS

The one- and three-dimensional clustering methods were complementary as they yielded distinct clustering results. The combined analysis recovered both known disease genes, as well as a novel hotspot in the immune regulatory gene IRF5.

CONCLUSIONS

Our analyses implicate IRF5 in ALS risk. In addition, our findings demonstrate that the application of spatial clustering methods can improve the power of ALS gene discovery.

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PolyGenius Enables Scalable End-to-End Analysis of Thousands of Polygenic Scores Across Multiple Cohorts

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PHD YEAR
Year 3

POSTER NO.
26

LOCATION
Foyer top floor · Thu

KEYWORDS
Polygenic Scores · Dementia · PGS-WAS

BACKGROUND

Polygenic scores (PGSs) are widely used to study genetic predisposition, but complex, disconnected workflows hinder reproducible analyses and often restrict studies to a single PGS within one cohort.

METHODS

We present PolyGenius, an R framework integrating PGS retrieval, construction, scoring, association testing, evaluation and meta-analysis. We demonstrate three applications: first, applying a published Alzheimer's disease (AD) PGS in ROSMAP to study diagnosis, neuropathology and age at onset, including APOE genotype analyses; second, conducting a multi-cohort dementia PGS-wide association study (PGS-WAS) using GWAS-derived scores and meta-analysis; and third, constructing and validating new AD-PGSs using four algorithms.

RESULTS

Starting from 4,675 UK Biobank-derived GWAS datasets, PolyGenius generated a library of 2,219 PGSs comprising 94,242 distinct variants in 35 minutes using 16 CPU cores. We subsequently applied this library to four independent cohorts comprising 17,735 unrelated participants and combined associations with dementia through random-effects meta-analysis. PGS-WAS identified 23 associated PGSs (FDR<0.01), including scores related to hypercholesterolaemia and parental longevity. Variant-level analyses revealed shared genomic contributions at the APOE and LDLR loci. In the other applications, a published AD-PGS was associated with AD diagnosis, neuropathology and age at onset, while a newly developed lassosum2-based score showed similar performance in held-out validation.

CONCLUSIONS

PolyGenius lowers technical barriers to reproducible PGS analysis, supporting applications from individual-score evaluation and construction to systematic, multi-cohort association discovery and investigation of underlying genomic signals.

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A Scaffold Hopping Approach Toward Novel Alpha-Synuclein PET Tracers

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PHD YEAR
Year 2
POSTER NO.
28
LOCATION
Zaal 22 + 23 Woudvleugel · Thu
KEYWORDS
Neurodegenerative Diseases
PET Imaging
Molecular Design

BACKGROUND

Alpha-synuclein aggregates are a key pathological hallmark of Parkinson's Disease. Non-invasive quantitative assessment of these aggregates by Positron Emission Tomography (PET) could aid diagnosis and drug development, but a suitable PET tracer is still lacking. This work builds on a reported compound (SKP08), which shows high affinity for alpha-synuclein fibrils but lacks selectivity and stability. Through scaffold hopping, we aim to improve binding affinity and selectivity.

METHODS

The central core of SKP08 was replaced using a scaffold hopping protocol in ICM-Pro (version 3.9.1c, Molsoft L.L.C). A library of >47,000 cores was screened and filtered by molecular properties (molecular weight<500 g/mol, blood-brain barrier score<3). A low-energy conformation and atomic property field (APF) maps of SKP08 served as templates for subsequent APF screening.

RESULTS

Property filtering and APF-based screening narrowed the library to 540 candidates. Self-superposition of SKP08 established a benchmark APF score (-229.6, RMSD=0.11), used to select 20 structurally diverse in silico hits based on strategic introduction or removal of hydrogen bond donors/acceptors relative to the reference. These compounds are currently being synthesized, after which they will be tested for affinity and selectivity with in vitro fibril binding assays for alpha-synuclein, amyloid beta and tau aggregates.

CONCLUSIONS

This scaffold hopping approach identified 20 promising alpha-synuclein-targeting compounds using an APF model derived from SKP08, a step toward a viable PET tracer for alpha-synuclein aggregates. Figure 1. A. Structure of SKP08 and highlighted central core, B. Low-energy conformation and APF of SKP08, C. Alignment examples between SKP08 (pink) and new scaffolds (yellow).

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Automated Ventricle Segmentation on Brain MRI in Syndromic Craniosynostosis: A Practical Deep Learning Pipeline for Small and Heterogeneous Datasets

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PHD YEAR
Year 2

POSTER NO.
23

LOCATION
Foyer top floor · Thu

KEYWORDS
Syndromic Craniosynostosis | Ventricular Segmentation | Magnetic Resonance Imaging

BACKGROUND

Assessment of ventricular morphology in syndromic craniosynostosis is challenging due to anatomical variability and limited applicability of existing segmentation methods. This study aimed to develop and evaluate a fully automated deep learning pipeline for segmentation of the cerebral ventricles, and to compare its performance with a conventional neuroimaging pipeline.

METHODS

This retrospective study included 262 T1-weighted MRI scans from 130 patients with Crouzon-Pfeiffer and Muenke syndromes. External validation was performed using 45 scans from another centre and 71 scans from the Baby Open Brains dataset. An nnU-Net-based deep learning model, CranioVentricleSeg (CVS), was trained using an iterative human-in-the-loop approach starting from 10 manually segmented scans, followed by iterative refinement with corrected and automatically generated segmentations. Performance was assessed using overlap and volumetric metrics, and compared with FreeSurfer.

RESULTS

The best-performing model (CVS-68) achieved high accuracy on internal and external test sets (Dice similarity coefficient = 0.96, normalized surface Dice = 0.98, relative volume error = 3.0%, absolute volume error = 1.1 mL), thereby outperforming FreeSurfer. On the Baby Open Brains dataset, performance was lower across all methods. In this cohort, FreeSurfer showed lower volumetric error for total ventricular volumes, whereas CVS-68 achieved higher spatial overlap for the third and fourth ventricles. The cavum septum pellucidum was more challenging to segment across all methods.

CONCLUSIONS

CranioVentricleSeg enables accurate automated ventricular segmentation in syndromic craniosynostosis despite anatomical variability and limited annotated data. The iterative training strategy maintains strong performance and generalizability, outperforming FreeSurfer in internal and external datasets.

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Cost-Effectiveness Study of Newborn Screening for Metachromatic Leukodystrophy

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PHD YEAR
Year 3

POSTER NO.
7

LOCATION
Foyer ground floor · Thu

KEYWORDS
HTA NBS MLD

Metachromatic Leukodystrophy (MLD) is a rare neurodegenerative disorder caused by bi-allelic pathogenic variants in ARSA. Current treatment options include hematopoietic stem cell transplantation (HSCT) for select pre-symptomatic patients, symptomatic care, and most recently, gene therapy for early-onset pre- and early-symptomatic patients. This study aims to evaluate the cost-effectiveness of newborn screening (NBS) compared with no NBS for Metachromatic Leukodystrophy (MLD), stratified by early- and late-onset subtypes and treatment strategies. A model-based cost-effectiveness analysis was conducted with a hybrid decision tree-Markov cohort model. The analysis was performed from both a healthcare system perspective and a societal perspective, incorporating direct medical costs, non-medical costs, and caregiver burden. A lifetime time horizon was adopted, and both costs and health outcomes were discounted. Preliminary analysis shows promising result with an incremental cost-effectiveness ratio (ICER) in favour of the willingness-to-pay threshold (WTP) per quality-adjusted life year (QALY) gained for implementation of MLD to the NBS. Beyond the high analytical performance of the tiered testing strategy for MLD within NBS, the findings of this study support the inclusion of MLD in NBS. Implementation of such a screening strategy has the potential to enable presymptomatic treatment, prevent irreversible disease progression, and ultimately improve survival and outcomes in affected children.

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Mouse Subcortical Population Dynamics During Innate Defense Behavior

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PHD YEAR
Year 3
POSTER NO.
41
LOCATION
Zaal 24 Woudvleugel · Thu
KEYWORDS
Computation Behavior Vision

BACKGROUND

The superior colliculus (SC) and periaqueductal grey (PAG) are subcortical brain regions crucial for visually-evoked innate defense responses. How the SC and PAG transform visual information into a decision to freeze remains to be fully elucidated. Here we employ population-level analysis techniques, typically reserved for higher-order brain regions, to explore latent activity patterns in the SC and PAG.

METHODS

Mice were shown a visual stimulus known to elicit freezing responses. Single-unit spiking activity in the SC and PAG was recorded during behavior with neuropixels. Spike data was categorized by response type (freeze vs nonfreeze) and analyzed in two ways: first, with a simple averaging of firing rates across all units and trials, and second, with a dimensionality-reduction technique used to determine how neural activity unfolds over time in latent spaces.

RESULTS

For both SC and PAG, point-wise permutation tests occasionally revealed significant differences between population-averaged firing rates of freezing and non-freezing conditions. However, significant epochs were brief, unstable, and rarely appeared before response onset. In contrast, mahalanobis distance analysis of neural trajectories after dimensionality reduction revealed stable significant differences that also start before response onset.

CONCLUSIONS

Neural activity in both SC and PAG changes before freezing onset. This change in pre-response activity was only revealed via smoothed neural trajectories, as coarse averaging of activity obscured differences. These findings suggest subcortical regions SC and PAG employ complex activity patterns when processing visual stimuli to drive innate behavior.

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Neuroline: A Modular Pipeline for FAIR Multimodal Neurophysiology Data Processing

Andreas Knoben

PHD YEAR
Year 2

POSTER NO.
91

LOCATION
Zaal 22 + 23 Woudvleugel · Fri

KEYWORDS
Data Processing-Neurophysiology-Software Package

In systems neuroscience, sharing code and data openly and according to FAIR (Findable, Accessible, Interoperable, Reusable) principles is increasingly difficult because of the size of datasets, integration of different modalities, complex analysis pipelines and a variety of possible data formats. To streamline processing and storage of such multimodal datasets, we developed Neuroline, a Python package that provides a modular processing pipeline integrating established tools for electrophysiology, optical imaging, and behavioural data. It integrates these results in a standard output, namely the Neurodata Without Borders format. Neuroline can be run using a relatively simple syntax, yet it remains flexible, modular, and extensible: new modalities and functionality can be added using existing scaffolding and integrate into the pipeline without disrupting other parts. Tackling a number of challenges in neurophysiological data processing, Neuroline presents a practical step towards simplifying FAIR data processing in neuroscience. In this poster, the package is presented, as well as a practical use case and challenges that were encountered during development.

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Parallel Multidimensional Questionnaire and EEG Indices for Longitudinal Monitoring of Bumetanide Treatment in Neurodevelopmental Disorders

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PHD YEAR
Year 3

POSTER NO.
16

LOCATION
Foyer ground floor · Thu

KEYWORDS
Neurodevelopmental Disorders (NDDs)
Electroencephalography (EEG)
Machine-Learning

BACKGROUND

Conventional randomized controlled trials estimate average treatment effects, often using a single prespecified primary outcome. This approach may be poorly suited to neurodevelopmental disorders (NDDs), in which clinically relevant change can occur across different domains and follow markedly different trajectories within individuals. Following earlier bumetanide trials showing variable clinical response, the Bumetanide for Developmental Disorders (BUDDI) study was designed as an open-label, multiple-baseline single-case experimental study with repeated multidimensional questionnaire and electroencephalographic (EEG) assessments.

METHODS

We investigated whether these data could be integrated into parallel indices for following reported and neurophysiological change within individuals over time. In this secondary analysis, questionnaire and patient-reported outcome measure data (n = 87) and eyes-closed resting-state EEG recordings (n = 89) from participants aged 7–19 years were integrated separately using nested cross-validated logistic regression. The resulting questionnaire-derived (BI-Q) and EEG-derived (BI-EEG) Bumetanide Indices quantified the extent to which each participant's multidimensional profile shifted from baseline towards the pattern observed after six months.

RESULTS

Both indices distinguished baseline from six months with 78% balanced accuracy. Applied without refitting at three months, both showed intermediate group-level values, although individual EEG trajectories were more heterogeneous. BI-Q change was greater in clinician-defined responders than non-responders, whereas BI-EEG change was neither associated with BI-Q change nor different between responder groups. Thus, multidimensional questionnaire and EEG changes could be followed in parallel but did not follow a common trajectory.

CONCLUSIONS

These findings provide proof-of-concept for multidimensional longitudinal outcomes that follow reported and neurophysiological change without relying on single questionnaires or EEG marker.

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When Does a Simple T-Test Suffice? Handling Nested Data in Realistic Neuroscientific Settings.

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PHD YEAR	POSTER NO.	LOCATION	KEYWORDS
Year 2	81	Foyer top floor · Fri	Multilevel Modelling · Nested Data · Unbalanced Design

BACKGROUND

In neuroscience studies, multiple measurements are commonly collected from the same sampling unit (e.g., multiple neurons derived from the same individual induced pluripotent stem cell, or iPSC, line). Consequently, inherent dependency is introduced since measurements from the same sampling unit tend to show similarity (e.g., neurons induced from the same iPSC line tend to be more similar compared to neurons acquired from another iPSC line). Such dependency in the data or clustering compromises the validity of statistical conclusions derived using conventional methods (e.g., standard t-test or ANOVA), as these approaches assume measurements to be independent. To address the dependency, alternative methods which accommodate the clustering by either data reduction or explicit modelling of clusters have been advocated for. The former, simpler method comprises of combining the data in each cluster by calculating a suitable summary, such as the mean, and then using these cluster means in a statistical analysis, e.g., the summary statistics t-test (SST) approach. The latter, more complex method explicitly captures the clustering by incorporating it as part of a statistical model, e.g., the multilevel modelling (MLM)

METHODS

Literature to date directed at assessing and contrasting the performance (in terms of Type I error rate and statistical power) of these aforementioned approaches have only deliberated designs which are balanced (i.e., equal numbers of (measurements per) clusters per group) with sufficient (i.e., not very small) sample sizes and without covariates. The upshot of these papers points to alike performance across both methods, meaning it is adequate enough to simply revert to a statistically-easier approach to handle such dependent data in the said design. Though, the unexplored question is whether this result remains true under less ideal and more realistic designs. To this end, the aim of my present project is to consider and compare the performance of the two statistical approaches in settings more typically seen in neuroscience – analyzing clustered data that is imbalanced, has small(er) sample sizes, and also includes a covariate.

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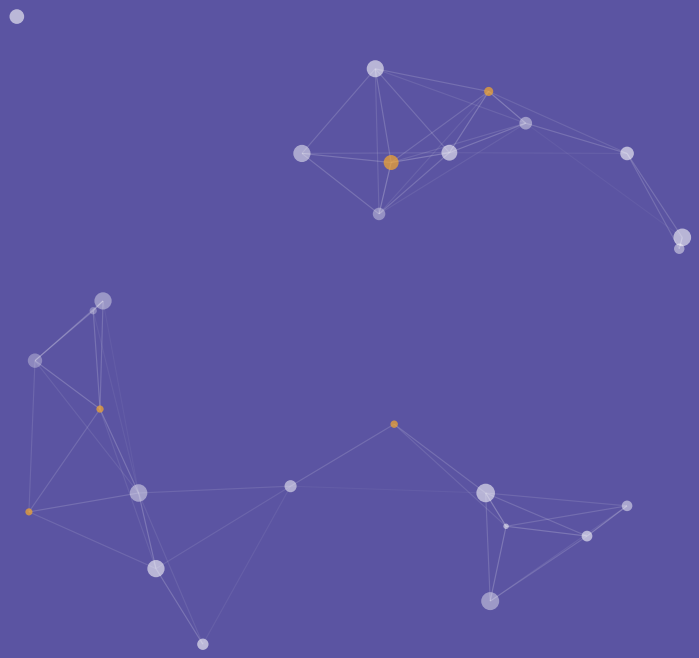

07

THEME

Sensory and Motor Systems

Vision and Visual processing p. 192

Other sensory systems p. 199

Causal Relevance of Areas of the Dorsal Mouse Cortex in Audiovisual Representations: An Optogenetic Scanning Study

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PHD YEAR
Year 4

TALK
Session 2B

WHEN · WHERE
Thu 16:00–17:30 · Zaal 30

KEYWORDS
Optogenetics Perception Higher-Order Visual Areas

BACKGROUND

Multisensory decision-making is hypothesized to rely on cortical substrates combining distinct properties of specific modalities into unified sensory representations. Such representations are thought to emerge not in specialized integration areas, but rather through feedforward and lateral connectivity between sensory and association cortices, enabling the distinction of statistical features (e.g. spatiotemporal signal properties) unique to each modality. Growing evidence challenges the notion of strict functional segregation between sensory cortices. For example, primary visual cortex (V1) encodes multisensory, task-related and motor information in addition to visual signals, suggesting less functional specialization than previously assumed. However, the causal necessity of this multisensory activity for perception remains unclear, raising the critical question: which cortical areas are causally required for forming both unisensory and multisensory representations driving behavior?

METHODS

We trained 5 VGAT-ChR2+ mice to detect changes in continuously presented auditory and visual stimuli, achieving comparable stimulus sensitivity across modalities. We then optogenetically inhibited selected dorsal cortical targets during change detection.

RESULTS

Inhibition of V1 produced the strongest visual performance reduction ($p<10\text{-}5$), followed by significant inhibition of anterolateral (AL; $p<10\text{-}5$), rostrolateral (RL; $p>0.05$), and lateromedial (LM; $p>0.05$) higher-order visual areas (HVAs). Effects were most pronounced for near-threshold compared to high-saliency changes. Inhibiting anterior cingulate cortex (ACC), and anteromedial (A/AM) and posteromedial (AM/PM) HVAs induced an increased error rate to the auditory lickspout during visual trials ($p<0.05$). Auditory performance increased upon inhibition of A/AM ($p<0.05$).

CONCLUSIONS

Our results demonstrate an extended visual network beyond V1 that is causally driving visual change detection, as well as a network supporting motor disinhibition and auditory dominance. Despite multisensory correlates previously observed in these regions, they selectively support visual perception while leaving auditory detection largely unaffected by inhibition.

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Dopaminergic Role in the Superior Colliculus

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PHD YEAR: Year 3
POSTER NO.: 8
LOCATION: Foyer ground floor · Thu
KEYWORDS: Dopamine Sensor, Superior Colliculus, Innate Behavior

BACKGROUND

The superior colliculus (SC), a subcortical structure receiving topographic input from retinal afferents, plays a key role in sensorimotor integration and mediates innate behaviors such as approach, freezing, and escape. Dopamine receptors are abundantly expressed in the SC. In particular, D1 receptor-expressing neurons are more prevalent in the superficial layers, whereas D2 receptor-expressing neurons are mainly located in the intermediate layers (Bolton et al., Cell Reports, 2015). Dopamine receptors from both families are present in the superior colliculus, or its homologous structure, the optic tectum, across vertebrate species. The abundance and evolutionary conservation of dopamine receptors suggest that dopamine may play an important role in SC function, raising the question: When is dopamine released in the SC?

METHODS

We injected AAV9 viruses encoding the third-generation genetically encoded fluorescent dopamine sensors gDA3m and dLight3.8 into the SC of mice. Optical fibers were implanted above the superficial and deep layers of the SC to monitor dopamine release during different behaviors. Besides, we also inject chrimsonR virus into the potent dopaminergic source in the superior colliculus, locus coeruleus and zona incerta, and simultaneously record the dopamine signal.

RESULTS

When we stimulated the locus coeruleus (LC), we observed strong responses with both dopamine sensors.

CONCLUSIONS

Stimulating LC axon terminals in the SC may induce an increase in dopamine levels and promote flight behavior.

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Engineering a Biomimetic 3D-Bioprinted Outer Blood–Retina Barrier

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PHD YEAR
Year 2

POSTER NO.
112

LOCATION
Zaal 25 Woudvleugel · Fri

KEYWORDS
Outer Blood-Retinal Barrier (oBRB) · 3D Bioprinting · Induced Pluripotent Stem Cells (iPSCs)

BACKGROUND

The outer blood–retinal barrier (oBRB) is essential for retinal homeostasis and comprises the retinal pigment epithelium (RPE), Bruch's membrane (BrM), and the underlying choroidal endothelium. Dysfunction of this interface contributes to retinal degeneration. Current in-vitro models do not fully recapitulate its structural and cellular complexity. This project aims to engineer a biomimetic 3D-bioprinted oBRB construct for future retinal tissue regeneration and disease modeling.

METHODS

A multidisciplinary tissue-engineering approach is being used to combine a biomimetic scaffold mimicking BrM with human induced pluripotent stem cell (iPSC)-derived RPE and a choroidal endothelial component. Scaffold materials are characterized for their structural and physical properties, and 3D bioprinting is being developed to establish a reproducible construct geometry. RPE cells are established and characterized using morphological assessment and molecular markers, including RPE65, ZO-1, DAPI, and ezrin. The integration of the scaffold and cellular components will be further investigated, with subsequent evaluation of cell–material interactions, barrier integrity, and the functional characteristics of the engineered construct.

RESULTS

Initial scaffold characterization showed promising properties for mimicking BrM. Moreover, control iPSC-derived RPE cells were characterized using established biomarkers, supporting their mature and functional phenotype. In parallel, work is ongoing to establish the choroidal endothelial cell component for integration into the engineered oBRB construct.

CONCLUSIONS

These initial findings provide a promising foundation for engineering a biomimetic 3D-bioprinted outer blood–retinal barrier. By bringing together a BrM-mimicking scaffold, mature iPSC-derived RPE cells, and a choroidal endothelial component, this project aims to establish a physiologically relevant platform for retinal tissue engineering, with potential applications in transplantation and future studies of retinal degeneration.

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Evaluation of Image Segmentation Algorithms for Visual Neuroprostheses Using Virtual Reality

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PHD YEAR: Year 2
POSTER NO.: 87
LOCATION: Zaal 22 + 23 Woudvleugel · Fri
KEYWORDS: Visual Neuroprosthesis, Virtual Reality, Image Segmentation

BACKGROUND

Visual neuroprostheses aim to restore useful visual function in people with blindness. However, direct evaluation of image-processing strategies in implanted individuals is limited by the small number of recipients and by ethical and practical constraints associated with human implantation. Virtual reality (VR) enables simulation of phosphene-based vision in healthy sighted participants, allowing systematic evaluation of image-processing algorithms and stimulation resolutions. This study investigates how segmentation algorithm and phosphene resolution affect visual acuity, navigation, and scene recognition.

METHODS

Participants will perform three tasks under simulated phosphene vision in VR: visual acuity assessment using a LogMAR chart, a door-finding navigation task, and a scene-recognition task. Visual input will be processed using either Canny edge detection or FastSAM segmentation and presented at resolutions of 500, 1,000, or 2,000 phosphenes. Task accuracy and response time will be compared across algorithms and phosphene resolutions.

RESULTS

Data collection is ongoing. Analyses will assess differences in accuracy and response time between segmentation algorithms and phosphene resolutions and determine the minimum phosphene resolution supporting successful task performance.

CONCLUSIONS

This study provides a systematic VR framework for evaluating image-processing strategies for simulated prosthetic vision. The findings may inform the selection of segmentation algorithms and stimulation resolutions for future visual neuroprostheses.

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From Thalamic Stimulation to Perception: Cortical and Perceptual Detection Responses to Electrical Activation of the LGN

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PHD YEAR
Year 4

TALK
Session 2B

WHEN · WHERE
Thu 16:00–17:30 · Zaal 30

KEYWORDS
Lateral Geniculate Nucleus · Electrical Stimulation · Perceptual Detection

BACKGROUND

Electrical stimulation of the visual thalamus has been proposed as a potential strategy for restoring vision in cases of cortical blindness or retinal degeneration. However, it remains unclear how artificial activation of the lateral geniculate nucleus (LGN) is transmitted through cortical circuits and whether it can generate perceptually relevant signals. Here, we investigate the impact of LGN stimulation on cortical activity and perceptual detection in mice.

METHODS

We combined focal electrical stimulation of the LGN with widefield calcium imaging and two-photon imaging in mouse visual cortex (V1) to characterize cortical responses at population and cellular resolution. In parallel, mice were trained in a perceptual detection task to assess whether LGN stimulation is behaviourally detectable as a visual percept. Stimulation intensity was systematically varied to determine optimal stimulation parameters.

RESULTS

Electrical stimulation of the LGN reliably evoked activity in V1, with response amplitude scaling with stimulation intensity. Widefield imaging revealed structured cortical activation patterns consistent with feedforward thalamocortical propagation. At the cellular level, preliminary two-photon imaging showed recruitment of V1 neurons. Moreover, behavioural data indicate that mice can learn to detect LGN stimulation, suggesting that artificial thalamic activation can generate perceptually relevant signals.

CONCLUSIONS

These findings demonstrate that electrical stimulation of the LGN can drive cortical activity and is capable of supporting perceptual detection behaviour. This supports the feasibility of the visual thalamus as a target for vision restoration approaches and provides insight into thalamocortical processing mechanisms.

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Testing the Neural Mechanisms of Visual Consciousness

Sabine Gnodde

PHD YEAR
Year 4

TALK
Session 4C

WHEN · WHERE
Fri 13:50–15:20 · Zaal 15 (45 places)

KEYWORDS
Consciousness · Visual Perception · Electrophysiology · EEG

A central question in consciousness research is whether perceptual awareness arises primarily from early activity in posterior sensory regions or from later processes involving the prefrontal cortex (PFC). Addressing this question is challenging, as most human paradigms rely on explicit reports, introducing motor and decisional confounds, while causal tests of underlying neural mechanisms remain limited. In this talk, I present a combined human and mouse approach to identify the neural correlates of visual consciousness and to experimentally test competing theories of consciousness. In humans, we used EEG-recordings with a cross-decoding design, combining a backward-masking task with subjective visibility reports and a separate no-report task. Classifiers trained on stimulus location in the no-report condition were tested on masked trials sorted by subjective visibility, isolating report-independent neural representations. This revealed early differences between visible and invisible stimuli (130–170 ms) over posterior regions, with no corresponding frontal effects, suggesting that subjective awareness is linked to early sensory processing. To causally test the role of prefrontal feedback, we developed a complementary mouse paradigm. Head-fixed mice perform a visual discrimination task with backward masking, while projection-specific optogenetic inhibition selectively silences feedback from PFC to primary visual cortex (V1). Simultaneous Neuropixels recordings enable circuit-level analysis of neural activity during perception, allowing a direct test of whether prefrontal feedback is necessary for conscious perception. Together, these paradigms bridge human and animal research, combining report-independent neural measures with causal circuit manipulations to evaluate competing theories of consciousness.

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The Neural Dynamics of Prosthetic Vision: From Simulations to Perception

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PHD YEAR
Year 4

TALK
Session 4B

WHEN · WHERE
Fri 13:50–15:20 · Woudzicht

KEYWORDS
Visual Prosthesis · Visual Processing · Neurotechnology

BACKGROUND

Visual prostheses aim to restore a rudimentary form of vision to blind individuals by converting camera input into electrical stimulation of the visual system, evoking localised percepts of light, or phosphenes. This has been demonstrated successfully in both human and animal studies, but percepts vary between subjects, stimulated electrode and even over time, leading to phosphenes with unexpected shapes, colour or that fade as stimulation continues. Understanding the neural basis of this variability is essential for prostheses that deliver a stable, reliable percept.

METHODS

We first present a biologically plausible simulator of prosthetic vision, integrating human and non-human primate electrophysiological findings on cortical stimulation. We then combine perceptual reports and simultaneous neural recordings from blind participants implanted with intracortical arrays in V1, alongside non-human primate recordings across V1, V4 and IT. We characterise how phosphenes and their neural correlates change with repeated stimulation and use these data to fit a computational model of the underlying dynamics.

RESULTS

The simulator accurately reproduces established phosphene characteristics, including cortical magnification and current-dependent size and brightness. When stimulation is applied repeatedly, we show that shorter inter-train intervals lead to faster fading, and this behavioural effect is closely mirrored by the rate of adaptation in simultaneously recorded neural activity. A divisive normalisation model captures these dynamics.

CONCLUSIONS

Together, these results show that phosphene phenomenology can be predicted not only in space, but increasingly also in time, providing a foundation for model-based, closed-loop stimulation strategies aimed at delivering stable prosthetic vision.

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Dissecting the Relationships Between Biophysical, Morphological and Electrophysiological Properties of Cortical Dendrites

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PHD YEAR
Year 3

POSTER NO.
60

LOCATION
Zaal 25 Woudvleugel · Thu

KEYWORDS
Dendritic Integration · Sensory Processing · Ion Channel Degeneracy

BACKGROUND

How do neurons transform synaptic inputs into action potential (AP) outputs? Computational models that capture biophysical, morphological and electrophysiological properties of neurons offer a powerful means for addressing this question. However, even within a cell type, neurons show enormous variability in their morphologies and electrophysiological responses. Moreover, a wide range of biophysical parameter configurations can lead to the same electrophysiological responses, a phenomenon commonly called degeneracy. Thus, understanding how neurons transform synaptic input into APs requires models that account for their morphological diversity, electrophysiological variability and biophysical degeneracy, and disentangle how these three modalities relate to one another to implement robust input-output computations.

METHODS

Here we address these challenges for the major output cell of the cortex – layer 5 pyramidal tract neurons (L5PTs). We demonstrate computational approaches to generate biophysically detailed models for any in vivo labeled morphology from a morphologically diverse set of L5PTs in the rat barrel cortex.

RESULTS

Strikingly, for each morphology, we identify hundreds of thousands of biophysical parameter configurations that capture 55 electrophysiological properties. Overall, we present a database of millions of models that account for the morphological diversity, electrophysiological variability and biophysical degeneracy. Based on this unique database of models, we provide first insights into relationships between the biophysical, morphological and electrophysiological properties of L5PTs, and how these relationships impact the transformations of sensory-evoked synaptic inputs into single AP and burst outputs.

CONCLUSIONS

Finally, we demonstrate that our approaches are readily applicable to other cell types, brain areas and species, including investigations of pathological conditions.

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Hearing More than Sound: Characterizing Multisensory Neurons in the Inferior Colliculus

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PHD YEAR: Year 4
TALK: Session 3C
WHEN · WHERE: Fri 11:00–12:30 · Zaal 15
KEYWORDS: In-Vivo Patch-Clamp, Multisensory Integration, Anatomical Tracing

BACKGROUND

The inferior colliculus (IC) is a midbrain nucleus playing a major role in the auditory pathway. Its multisensory region, the lateral cortex (LCIC), was shown to receive inputs from somatosensory regions such as the somatosensory cortex and the dorsal column nuclei. The function of those projections is still largely unclear, especially on the single cell level. Here we wanted to investigate the effects of somatosensory stimulation and the interaction with simultaneous auditory stimulation within a single neuron.

METHODS

We conducted viral tracing studies to localize somatosensory recipient cells, followed by somatosensory activation of c-fos expression and subsequent immunohistochemistry to characterize these cells. Finally we performed in-vivo whole cell recordings, paired with auditory, somatosensory and multisensory stimulation.

RESULTS

Preliminary data suggested that all recorded neurons showed at least subthreshold responses to sound stimulation (excitatory, inhibitory or mixed), and approximately half of the recorded neurons showed at least subthreshold responses to somatosensory stimulation. Responses to pressure step stimulation can be subdivided into onset depolarization, offset depolarization and onset hyperpolarization. In a subset of somatosensory-responsive neurons, vibratory stimulation alone was enough to drive action potentials (APs), while simultaneous auditory stimuli reduced the amplitude of vibratory excitatory postsynaptic potentials and suppressed vibration-evoked APs.

CONCLUSIONS

These findings suggest a heterogeneous multisensory neuronal population present within the IC with multimodal interactions within a singular cell.

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Labelling and Investigating Hyperactive Auditory Neurons After Sound Overexposure

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PHD YEAR
Year 3
POSTER NO.
30
LOCATION
Zaal 22 + 23 Woudvleugel · Thu
KEYWORDS
Tinnitus | Inferior Colliculus | TRAP2

BACKGROUND

Tinnitus, the perception of sound without an external source, affects roughly 14% of adults. It lacks effective treatment because its underlying mechanisms remain unclear. Sound overexposure (SO) causes hearing loss and shifts excitation/inhibition balance toward hyperactivity in the inferior colliculus (IC), a tonotopically organized auditory hub; IC hyperactivity is thought to be an electrophysiological correlate of tinnitus. This study asks which IC cells become hyperactive after SO.

METHODS

Mice received unilateral SO (116 dB SPL, one-octave band centered at 16 kHz, 1 hr). Three days later, mice were placed in a silent room with both ears plugged and injected with tamoxifen to permanently tag activated neurons. In TRAP2xAi14 mice, tdTomato expression revealed the labeled cells. TRAP2 mice were injected with an AAV encoding the inhibitory opsin GtACR2 for optotagging, then underwent the same SO paradigm, and received 4-OHT, rendering SO-activated cells optogenetically accessible. A multielectrode probe was then inserted into the IC to record neuronal activity and identify opto-inhibited (SO-labeled) units by their response to light.

RESULTS

Three days after SO, tdTomato+ cells in TRAP2xAi14 mice formed a pattern resembling a tonotopic band. In TRAP2 mice, SO-labeled, optotagged neurons showed significantly higher spontaneous firing rates than surrounding cells, and appeared to share similar frequency tuning.

CONCLUSIONS

These results suggest SO drives a tonotopically restricted population of hyperactive IC neurons that can be optogenetically identified and suppressed, offering a promising strategy for labelling and characterizing cells that contribute to tinnitus.

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Somatosensory Layer 5 Pyramidal Tract Neurons Efficiently Encode Diverse Whisker Stimuli via Broad and Variable Receptive Fields

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PHD YEAR: Year 3

POSTER NO.: 20

LOCATION: Foyer top floor · Thu

KEYWORDS: Primary Somatosensory Cortex · Sensory Encoding · Population Coding

BACKGROUND

Layer 5 pyramidal tract neurons (L5PTs) are a major output class of the cortical column in the barrel cortex. In the rodent primary somatosensory cortex (S1), one of the prominent characteristics of L5PTs is their broad receptive fields. The principles by which individual L5PTs encode sensory stimuli remain poorly understood.

METHODS

We perform in vivo extracellular recordings from the mouse barrel cortex during various single-whisker stimulations under anaesthesia to investigate these encoding mechanisms. Using 64-channel silicon probes spanning the cortical column, we extract laminar activity and isolate putative L5PTs based on location depth, action potential waveform, and sensory responsiveness.

RESULTS

Our analysis targets single-cell responses that potentially contribute to the representation of individual whisker deflections at the level of an inter-barrel layer 5 population. The resulting dataset will serve as a biological reference for constraining and validating the decoding analysis that uses computational models of the barrel cortex L5PT population code.

CONCLUSIONS

By providing ground truth, our study enables testing whether the broadness and variability of the L5PT receptive fields support efficient population coding, with fewer neurons being sufficient to reliably represent a diverse range of whisker stimuli.

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Tactile Processing in the Mouse Inferior Colliculus

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PHD YEAR
Year 4

TALK
Session 3A

WHEN · WHERE
Fri 11:00–12:30 · Zaal 30

KEYWORDS
Multisensory Integration · Auditory Midbrain

BACKGROUND

The inferior colliculus is a crucial auditory midbrain processing center. The lateral cortex of the inferior colliculus (LCIC) also receives non-auditory inputs; LCIC neurons respond to high frequency vibrations in isolation and concurrent sound enhances their responses further. The question remains if this is specific to vibrotactile stimuli or if simple pressure to the skin is also processed by the LCIC.

METHODS

To answer these questions, we performed in vivo electrophysiological recordings in the LCIC of anesthetized mice using multi-electrode silicon probes while presenting a variety of auditory and tactile stimuli, both separately and simultaneously.

RESULTS

A subset of recorded units (n = 26, in 6 mice) responded robustly to on- and offset of pressure stimuli to the hind paw. Increasing stimulus strength increased the onset response rate and decreased the response latency. The response to repeated (10-50Hz) pressure stimuli followed the stimulation frequency with high fidelity, but often showed adaptation. This phenomenon persisted in a subset of units in combination with sustained sound presentation. Our finding showed that low frequency, repeated pressure steps are robust somatosensory stimuli that drive LCIC neurons with high temporal fidelity.

CONCLUSIONS

Ongoing experiments are examining how stimulus onset asynchrony and relative stimulus strength (inverse effectiveness) shape multisensory responses. To understand the perceptual relevance of the LCIC multisensory integration in the LCIC, future work will focus on the underlying local circuit facilitating cross-modal processing. We hope our and other's findings will resolve the LCIC's non-auditory role and help understand the function of pre-thalamic sensory processing centers in multisensory integration.

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Touch Responses in Barrel Cortex Layer 5 Pyramidal Cell Types Are Differentially Shaped by Visuotactile Experience

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PHD YEAR
Year 4

TALK
Session 2B

WHEN · WHERE
Thu 16:00–17:30 · Zaal 30

KEYWORDS
CellType Experience Multisensory

BACKGROUND

The primary somatosensory cortex (S1) contains two major projection-defined Layer 5 excitatory cell types: intratelencephalic (IT) and pyramidal-tract (PT) neurons. As the main output of the cortex, understanding how experience shapes their responses to touch is important for deciphering how learning affects cortical output. Yet, while natural experience is multisensory, this has been typically studied using unisensory stimuli, leaving this gap unaddressed.

METHODS

To tackle this, we recorded spiking activity from genetically defined IT and PT neurons in the S1 whisker field of head-fixed mice exposed to a visuotactile virtual environment

RESULTS

We find that experience in this rewarded visuotactile context specifically affects touch responsiveness but not response amplitude in a cell type specific manner: the fraction of touch-responsive IT cells increases, while that of PT cells decreases. Despite this experience-dependent reorganization, neither visual stimuli nor visuotactile mismatches were encoded in either cell type.

CONCLUSIONS

These results demonstrate that multisensory experience reshapes S1 output through differential recruitment of cell types, rather than changes in response gain or the emergence of visual encoding.

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08

THEME

Other

No topic registered p. 206

Applicability of Co-Implantable Gelatin-Tyramine Hydrogels for Sustainable Intracochlear Release of Dexamethasone After Cochlear Implantation

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PHD YEAR
Year 1

POSTER NO.
43

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Cochlear Hearing Hydrogel

BACKGROUND

Hearing-impaired patients may be eligible for a cochlear implant (CI) if insufficiently treated with conventional hearing aids. Insertion of the CI electrode array into the cochlea may trigger an inflammatory response leading to delayed loss of residual hearing through oxidative stress on hair cells. As residual hearing has been shown to improve quality of hearing with a CI, it is important to protect residual hair cells. Sustained intracochlear administration of corticosteroids, such as dexamethasone, has demonstrated potential to reduce inflammatory response. Here, we propose first steps towards a drug-loaded co-implantable hydrogel for sustained intracochlear release of dexamethasone.

METHODS

A gelatin-tyramine hydrogel formulation protocol was based on Steverink et al. (Acta Biomaterialia, 2021) and modified to exhibit desired mechanical properties. A hydrogel degradation assay was performed in various media. The in vitro dexamethasone release profile was assessed and hydrogels were co-implanted ex vivo in human cadaveric temporal bones.

RESULTS

A C-shaped hydrogel was designed that remains around the array while handling it with surgical instruments. In vitro, hydrogels fully degrade in 15 days and cumulatively releases 200 µg dexamethasone over 72 h in vitro. We show that the hydrogel can be co-implanted reproducibly ex vivo by multiple otologists.

CONCLUSIONS

We present a hydrogel that can be co-implanted reproducibly ex vivo and degrades within 15 days in vitro, while releasing dexamethasone over 72 h. Future research may be conducted towards optimization of the release profile and in vivo experiments investigating the hydrogel's potential ability to protect residual hearing after cochlear implantation.

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Modeling and Gene Therapy Development for X-Linked Retinoschisis in Rats

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PHD YEAR
Year 1

POSTER NO.
121

LOCATION
· Fri

KEYWORDS
X-Linked Retinoschisis (XLRS) | Founder Mutation | Gene-Therapy

BACKGROUND

X-linked retinoschisis (XLRS), caused by RS1 variants, disrupts retinal structure and function. Models representing distinct variants are needed to investigate variant-specific disease mechanisms and responses to therapy. We generated Brown Norway rats carrying the patient-derived E72K missense variant or the E4DEL frameshift variant to characterize disease progression and inform future therapeutic studies.

METHODS

CRISPR/Cas9-generated lines were validated by Sanger sequencing. Retinal Rs1 transcripts and protein were assessed using RT-PCR, western blotting, and immunofluorescence. Hemizygous males underwent longitudinal optical coherence tomography and scotopic and photopic full-field electroretinography from approximately 2 to 12 weeks. Retinal thickness, schisis cavities, response amplitudes, and implicit times were compared with wild-type controls.

RESULTS

Rs1 transcripts were detected in both lines. Monomer-sized RS1 bands were detected by western blotting in E72K but not E4DEL mutants. Retinal immunostaining was undetectable in hemizygous males and homozygous females of both lines. At 2 weeks, schisis increased retinal thickness to 196% and 166% of wild-type values in E72K and E4DEL males, respectively. Cavities collapsed by 3 weeks, followed by thinning to 71% and 75% of wild-type thickness at 12 weeks. Both lines showed early, sustained reductions in scotopic a- and b-wave amplitudes, without significant between-line amplitude differences. Scotopic flicker responses were reduced, while implicit-time abnormalities varied with age, stimulus intensity, and mutant line.

CONCLUSIONS

Both models exhibit rapid structural deterioration and sustained retinal dysfunction, supporting early intervention studies. Future work will evaluate AAV-mediated RS1 delivery with Tet-regulated expression to control transgene levels and investigate retinal rescue.

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The Cortical Caudal ACC-to-PL Projection Suppresses Remote Fear Memory Expression

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PHD YEAR
Year 1

POSTER NO.
44

LOCATION
Zaal 24 Woudvleugel · Thu

KEYWORDS
Engrams Prefrontal Cortex Memory Consolidation

Remote memories require reactivation of sparsely distributed cortical neurons defined during learning, so-called engram neurons. To support the persistence of these memories, intercortical connectivity is thought to strengthen over time during systems consolidation. Engram neurons in both the caudal anterior cingulate cortex (cACC) and prelimbic cortex (PL) play a pivotal role in remote memory retrieval. However, little is known about how the connection between the cACC and PL contributes to systems consolidation and remote memory retrieval. Using neuronal activity-dependent retrograde tracing, we observed preferential reactivation of cACC engram neurons that project to the PL during remote memory retrieval, suggesting a functional role for this projection. Next, we performed several tracing strategies, including anterograde transsynaptic tracing, to characterize the cACC-to-PL projection. We found that the cACC projects to a substantial proportion (~35%) of PL engram neurons. However, cACC input did not influence the reactivation rate of PL engram neurons. In contrast, non-engram PL neurons that received cACC input were activated to a greater extent than non-engram neurons without cACC innervation. Interestingly, chemogenetic inhibition of the cACC-to-PL projection enhanced freezing during a remote memory test, whereas activation reduced freezing. Together, these findings indicate that the cACC-to-PL projection modulates remote fear memory through suppression of freezing, potentially via recruitment of a new (non-engram) ensemble in the PL. Further elucidating the mechanisms by which this projection dampens freezing responses may inform strategies for regulating remote fear memory retrieval.

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THANK YOU

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See you next year!