2023

AWCBR

Australasian Winter Conference on Brain Research

AWCBR 2023

Neurological Foundation

A pathway to hope

SYMBIOTIC DEVICES

Aotearoa Brain Project | Kaupapa Roro o Aotearoa

Saturday 26 August 2023

3:30 pm-6:00 pm		Registration, Crowne Plaza Hotel
6:00 pm		Opening Reception, Cash Bar and Light Food, Atrium
7.15 pm		Chair's Opening Remarks

1. PLENARY LECTURE:
CHAIR: SIMON O'CARROLL

7:30 pm 1.1

Peter Mombaerts,

Max Planck Research Unit for Neurogenetics, Frankfurt, Germany

Visualizing how SARS-CoV-2 attacks the olfactory system in COVID-19 patients

Sunday 27 August 2023

8:15 am		COFFEE/TEA BREAK

2. Novel Methods

CHAIR: ADELIE TAN

8:30 am	2.1	**Rachael Sumner,** ***University of Auckland, Auckland, New Zealand*** Neurophysiological evidence that frontoparietal connectivity and GABA-A receptor changes underpin the antidepressant response to ketamine
8:45 am	2.2	**Pang Ying Cheung,** ***University of Auckland, Auckland, New Zealand*** In vivo imaging of developmental neural activity in neonatal mice
9:00 am	2.3	**Lucy Anderson,** ***University of Otago, Dunedin, New Zealand*** Exploring novel functional connectivity neurofeedback training for treatment of fibromyalgia: a pilot randomised placebo-controlled study
9:15 am	2.4	**Alireza Nia,** ***Auckland Bioengineering Institute, Auckland, New Zealand*** Leveraging the complementary nature of EEG and fNIRS for improved emotion recognition: A neuroimaging perspective
9:30 am	2.5	**Jake McNaughton,** ***University of Auckland, Auckland, New Zealand*** Synthesising MRIs from CTs to improve stroke treatment using deep learning
9:45 am	2.6	**Erin Cawston,** ***University of Auckland, Auckland, New Zealand*** The New Zealand-Dementia Prevention Research Clinics: Plasma biomarkers and the Alzheimer's disease continuum

10:00 am		MORNING TEA BREAK

3. Cognition and Behaviour

CHAIR: RACHAEL SUMNER

10:30 am	3.1	**Robert Munn, *University of Otago, Dunedin, New Zealand*** Hippocampal dysfunction: it's all about timing! Insights from two model systems
10:45 am	3.2	**Nicola Slater, University of Canterbury, *Christchurch, New Zealand*** Cortical cholinergic pathway integrity in Parkinson's disease
11:00 am	3.3	**Skylar Pollack, *University of Auckland, Auckland, New Zealand*** Measuring hippocampal activity in conjunction with behaviour utilising head-mounted miniaturised microscopes
11:15 am	3.4	**Kyla-Louise Horne, University of Otago, Christchurch, *New Zealand*** Understanding the development of anxiety over the disease course in Parkinson's disease
11:30 am	3.5	**Narun Pat, *University of Otago, Dunedin, New Zealand*** The (limited?) utility of brain age as a biomarker for capturing fluid cognition in older individuals
11:45 am	3.6	**Eddie Wise, *University of New South Wales, Sydney, Australia*** Basolateral amygdala local circuit plasticity in instrumental learning processes

12:00 pm BREAK

4. Student and Early Career Researcher Session

CHAIR: JENNIFER HAMILTON

12:15 pm

Open to all students and ECR's attending AWCBR.
Nibbles will be provided as a light lunch.

Meg Spriggs, Sophie Mathiesen, Victor Dieriks

I am more than an H index - Finding the balance of science and wellbeing

Navigating life as an early career researcher is complex. Alongside

grants, publishing, and academic goals, we are people with lives outside of academia. Finding the balance can be challenging. This session will dive into some of these lesser explored topics of life as a student and ECR including identity, burnout, family, work-life-balance, and passion.

A talk by Meg Spriggs will be followed by a panel discussion and Q&A with Jenny Hamilton, Sophie Mathiesen, and Victor Dieriks.

2:15 pm AFTERNOON TEA

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5. Poster Session

2:30 pm-6:00 pm All posters should be put up by 2:30 pm and remain up until at least 5:30 pm.
Presenters with odd numbers should be in attendance at their poster from 2:45 pm – 4:00 pm.
Presenters with even numbers should be in attendance at their poster from 4:15 pm – 5:30 pm.
All presenters need to remove their poster by 6:00 pm.

5.1 **Milly Darragh,** ***University of Auckland, Auckland, New Zealand***
White matter abnormalities in aMCI patients

5.2 **Estelle Miller,** ***University of Auckland, Auckland, New Zealand***
Psychedelic drug microdosing practices: A qualitative netnographic exploration

5.3 **Fu-Yu Beverly Chen,** ***Chung Yuan Christian University, Taoyuan, Taiwan***
Contralateral theta burst stimulation on motor excitability and performance in rats with focal cerebral ischemia

5.4 **Diana Atigari,** ***Massey University, Wellington, New Zealand***
Monoamine oxidase inhibitors from tobacco smoke as a potential smoking cessation therapy

5.5 **Dipshay Avi Chand,** ***University of Auckland, Auckland, New Zealand***
Absolute quantification of neuromelanin in formalin-fixed human brains using absorbance spectrophotometry

5.6 **Soniya Raju, *University of Waikato, Hamilton, New Zealand***
Electronic circuitry for shaping current pulses for small-scale transcranial magnetic stimulation (TMS) coil

5.7 **Alexandra Lister, *Te Herenga Waka -Victoria University of Wellington, Wellington, New Zealand***
Embryonic mRNA expression of serotonin-associated genes following maternal immune activation

5.8 **Adelie Tan, *University of Auckland, Auckland, New Zealand***
Neuropathology of the striatum in X-linked Dystonia Parkinsonism

5.9 **Lance Martinez, *University of Auckland, Auckland, New Zealand***
Characterising Tau pathology in the Huntington's disease human brain

5.10 **Abbie Harris, *University of Canterbury, Christchurch, New Zealand***
Grey matter and cognitive impairment in Parkinson's disease

5.11 **Susan Li, *University of Auckland, Auckland, New Zealand***
From expression to activation: PDGF ligands and receptors in the adult human brain

5.12 **Carina Lee, *University of Auckland, Auckland, New Zealand***
Developing novel therapeutics for Glioblastoma

5.13 **Stephanie Huang, *Victoria University of Wellington, Wellington, New Zealand***
A low-cost method for high-throughput DiI labelling of neurons

5.14 **Larissa Rocha, *Victoria University of Wellington, Wellington, New Zealand***
Behavioural effects of high doses of psilocybin in female rats

5.15 **Aimee Mills, *University of Auckland, Auckland, New Zealand***
Microglial and astrocytic responses in the human midcingulate cortex in Huntington's disease

5.16 **Oliver Burnett, *University of Auckland, Auckland, New Zealand***
The caudate nucleus is more susceptible to gliosis in X-linked Dystonia Parkinsonism

5.17 **Ashley Simons, *Victoria University of Wellington, Wellington, New Zealand***
Novel kappa opioid receptor agonists attenuate chemotherapy-induced neuropathic pain

5.18 **Daiana Yedgey,** ***University of Auckland, Auckland, New Zealand***
Investigation of pathology presentation within the human olfactory system

5.19 **Taylor Stevenson,** ***University of Auckland, Auckland, New Zealand***
Meningeal explants as a responsive model for drug discovery: investigating inflammatory stimuli and potential therapeutic applications

5.20 **Henry Liu,** ***University of Auckland, Auckland, New Zealand***
Increased expression of Kir4.1, AQP-4 and GLT-1 in the Alzheimer's disease human brain

5.21 **Cindy van Sleeuwen,** ***University of Otago, Dunedin, New Zealand***
High-definition transcranial grey noise stimulation (HD-tGNS) as an intervention for generalized anxiety disorder: A pilot randomised sham-controlled trial

5.22 **Hanna Friedlander,** ***University of Otago, Dunedin, New Zealand***
A novel role for the central amygdala in the processing and transfer of recently acquired information

5.23 **Gloria Tian,** ***University of Toronto, Toronto, Canada***
Music-evoked versus visual-evoked autobiographical memories: An fMRI study in older adults with neurodegeneration and cognitive impairment

5.24 **Katya Sellen,** ***Victoria University of Wellington, Wellington, New Zealand***
Investigating the mechanism of action of promotion of remyelination by kappa opioid receptor agonists

5.25 **William van der Vliet,** ***University of Otago, Dunedin, New Zealand***
Parcels or voxels? Better methods for predicting cognition from task-based fMRI

5.26 **Jena Macapagal Foliaki,** ***University of Auckland, Auckland, New Zealand***
The Hugh Green Biobank: a facility for the isolation, study, and testing of primary human brain cells for advancing brain research and therapeutic development

5.27 **Zoe Woolf,** ***University of Auckland, Auckland, New Zealand***
In vitro models of brain macrophages: A comparative study

5.28 **James Davies,** ***University of Otago, Dunedin, New Zealand***
ADAM10/17 mediation of Group I mGluR-dependent synaptic plasticity

5.29 **Beth Ryalls,** ***University of Otago, Dunedin, New Zealand***
Developing a relevant model of cannabinoid receptor signalling using human iPSC-derived neurons

5.30 **Richard Roxburgh,** ***University of Auckland, Auckland, New Zealand***
Can you predict which neuropathy patients have CANVAS?

5.31 **Irina Buianova,** ***University of Otago, Dunedin, New Zealand***
Exploring the predictive association between mental health and cognition in older adults from the UK Biobank cohort

5.32 **David Gordon,** ***University of Auckland, Auckland, New Zealand***
Why are two X's better than one? Modifying X inactivation for the treatment of X-linked neurological disorders

5.33 **Miriam Rodrigues,** ***Te Whatu Ora - Te Toka Tumai, Auckland City Hospital, Auckland, New Zealand***
Pūnaha Io – the New Zealand NeuroGenetic Registry & Biobank Update

5.34 **Sara Crellin,** ***University of Otago, Dunedin, New Zealand***
Modulation of axonal action potential conduction with bipolar disorder therapeutics

5.35 **Kiri Barr-Glintborg,** ***University of Canterbury, Christchurch, New Zealand***
Cross hemisphere dysfunction of the anterior thalamic nuclei does not impair spatial working memory in rats

5.36 **Malak Alshakhouri,** ***University of Auckland, Auckland, New Zealand***
Investigating the neurosteroid withdrawal hypothesis of pericatamenial epilepsy using visual long term potentiation

5.37 **Christina Buchanan,** ***Te Whatu Ora - Te Toka Tumai, Auckland City Hospital, Auckland, New Zealand***
Tracking down PINK1 Parkinsonism in Aotearoa

5.38 **Gabrielle Pereira,** ***Federal University of Sao Paulo, Santos, Brazil***
Effects of cannabidiol (CBD) in an animal model of Alzheimer's disease induced by streptozotocin

5.39 **Danielle Rutter,** ***University of Otago, Dunedin, New Zealand***
Investigating the relationship between L-type calcium channels and neuronal excitability in the P301S (PS19) tauopathy model of Frontotemporal Dementia

5.40 **Jemima Ganderton,** ***University of Canterbury, Christchurch, New Zealand***
Reflex tears to target alpha-synuclein in Parkinson's disease

5.41 **Panzao Yang,** ***University of Auckland, Auckland, New Zealand***
Connexin 43 hemichannels — a potential therapeutic target for attenuating preterm inflammation-related brain injury

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6:00 pm BREAK

Conference Dinner

7:00 pm – 11:00 pm

El Camino Cantina

Tickets must be purchased in advance.

All tickets include food, drinks (including wine, beer, and signature margaritas from 7-9 pm) and musical entertainment, so put on those dancing shoes!

Cash bar after 9pm

8:45 am		COFFEE/TEA

6. Sensory and Motor Systems

CHAIR: KYLA-LOUISE HORNE

9:00 am	6.1	**Anna Mitchell,** ***University of Canterbury, Christchurch, New Zealand*** Olfactory processing in thalamocortical circuits in monkeys
9:15 am	6.2	**John Reynolds,** ***University of Otago, Dunedin, New Zealand*** Targeted brain delivery of therapeutics using focused ultrasound in a sheep model of Parkinson's disease
9:30 am	6.3	**Stephanie Glover,** ***University of Auckland, Auckland, New Zealand*** Changes in pre-attentive auditory processing in depression using the roving-MMN EEG task
9:45 am	6.4	**James Phillips,** ***Auckland University of Technology, Auckland, New Zealand*** Handle incompatibility, cup size, and contents influence finger trajectories during pointing movements
10:00 am		MORNING TEA BREAK

7. Symposium: The Evolution of Engagement

CHAIR: INDRANIL BASAK

10:30 am	7.1	**Louise Parr-Brownlie,** ***University of Otago, Dunedin, New Zealand*** Ka mua, ka muri. Walking backwards into the future
10:50 am	7.2	**Makarena Dudley,** ***University of Auckland, Auckland, New Zealand*** From the lab to the lounge: Engaging with Māori communities is critical to achieve equity in outcomes for whānau living with mate wareware
11:10 am	7.3	**Malvindar Singh-Bains,** ***University of Auckland, Auckland, New Zealand*** From test tubes to TV

11:30 am	7.4	**Julie Wharewera-Mika, *Aotearoa Brain Project - Kaupapa Roro o Aotearoa, New Zealand*** 'Ma te kahukura, ka rere te manu – Adorn the bird with feathers so it may fly': Engagement for the future through systems-wide change
11:50 pm		BREAK FOR LUNCH

8. Development

CHAIR: NICKY SLATER

2:30 pm	8.1	**Rashi Karunasinghe, *University of Auckland, Auckland, New Zealand*** Functional neuronal hyaluronidase enzymes regulate the extracellular matrix in association with neurite outgrowth in vitro
2:45 pm	8.2	**Catriona Miller, *University of Auckland, Auckland, New Zealand*** An unbiased de novo network analysis uncovering the developmental intersection between autism and co-occurring traits
3:00 pm	8.3	**Rebecca Lee, *University of Otago, Christchurch, New Zealand*** Long-term impacts of cannabis on resting state functional networks: are there any?
3:15 pm	8.4	**Kate Witt, *Victoria University of Wellington, Wellington, New Zealand*** The role of the dopamine D1 receptor in the anticipation of and engagement in social play
3:30 pm		BREAK/WALK TO THE RYDGES FOR JOINT QRW SESSIONS

9. AWCBR/Kai mō Aotearoa – Food Science/Microbiome Satellite
Food, Microbiome and Brain Health
Queenstown Room,
CHAIR: SIMON O'CARROLL

4:00 pm	9.1	**Nicola Gilles, *University of Otago, Dunedin, New Zealand*** The effect of fruits and vegetables on children's mental and cognitive health: A systematic review of intervention studies and perspective for future research
4:15 pm	9.2	**Fiona Lithander, *University of Auckland, Auckland, New Zealand*** Parkinson's disease and nutrition: what is the link?
4:30 pm	9.3	**Theo Portlock, *University of Auckland, Auckland, New Zealand*** Linking the Gut Microbiome to Neurocognitive Development in Bangladesh Malnourished Infants
4:45 pm	9.4	**Rebecca Slykerman, *University of Auckland, Auckland, New Zealand*** The effect of milk fat globule membrane supplementation on cognitive and psychological outcome in adults
5:00 pm	9.5	**Michael Kendig, *University of Technology Sydney, Sydney, Australia*** Effects of intermittent access to high-fat, high-sugar diets on behaviour and gut microbiota
5:15 pm		BREAK
6:00 pm		**QRW Nobel Laureate lecture - Professor David Julius** Rydges Hotel
7:30pm		**AWCBR Student Dinner** Winnie's, Queenstown All tickets must be purchased in advanced.

8:15 am		COFFEE/TEA

10. Disorders of the Nervous System
CHAIR: BART ELLENBROEK

8:30 am	10.1	**Bronwyn Kivell,** ***Victoria University of Wellington, Wellington, New Zealand*** Nalfurafine alleviates neuroinflammation by promoting an anti-inflammatory microglia phenotype in preclinical models of multiple sclerosis
8:45 am	10.2	**Ben Moloney,** ***University of Auckland, Auckland, New Zealand*** Exploring chronic low-grade inflammation-associated white matter alterations in major depressive disorder
9:00 am	10.3	**Farheen Kothiwala,** ***University of Auckland, Auckland, New Zealand*** Using EEG to assess neural effects of Estradiol: Progesterone ratio in females with and without epilepsy
9:15 am	10.4	**Matthew Boag,** ***Griffith University, Gold Coast, Australia*** Ginkgolic acid restores ferritinophagy in a Parkinson's disease cell model
9:30 am	10.5	**Sa Weon Hong,** ***Massey University, Wellington, New Zealand*** Identification of six new monoamine oxidase (MAO) inhibitors from tobacco smoke and their biochemical characterisation
9:45 am	10.6	**Ozasvi Shanker,** ***University of Delhi, Delhi, India*** Region-specific activation of protein tyrosine kinase 2 (Pyk2) in temporal lobe epilepsy

10:00 am	MORNING TEA

11. Cellular Mechanisms

CHAIR: TAYLOR STEVENSON

10:30 am	11.1	**Timothy Sargeant,** ***South Australian Health and Medical Research Institute, Adelaide, Australia*** Autophagy decreases in the ageing mouse brain in a sex dependent manner
10:45 am	11.2	**Prakshit Niraula,** ***Massey University, Wellington, New Zealand*** Investigating the impact of tobacco particulate matter and selected components on monoamine oxidase activity, protein expression, and gene expression in brain SH-SY5Y cells
11:00 am	11.3	**Kirstin McDonald,** ***University of Otago, Dunedin, New Zealand*** Deciphering the role of lncRNAs in lysosome and neuron health
11:15 am	11.4	**Siddhant Kumar,** ***University of Canterbury, Christchurch, New Zealand*** Study of molecular interactions of TREM2 in Alzheimer's disease
11:30 am	11.5	**Amy Smith,** ***University of Auckland, Auckland, New Zealand*** A human functional genomics approach to investigate inflammation in dementia
11:45 am		AWCBR AGM All attendees are invited to join
12:15 pm		BREAK FOR LUNCH

12. Symposium: Translational Research in Genetic Brain Disease

CHAIRS: CHRISTINA BUCHANAN AND MIRIAM RODRIGUES

3:00 pm	12.1	**Emma Scotter,** ***University of Auckland, Auckland, New Zealand*** Causative variant discovery in motor neuron disease

3:20 pm	12.2	**Stephanie Hughes,** ***University of Otago, Dunedin, New Zealand*** Development of iPSC-derived neuronal models to study Batten disease; a group of childhood dementias
3:40 pm	12.3	**Richard Roxburgh,** ***Te Whatu Ora – Health New Zealand Te Toka Tumai, Auckland, New Zealand*** Pūnaha Io – the New Zealand Neuro-Genetic Registry and BioBank – Lowering barriers to research in Aotearoa
4:00 pm	12.4	**Gina O'Grady,** ***Te Whatu Ora – Health New Zealand Te Toka Tumai, Auckland, New Zealand*** Balancing hope and reality: Clinical trials for Duchenne Muscular Dystrophy in Aotearoa

4:20 pm AFTERNOON TEA

13. Novel Methods

CHAIR: TRACY MELZER

4:50 pm	13.1	**Vanessa Morris,** ***University of Canterbury, Christchurch, New Zealand*** Unravelling molecular details of protein interactions in Alzheimer's disease
5:05 pm	13.2	**William Aye,** ***University of Otago, Christchurch, New Zealand*** Early-phase amyloid PET as a cerebral perfusion surrogate in cognitively impaired Parkinson's disease
5:20 pm	13.3	**Alexander Yang,** ***University of Otago, Dunedin, New Zealand*** Cybersickness prevention and alleviation via machine learning-guided high-definition transcranial direct current stimulation
5:35 pm	13.4	**Tabitha Manson,** ***University of Auckland, Auckland, New Zealand*** Does extravascular water extraction rate differ in Alzheimer's disease compared to healthy aging?

8:15 am		COFFEE/TEA

14. Cognition and Behaviour
CHAIR: JOANNE LIN

8:30 am	14.1	**Penelope Truman,** ***Massey University, Wellington, New Zealand*** Expanding our understanding of tobacco dependence
8:45 am	14.2	**Alina Tetereva,** ***University of Otago, Dunedin, New Zealand*** Capability of multimodal MRI to capture cognitive abilities across the lifespan: Predictability, reliability and generalizability
9:00 am	14.3	**Jennifer Hamilton,** ***University of Canterbury, Christchurch, New Zealand*** Long-term recall of non-spatial memory and the thalamic reuniens
9:15 am	14.4	**Justine Fam,** ***University of New South Wales, Sydney, Australia*** Oxytocin receptor activation in the basolateral amygdala complex enhances stimulus detection, and facilitates aversive, but not appetitive, learning
9:30 am	14.5	**Tessa Chaffey,** ***University of Auckland, Auckland, New Zealand*** The relationship between cortical thinning, grey matter atrophy, and cognitive performance in mild cognitive impairment
9:45 am	14.6	**Joon Kim,** ***University of Otago, Dunedin, New Zealand*** Scaling of avoidance behaviours by hypothalamic stress neural activity

10:00 am		MORNING TEA

15. Disorders of the Nervous System

CHAIR: VICTOR DIERIKS

10:30 am	15.1	**Anne La Flamme,** ***Victoria University of Wellington, Wellington, New Zealand*** The novel HS-mimetic, Tet-29, regulates immune cell trafficking across CNS barriers
10:45 am	15.2	**Mackenzie Kiernan,** ***Victoria University of Wellington, Wellington, New Zealand*** The role of regulatory T cells in remyelination, following kappa opioid receptor agonist treatment
11:00 am	15.3	**Y Mukish M Yelanchezian,** ***University of Auckland, Auckland, New Zealand*** Texture analysis as a biomarker for Alzheimer's disease
11:15 am	15.4	**Kreesan Reddy,** ***University of Auckland, Auckland, New Zealand*** Unique Alpha-synuclein strains enable the exploration of novel targets associated with Parkinson's disease risk genes
11:30 am	15.5	**Ross van de Wetering,** ***Victoria University of Wellington, Wellington, New Zealand*** Nalfurafine facilitates recovery from cuprizone + rapamycin-induced demyelination
11:45 am	15.6	**Sonali Kumar,** ***University of Delhi, Delhi, India*** Potential role of deregulated Histone Deacetylase 4 (HDAC4) in the pathogenesis of temporal lobe epilepsy

12.00 pm	CLOSING REMARKS AND PRESENTATION OF PRIZES LIGHT LUNCH, THREESIXTY RESTAURANT

Acknowledgements

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1992	**Nadia Solowij,** University of New South Wales, Australia
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1994	**Niki Butterworth,** University of Auckland, New Zealand
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1997	**Donna Briggs,** University of Otago, New Zealand
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2022	**Macarena Pavez,** University of Otago, New Zealand
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Abstracts in Presentation Order

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1.1

Visualizing how SARS-CoV-2 attacks the olfactory system in COVID-19 patients

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Anosmia, the loss of smell, is a common and often the sole symptom of COVID-19. The onset of the sequence of pathobiological events leading to olfactory dysfunction remains obscure. We reasoned that the neurotropic or neuroinvasive capacity of SARS-CoV-2, if it exists, should be most easily detectable in individuals who died in an acute phase of the infection. Procuring high-quality fresh tissue samples from the human olfactory mucosa and olfactory bulb has proved challenging, both from living patients and during an autopsy. We have developed a protocol for rapid post-mortem bedside sampling of these structures, using an endoscopic endonasal surgical technique that we adapted from skull base surgery. The procedure leaves no visible incisions and enables a rapid response and logistic flexibility in a variety of hospital settings including a ward. Compared to a typical autopsy, the protocol drastically reduces the post-mortem interval — in our experience with a cohort of 138 cases, the median was 89 minutes — thereby contributing to preserving the tissue samples in pristine condition. Our cohort included 115 COVID-19 patients who died a few days after infection with SARS-CoV-2, enabling us to catch the virus while it was still replicating. We found that sustentacular cells are the major target cell type in the olfactory mucosa. We failed to find evidence for infection of olfactory sensory neurons. We postulate that transient insufficient support from sustentacular cells triggers transient olfactory dysfunction in COVID-19 and that olfactory sensory neurons would become affected without getting infected. Confocal imaging of sections stained with fluorescence RNAscope and immunohistochemistry also afforded the light-microscopic visualization of extracellular SARS-CoV-2 virions in tissues. We failed to find evidence for viral invasion of the parenchyma of the olfactory bulb and the frontal lobe of the brain. Instead, we identified anatomical barriers at vulnerable interfaces, exemplified by perineurial olfactory nerve fibroblasts enwrapping olfactory axon fascicles in the lamina propria of the olfactory mucosa. This poorly characterized cell type appears to seal olfactory axon fascicles hermetically from invasion by SARS-CoV-2 virions. We speculate that this barrier may also be effective against some of the many other pathogens that infect the nasal mucosa and could threaten the brain. In conclusion, SARS-CoV-2 appears to be stopped dead in its tracks by several anatomical barriers at vulnerable interfaces, even in extremely weak individuals with an abysmal level of defence who lost the battle.

2.1

Neurophysiological evidence that frontoparietal connectivity and GABA-A receptor changes underpin the antidepressant response to ketamine

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Revealing the acute cortical pharmacodynamics of an antidepressant dose of ketamine in humans with depression is key to determining the specific mechanism(s) of action for alleviating symptoms. While the downstream effects are characterised by increases in plasticity and reductions in depressive symptoms – it is the acute response in the brain that triggers this cascade of events. Computational modelling of cortical interlaminar and cortico-cortical connectivity and receptor dynamics provide the opportunity to interrogate this question using human electroencephalography (EEG) recorded during a ketamine infusion. Resting-state EEG was recorded in a group of 30 patients with major depressive disorder at baseline and during a 0.44 mg/kg ketamine dose comprising a bolus and infusion. Fronto-parietal connectivity was assessed using dynamic causal modelling to fit a thalamocortical model to hierarchically connected nodes in the medial prefrontal cortex and superior parietal lobule. There was a significant increase in parietal-to-frontal AMPA-mediated connectivity and a significant decrease in the frontal GABA time constant. Both parameter changes were correlated with the antidepressant response to ketamine. Changes to the NMDA receptor time constant and inhibitory intraneuronal input into superficial pyramidal cells did not survive correction for multiple comparisons and were not correlated with the antidepressant response. This study provides evidence that the antidepressant effects of ketamine may be mediated by acute fronto-parietal connectivity and GABA receptor dynamics. Furthermore, it supports the large body of literature suggesting the acute mechanism underlying ketamine's antidepressant properties is related to GABA-A and AMPA receptors rather than NMDA receptor antagonism.

2.2

In vivo imaging of developmental neural activity in neonatal mice

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During the first three postnatal weeks the mouse brain undergoes major developmental rewiring that establishes the neural circuitry seen in the adult brain. Alterations during this period contribute to the miswiring of neural connections and lead to circuit dysfunction. Therefore, studying neural activity during this period is important for understanding the mechanisms of circuit dysfunction associated with neurodevelopmental disorders such as autism spectrum disorder. However, technological limitations meant there are limited options to study widespread neural activity in pre-weaned mice. Using recent advancement in calcium imaging, we developed a novel method to study developmental neural activity in neonatal mice using mesoscopic in vivo calcium imaging. First, neurons were transfected with the genetically encoded calcium indicator, GCaMP7 by injection into the transverse sinus of mouse pups at postnatal day 1. Next, spontaneous neural activity was recorded in sedated neonatal mice at postnatal day 8-10 using a custom-built mesoscope. The large field of view of the mesoscope (10.5 mm x 12.6 mm) allows widefield imaging of the entire cortex with good signal-to-noise ratio. The combination of these methodologies of GCaMP7 transfection and the use of the mesoscope was able to record fluorescence intensity changes that reflect neuronal activity, from the whole brain of a neonatal mouse. Our method of visualising neural activity has enabled our current investigation into mechanisms of neural circuit dysfunction in a mouse model of autism spectrum disorder.

2.3

Exploring novel functional connectivity neurofeedback training for treatment of fibromyalgia: a pilot randomised placebo-controlled study.

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Fibromyalgia (FM) is a chronic primary pain condition contributing to significant disability worldwide. Abnormal somatosensory processing within the nervous system is a key contributor to pain experience in people with FM. Brain imaging demonstrated decreased functional connectivity between cortical areas mediating descending pain modulation [pregenual anterior cingulate cortex (pgACC)] and sensory perception [primary somatosensory cortex (S1)]. Moreover, such functional connectivity alterations were related to FM severity. Neurofeedback, a brain-computer interface technique, can normalize dysfunctional brain activity, thereby improving pain and function. The aim of this double-blinded randomised placebo-controlled pilot study was to investigate the safety and acceptability of a novel electroencephalography-based neurofeedback (EEG-NF) training targeting pgACC-S1 functional connectivity and exploring its immediate trend of effect on pain and function. Participants with FM were randomised to receive either 12 sessions of EEG-NF (n=8) increasing pgACC-S1 functional connectivity in the alpha band or sham NF training (n=8). Outcome measures include pain severity [Brief pain inventory] and functional impact [Revised Fibromyalgia Impact Questionnaire (RFIQ)] were collected at baseline and 2 days post-intervention. No serious adverse events were reported following EEG-NF training, and participants perceived EEG-NF as a highly acceptable intervention. Reduction in the average pain severity (Average pain: -25.2±26.5, $p<0.05$) and RFIQ scores (-25.7±23.4, $p=0.06$) in the EEG-NF group, when compared to the sham group (Average pain: 1.9±19.3, p.0.05; RFIQ scores: -10.2±13.9, p.0.05) were observed. EEG-NF training is a safe and acceptable treatment approach for FM. Future studies could evaluate the efficacy of this technique for improving clinical outcomes in people with FM.

2.4

Leveraging the complementary nature of EEG and fNIRS for improved emotion recognition: a neuroimaging perspective

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Human-computer interaction (HCI) research increasingly emphasizes the significance of emotion recognition in designing more intuitive and user-friendly systems. In our study, we explored the potential of an integrated electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS) approach in identifying emotional states, with an emphasis on the frontal lobe area. We conducted an experiment on 30 participants, using affective video content as stimuli, and extracted both temporal and spectral features from the recorded EEG and fNIRS data. Participants' emotional responses were classified into valence, arousal, and dominance states. Our baseline results showed no significant difference in the classification accuracy of fNIRS and EEG. The classification performance notably improved by 28% to 33% on average when dividing the experiment's trial into independent 8-second non-overlapping segments. Interestingly, while integrating both modalities did not provide a significant enhancement over single modality classification for whole trial data, there was a marked increase in accuracy when segmented data was used in our hybrid system. Our findings underline the complementary nature of EEG and fNIRS signals for emotion recognition by considering the dynamics of modalities together. The comparable performance achieved with fewer fNIRS optodes, ease of setup, and less susceptibility to artifacts, positions fNIRS as a promising alternative to traditional EEG. The significant accuracy improvement using segmented data in the hybrid system elucidates the complex, dynamic nature of affective states, thereby endorsing the utilization of a high temporal resolution, hybrid neuroimaging approach in HCI applications

2.5

Synthesising MRIs from CTs to improve stroke treatment using deep learning

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Patients who present with suspected stroke most commonly receive a CT scan for initial evaluation, due to lower cost and shorter acquisition time compared to MRI. However, MRI has been shown to be more accurate than CT for diagnosing stroke and can provide additional information that can have other advantages over CT scans for the purpose of diagnosis, treatment, and prognosis of stroke. The purpose of this study was to investigate the use of deep learning to generate a synthetic MRI from a patient's CT scan which could be used in a clinical setting of suspected stroke. Eight deep learning models were implemented for this purpose. These models were trained on a dataset of 181 stroke patients who received a CT and an MRI. The performance of these models at generating synthetic MRIs were assessed visually and through quantitative metrics. The synthetic MRIs were also evaluated on their performance at three clinical tasks: lesion segmentation, brain tissue segmentation, and registration to an MRI. All eight models generated synthetic MRIs which showed similarities to the true MRIs. The synthetic MRIs produced by a 3D UNet performed the best over all the quantitative metrics and most of the clinical tasks. All of the models were able to generate synthetic MRIs which could be accurately registered to MRI atlases, and multiple of the models were able to accurately translate the lesions from the CT to the synthetic MRI, and these lesions could be automatically segmented through a pre-trained segmentation model.

2.6

The New Zealand-Dementia Prevention Research Clinics: Plasma biomarkers and the Alzheimer's disease continuum

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The New Zealand-Dementia Prevention Research Clinics (NZ-DPRCs) have assessed participants spanning healthy older adults through subjective or mild cognitive impairment to a clinical diagnosis of Alzheimer's disease (AD). We interrogated baseline blood plasma samples from 253 NZ-DPRC participants (aged 55-87y) for blood biomarkers using the ultra-sensitive immunoassay provided by single molecule array (Simoa) technology. Participants were classified as cognitively normal (CN, n=34), subjective cognitive decline (SCD, n=64), non-amnestic mild cognitive impairment (single and multi-domain, non-aMCI, n= 23), amnestic MCI (single and multi-domain, aMCI, n=105), and AD (n=27). Six plasma biomarkers were examined using linear regression adjusted for age and sex: Amyloid-beta peptides (Aß1-40; Aß1-42); phosphorylated tau species (p-tau181; p-tau231); neurofilament light (NfL) and glial fibrillary acidic protein (GFAP). P-tau181, p-tau231, GFAP and NfL were natural log-transformed to approximate normality and improve homogeneity of variance. Biomarkers p-tau181, p-tau231, GFAP, NfL, Aß1-42/Aß1-40 ratio and Aß1-42, all showed group effects ($P < 0.05$). Pairwise group comparisons (Tukey's HSD) showed significant differences ($P < 0.05$) for p-tau181 comparing AD vs CN, SCD, non-aMCI, aMCI; GFAP comparing AD vs CN, SCD, non-aMCI, also SCD vs MCI; p-tau231 for AD vs non-aMCI; Aß1-42 for aMCI vs CN and SCD; Aß1-42/Aß1-40 ratio for SCD vs aMCI. Our findings show plasma biomarkers are altered cross-sectionally along the AD continuum in the NZ-DPRCs. Plasma p-tau181 and GFAP levels increased over the AD continuum with p-tau181 levels being significantly higher in AD versus all other classification levels.

3.1

Hippocampal dysfunction: it's all about timing! Insights from two model systems

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The hippocampal formation is a key structure in the encoding of memory. Recent evidence has demonstrated that information flow within the hippocampus and between structures in the hippocampal formation is tightly segregated and organized on the large, ongoing theta oscillation in local field potential. We have used two model systems of memory and hippocampal dysfunction; the maternal immune activation model of schizotypy, and the Ts65/DN mouse model of Down Syndrome to examine whether this organization breaks down in these disease states. We show that the MIA and Ts65/DN models both show disrupted hippocampal synchrony, but in different directions. These differences provide novel insight into the circuit-level dysfunction underlying each model, while underlining the importance of synchrony for hippocampal function.

3.2

Cortical cholinergic pathway integrity in Parkinson's disease

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Most Parkinson's disease (PD) patients experience cognitive impairment, albeit at variable rates and severity. Projections from cholinergic neurons in the nucleus basalis of Meynert (NBM) provide neuromodulatory input to the entire cortical mantle. Loss of cholinergic input is considered pivotal to cognitive decline in PD. Evidence for changes in the NBM in PD has been inconsistent, however, NBM projection integrity may provide important additional insight. We examined the integrity of three structurally-defined cerebral cholinergic pathways using probabilistic tractography. Structural and diffusion-weighted MRI was acquired from 108 PD patients, 60 with normal cognition (PD-N), 37 with mild cognitive impairment (PD-MCI), and 12 with dementia (PDD), and 42 controls. Accounting for age and sex, Bayesian mixed-effects models indicated overall PD status was not a predictor of any pathway integrity measure (FA, MD, orientation dispersion index [ODI], free water fraction [FWF], fibre density and cross section [FDC]; all 95% credible intervals include 0). A small effect of PDD was associated with worse MD (β_{PDD}=0.08x10^{-3}[0.04x10^{-3},0.12x10^{-3}]), FWF (□$_{PDD}$=0.05,[0.02,0.09]) and FDC (□$_{PDD}$=-0.03[-0.06,-0.01]) compared to controls, and worse MD (β_{PDD}=0.07x10^{-3}[0.03x10^{-3},0.11x10^{-3}]) and FWF (□$_{PDD}$=0.06[0.02,0.09]) compared to PD-N. Across all PD participants lower global cognitive score was associated with higher MD (β_{cog}=-0.02x10^{-3}[-0.03x10^{-3},-0.004x10^{-3}]), but not with other pathway integrity measures. These findings contradict the commonly-held view that a decline in cortical cholinergic pathway integrity may provide a major explanation for cognitive impairment in PD. Examining NBM subregions and projections to more specific cortical regions may help clarify the contribution of cortical cholinergic input to cognitive impairment in PD.

3.3

Measuring hippocampal activity in conjunction with behaviour utilising head-mounted miniaturised Microscopes

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Alzheimer's disease is a neurodegenerative disorder which produces atrophy and subsequent dysfunction with a marked reduction in the cerebral cortex and hippocampus. To date, nearly all human brain studies are post-mortem and very few studies have examined neuronal activity during animal behaviour in Alzheimer's transgenic models in vivo. Therefore, the aim of our research is to investigate neuronal function with simultaneous behavioural testing in APPswe/PS1dE9 mice utilising head-mountable miniaturised microscopes (miniscopes). Mice were injected with a genetically encoded activity reporter (GCaMP7 AAV1) and implanted with a gradient-refractive index (GRIN) lens and cranial baseplate, to allow attachment of the miniscope. APPswe/PS1dE9 and wildtype mice were subject to open field, y-maze, and novel object recognition tests to measure behaviour deficits in learning and memory, while neuron dynamics were simultaneously recorded by in vivo imaging of GCaMP7 expressing hippocampal CA1 neurons with miniscopes. We confirmed that APPswe/PS1dE9 mice show increased anxiety, as well as deficits in spatial memory. We have optimised our image processing and analysis routines to extract neuronal firing data and relate this to behaviour.

3.4

Understanding the development of anxiety over the disease course in Parkinson's disease

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Anxiety can be one of the most debilitating aspects of Parkinson's disease. Despite this, it remains unclear how anxiety develops over the disease course. Anxiety defined using the Neuropsychiatric Inventory was examined in 346 Parkinson's participants over a 15-year period (1392 sessions, median: 3 sessions per participant) from the New Zealand Parkinson's Progression Programme. Cross-sectional analyses (Bayesian regressions) were conducted, and a multi-state model was used to identify factors that predict the initial onset of anxiety in Parkinson's participants, whilst also accounting for the competing risk of death. At any one time, anxiety was present in 36% of Parkinson's participants. Cross-sectionally, anxiety was associated with shorter disease duration (parameter estimate [PE]: -0.54 [95%CI:-1.07, -0.01]), younger age at diagnosis (PE: -0.54 [-0.91, -0.18]), and higher levels of functional impairment (activities of daily living score; PE: 0.81 [0.52, 1.10]), but not sex, education, medication, motor symptoms, cognitive ability, or depression. There was, however, no evidence that any clinical features predicted anxiety development in those initially without anxiety. After controlling for all other factors, anxiety presence was not associated with a higher risk of death (HR: 1.29 [0.69, 2.38]). Although we found no clinical features that predicted the development of anxiety, younger age at diagnosis, higher functional impairment and shorter disease duration were associated cross-sectionally. As anxiety occurs across the disease course it may be important to determine if Parkinson's patients with higher levels of functional impairment also experience anxiety so that treatment strategies can be put in place to manage the condition.

3.5

The (limited?) utility of brain age as a biomarker for capturing fluid cognition in older individuals

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Neuroscientists have been on a quest to search for a biomarker to capture fluid cognition that usually declines as people grow older. One well-known candidate is Brain Age, or a predicted value based on machine-learning models built to predict chronological age from brain MRI data. Here we aim to formally evaluate the utility of Brain Age as a biomarker for capturing fluid cognition among older individuals. Using 504 aging participants (36-100 years old) from Human-Connectome-Project-Aging, we created 26 age-prediction models for Brain Age based on different combinations of MRI modalities. We first tested how much Brain Age from these age-prediction models added to what we had already known from a person's chronological age in capturing fluid cognition. Based on the commonality analyses, we found a large degree of overlap between Brain Age and chronological age, so much so that, at best, Brain Age could uniquely add only around 1.6% in explaining variation in fluid cognition. Next, the age-prediction models that performed better at predicting chronological age did not necessarily create better Brain Age for capturing fluid cognition over and above chronological age. Lastly, unlike Brain Age, Brain Cognition, or a predicted value based on machine-learning models built to predict cognitive abilities from brain MRI data, provided much higher unique effects, leading to around a $^1/_3$-time improvement of the total variation explained. Accordingly, while demonstrating the limited utility of Brain Age, we provided a solution to improve our ability to use brain MRI data as a biomarker for cognitive abilities.

3.6

Basolateral amygdala local circuit plasticity in instrumental learning processes

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The basolateral amygdala (BLA) is critical for forming emotional associations. While studies of Pavlovian (stimulus-response) conditioning have identified several conditioning-associated neurophysiological adaptions, the plasticity underlying instrumental (action-outcome) learning remains poorly- understood. We examined whether punishment training increases the intrinsic excitability and/or alters the local circuit of connectivity of BLA neurons. Rats were trained to lever press for a food reward daily on a VI30 schedule, before being exposed to a punishment contingency or behavioural control. Whole-cell patch-clamp recordings were made from projection neurons in ex vivo brain slices prepared 1h after the final session. In Experiment 1, the response to intracellular current injections was measured. Neurons from reward or punishment trained rats were generally more excitable (increased APs) than naïve rats and controls that received non-contingent shocks. BLA excitability correlated with punishment performance. In Experiment 2, local circuit plasticity was studied. Transgenic PV-Cre rats selectively expressed the light-activated cation channel ChR2 in parvalbumin GABAergic interneurons and nucleus accumbens-projecting BLA neurons were labelled with the retrograde tracer CTB555. The paired-pulse ratio of optically evoked IPSCs was greater in neurons from punished rats compared to naïve animals, indicating that punishment reduces GABA release probability from parvalbumin neurons. This reduced inhibition was more pronounced in CTB555 negative neurons. These results show that learning to avoid aversive outcomes is associated with both synaptic and non-synaptic BLA plasticity. These findings will serve to better understand neuropsychiatric disorders associated with altered punishment sensitivity such as major depressive disorder and provide treatment frameworks.

5.1

White matter abnormalities in aMCI patients

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This research project assessed whether diffusion tensor imaging (DTI) can reveal differences between amnestic mild cognitive impairment (aMCI) and control participants. Specifically, the hypothesised abnormalities in specific white matter tracts occurring in aMCI patients. The two tracts of interest were the fornix and the cingulum, with both known to be involved with memory and cognition. Previous research expected these tracts in aMCI participants to show decreased integrity due to neuronal atrophy. Two metrics were used (fractional anisotropy (FA) and mean diffusivity (MD)) to compare the structure of aMCI and control. Using FSL and TBSS (tractography based spatial statistics) to process the data, significant differences were observed between our participants. Relative to controls, aMCI participants had decreased FA and increased MD in both the fornix and the cingulum. This suggests decreased white matter integrity for aMCI patients, in tracts that likely contribute to memory and cognitive impairment. Decreased integrity in the superior fronto-occipital fasciculus and uncinate fasciculus was also found. FSL is a DTI software known for being conservative, but no issues with using FSL occurred.

5.2

Psychedelic drug microdosing practices: A qualitative netnographic exploration

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Recently, "microdosing" with psychedelic drugs has gained popularity for self-medication of psychiatric and neurological disorders, including migraines, depression, anxiety and more. "Microdosing" is defined as taking a small amount of a psychedelic drug on a schedule. No set guidelines exist on how to microdose. Consequently, people who microdose (PWM) utilise internet resources for guidance. We conducted a novel investigation of such guidance, enabling us to assess its safety and efficiency. We developed a unique netnographic approach to do so and searched numerous online platforms. 174 unique resources were found. LSD and psilocybin mushrooms were the most common substances used. Microdoses were often consumed orally every third day. Harm reduction strategies were mentioned by some, with considerable variation in such advice. The nascent nature of microdosing is apparent when examining the variety of guidance information online. As microdosing research continues and online microdosing communities continue growing, it is imperative that high quality information is available to PWM. Further, this research helps the field of psychedelic research in understanding self-medication for neurological and psychiatric conditions.

5.3

Contralateral theta burst stimulation on motor excitability and performance in rats with focal cerebral ischemia

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Theta burst stimulation (TBS) is an effective method for modulating motor excitability and has shown promise in stroke rehabilitation. In cases of focal stroke, engaging the healthy hemisphere may benefit brain remodelling and motor recovery. However, the clinical outcomes of using TBS to modulate the activity of the healthy hemisphere during stroke recovery have been inconsistent. This study aims to investigate the effects of contralateral intermittent TBS (iTBS) on focal stroke recovery. Focal infarction was induced in the left primary motor cortex (M1) of Sprague-Dawley rats through endothelin-1 (ET-1) injection. Screw electrodes were implanted above M1 for cortical stimulation and neurophysiological recording. Motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) amplitude from the lesioned hemisphere decreased following ET-1 injection, accompanied by significant deficits in behavioural tests. After 3 weeks of iTBS in the healthy hemisphere, MEP expression and motor performance improved. However, no significant changes were observed in SSEPs or sensory behaviour. These findings suggest that contralateral iTBS intervention may enhance motor excitability and motor recovery, while not affecting sensory recovery.

5.4

Monoamine oxidase inhibitors from tobacco smoke as a potential smoking cessation therapy

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We hypothesize monoamine oxidase inhibitors (MAOIs) in tobacco smoke will enhance tobacco dependence and will establish their potential for smoking cessation. In this study, we show, nicotine self-administration is enhanced significantly in rats in the presence of MAOIs with the concentrations doubled ($p=0.0081$) and quadrupled ($p<0.0001$) compared to the concentration found in tobacco smoke. Further, in the progressive-ratio paradigm, the average breakpoint to self-administer nicotine is significantly higher in the presence of MAOIs ($p=0.0185$ at 2x and $p<0.0001$ at 4x concentrations). In the conditioned-place preference model, rats spend more time in the drug-paired chamber on post-conditioning days and show a significantly higher change in preference when MAOIs are added ($p=0.048$). Additionally, the number of ambulatory counts is also significantly higher with MAOIs ($p=0.027$). MAOIs alone show no change in preference for both measures. Finally, in the locomotor sensitization testing nicotine induces a response but MAOIs treatment does not affect the behavioural sensitization to nicotine in rats. Overall, the study demonstrates that MAOIs treatment enhances the reinforcing effects and the motivational properties of nicotine in rats.

5.5

Absolute quantification of neuromelanin in formalin-fixed human brains using absorbance spectrophotometry

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Parkinson's disease is characterised by preferential degeneration of pigmented dopaminergic neurons in the substantia nigra. The neurons get their colour from neuromelanin, an elusive pigment in the brain. Studying neuromelanin is challenging, primarily due to its insolubility in most solvents except alkali. Quantifying it could progress the development of biomarkers such as neuromelanin-sensitive magnetic resonance imaging and give insights into neuromelanin's role in the brain. Light microscopy is an excellent tool for visualising, but not quantifying, neuromelanin concentrations. Absorbance spectrophotometry was previously used for quantifying neuromelanin but requires large amounts of fresh-frozen samples. We improved the quantification protocol to overcome these issues. Briefly, our protocol involves breaking down fixed tissue, dissolving the neuromelanin in sodium hydroxide, and measuring this solution's 350 nm absorbance. We also synthesised neuromelanin from dopamine and L-cysteine precursors to construct a calibration curve, preventing unnecessary waste of human tissue. This protocol enables parallel analysis of up to 100 samples using as little as 2 mg of tissue. Tissue breakdown and neuromelanin extraction from fixed substantia nigra samples was successful, with concentrations ranging from 0.23 - 0.55 µg neuromelanin per mg of tissue. Quantification was highly reproducible with an interassay coefficient of variation of 6.75 % (n=5). The elemental composition and absorbance spectrum of the synthetic and substantia nigra neuromelanin showed excellent overlap. Our protocol can reliably measure absolute neuromelanin concentrations in small amounts of formalin-fixed tissue. This will enable further development of Parkinson's disease biomarkers and investigation into neuromelanin's role.

5.6

Electronic circuitry for shaping current pulses for small-scale transcranial magnetic stimulation (TMS) coil

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Transcranial Magnetic Stimulation (TMS) works on the principle of Faraday's law of electromagnetic induction. A coil carrying a time-varying current is placed on the surface of the scalp to produce a magnetic field that permeates the brain and produces a current that may stimulate neurons. Small animal TMS coil studies are needed to help establish the mechanisms of TMS action. Constructing small coils capable of producing electric field strengths suitable for stimulation is challenging because the high currents required, and hysteresis of the core, cause heating. Previously, we constructed a TMS coil made from 50 turns of 0.4 mm diameter copper wire on a 19 mm long carbonyl powder iron core and applied this to mouse tissue in vitro. However, the shape of the pulse has not been controllable. In this research, we develop an electronic circuit that produces a pulse with configurable parameters such as shape, number of phases, width of phases, and field strength. We have developed a supercapacitor-based high-voltage pulse generator that produces 80 V output from a 2 V direct current supply, and we have obtained 250 mT magnetic flux density at 2 mm below the coil. The pulses are configurable via an Arduino microcontroller; pulse rise time can be varied around 100 us and the pulse length from 0.5 ms to 10 ms. The configurable pulse generator allows the investigation of how pulse shape influences stimulation and potentially allows optimization of pulse shape to reduce heating and maximize field strengths.

5.7

Embryonic mRNA expression of serotonin-associated genes following maternal immune activation

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Prenatal exposure to maternal immune activation (MIA) resulting from a maternal infection has been linked to increased risk of developmental/psychiatric disorders in offspring - such as autism spectrum disorder (ASD) and major depressive disorder (MDD) - however the driving mechanisms behind this association are poorly understood. Recent studies have suggested interaction between MIA and the serotonergic system, which acts as a key neurodevelopmental regulator also independently associated with ASD and MDD pathology. Given the dynamic role of serotonin (5-HT) during development, disturbances to this system by MIA may induce important and long-lasting effects that lead to disorder phenotypes. To explore this interaction, we model prenatal exposure to MIA in pregnant Sprague-Dawley rats using the viral mimic poly I:C at gestational day 12.5. Foetal brain and placental tissue were sampled at days 14.5 (yet to be analysed) and 18.5, to investigate mRNA expression of genes associated with 5-HT homeostasis and transport using selfie- ddPCR. Main targets of this study include Tph1, Tph2, Ddc, Slc6a4 (Sert), Slc22a3 (Oct3), and MaoA. Foetally-derived placental tissue at GD18.5 has not demonstrated significant treatment effects on mRNA expression thus far, however initial findings from GD18.5 frontal cortex suggest an increase in MaoA expression following MIA exposure. Additionally, mRNA expression of multiple 5-HT synthesis-related genes have been reliably demonstrated in the placenta, strengthening evidence for the placenta being a site of direct serotonin synthesis. Overall, this study improves our understanding of the serotonergic system during development and suggests MIA may impact serotonergic activity in the prenatal brain.

5.8

Neuropathology of the striatum in X-linked Dystonia Parkinsonism

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X-linked dystonia-parkinsonism (XDP) is a hereditary neurodegenerative disease recently discovered in Panay, Philippines. We have set up a brain bequest programme in the Philippines to undertake the largest neuropathological characterisation of XDP cases to shed light into the cellular and molecular basis of the unique disease profile. Previous studies denote marked atrophy and general neuronal loss within the striatum. However, detailed neuropathological studies characterising the human XDP striatum are still limited. To advance our understanding of XDP striatal pathology, immunohistochemistry coupled with automated analysis were conducted on post-mortem striatal tissue from 12 XDP and 5 age-matched neurologically normal cases to detail neurochemical changes in the striatal striosome and matrix sub-compartments, and investigate disease impact on specific neuronal populations. Neuroanatomical delineation of the XDP striatal compartments, through enkephalin, DARPP-32, and GABAA receptor β2/3 subunit immunohistochemistry, revealed patches of enhanced immunoreactivity, likely to be preserved striosomes. Furthermore, calbindin and substance P expression, typically localised to the matrix, appeared to be upregulated within striosomal patches in XDP. Whether this inversion in immunoreactivity reflects an upregulation of striosomal calbindin expression, or a selective loss of calbindin within the matrix is still unclear. At the cellular level, the XDP striatum presented with >50% loss of both calbindin+ spiny projection neurons and ChAT+ interneurons. Furthermore, XDP ChAT+ interneurons revealed disrupted morphology, evidenced by reduced somal size and processes. Together, the data demonstrates significant striatal involvement in XDP pathogenesis, including the pathological restructuring of striosomal and matrix compartments and detrimental loss of specific neuronal populations

5.9

Characterising Tau pathology in the Huntington's disease human brain

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Huntington's disease (HD) is a genetic neurodegenerative disorder characterised by variable motor impairment (chorea), psychiatric and cognitive symptoms. HD stems from a mutation in the huntingtin (HTT) gene, resulting in pathogenic production of mutant HTT protein (mHTT). Increasing evidence suggests other non-mHTT pathogenic proteins, including tau, may contribute to HD pathogenesis. In HD, abnormal accumulations of 4R- or 3R-tau isoforms, and the presence of aberrant hyperphosphorylated tau species have been reported. Additionally, the expression of an H2 tau gene haplotype detected in the blood of HD patients has been associated with greater cognitive decline. However, a comprehensive profile of tau isoform expression in the HD temporal cortex, an area associated with cognition, has not been conducted. This study aimed to immunohistochemically characterise tau pathology in human temporal cortex tissue microarrays constructed from ≤ 28 HD and ≤ 27 matching control cases. Quantitative analysis revealed 4R- and 3R-tau expression in a subset of HD and control cases. Greater 4R tau expression levels significantly correlated with earlier HD symptom onset and greater HTT aggregate deposition. The detection of hyperphosphorylated tau at serine 202 and threonine 205 (AT8 tau), and threonine 231 (pT231 tau) was present in all HD and control cases, however, HD cases tended to express more AT8 with advancing age. Future studies will investigate the cellular and spatial localisation of these tau forms in other cortical regions implicated in HD symptomatology, while extending to other pathogenic proteins to elucidate the role of pathogenic protein deposition in the HD human brain.

5.10

Grey matter and cognitive impairment in Parkinson's disease

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The neural changes underlying cognitive impairment in Parkinson's disease (PD) are yet to be elucidated. T1-weighted MRI enables in vivo quantification of neurodegeneration, offering potential insights into the pattern of cognitive decline in PD. We used voxel-based morphometry (VBM) and source-based morphometry (SBM) to examine structural brain differences in healthy controls (HC, n=43) and patients at varying stages of cognitive decline, including normal cognition (PD-N, n=66), mild cognitive impairment (PD-MCI, n=43), and dementia (PDD, n=14). VBM allows the determination of brain volume changes without a priori region of interest selection and SBM is a multivariate approach that takes into account cross-voxel information, yielding structural brain networks. VBM revealed significant reductions in grey matter volume (GMV) in PDD compared to PD-MCI, PD-N, and HC (corrected $p<.05$). In PDD relative to PD-MCI, decreased GMV was observed in the frontal and temporal cortices, left amygdala, cingulate gyrus, and parahippocampal gyrus. GMV reductions were identified in PDD versus both PD-N and HC in widespread areas of the cortex, bilateral hippocampus, thalamus, and amygdala. Significant reductions in PD-MCI compared to HC were identified primarily in frontal and occipital cortices. Using SBM, one pattern of GMV alteration was identified, including reduced GMV in the cerebellum and medial temporal lobe, which showed an association with global cognitive status. Our results suggest the involvement of limbic and cortical areas in PD-associated cognitive impairment.

5.11

From expression to activation: PDGF ligands and receptors in the adult human brain

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Platelet-derived growth factor (PDGF) signalling is essential in the development and homeostatic function of the neurovasculature, especially endothelial-derived PDGF-BB which is indispensable for the recruitment of pericytes to the neurovascular unit. However, the expression of the PDGF ligands and their signalling properties are scarcely characterised in the context of adult vascular function. We therefore sought to assess PDGF ligand expression in the adult human brain and to characterise PDGF signalling pathways in pericytes. Surgically resected epilepsy tissue were formalin fixed and used for combined RNAscope® and immunofluorescent labelling for PDGF probes and cell type markers. Patient-derived primary human pericyte cell lines were cultured to study PDGF signalling using in vitro assays. RNA transcripts of all four PDGF ligands could be found in the middle temporal gyrus. PDGF-BB and -DD displayed more vessel-specific expression, typically co-labelling with UEA-1 positive endothelial cells. PDGF-AA and -CC were found both in the vasculature and the parenchyma, with expression by both vascular and glial cells. Treatment of pericytes with exogenous PDGF ligands resulted in differential activation of MAPK and PI3K/Akt pathways. PDGF-DD was equipotent with PDGF-BB at driving pericyte proliferation via the activation of the MAPK pathway, while PDGF-AA and -CC only drove transient MAPK and PI3K/Akt activation and increased cell proliferation minimally. All four PDGF ligands are expressed in the brain, but only PDGF-BB and -DD have proliferative properties in pericytes, this can be explored further as a potential therapeutic target for restoring pericyte function at the Blood Brain Barrier.

5.12

Developing novel therapeutics for Glioblastoma

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Glioblastoma is the most common and malignant primary brain tumour in adults. The prognosis is poor, with various barriers impeding the development of effective therapies to improve patient survival. A class of near-infrared heptamethine cyanine dyes (HMCD) can cross the blood-brain barrier and selectively target tumour cells, showing promising potential as a brain-drug delivery molecule to increase therapeutic bioavailability in the brain. This allows the potential repurposing of anticancer agents that previously lacked efficacy in treating glioblastoma. Several HMCD compounds attached to different tyrosine kinase inhibitors (HMCD-TKI conjugates) were synthesised and screened on patient-derived primary glioblastoma stem cells and commercially available glioblastoma cell lines. Concentration-response curves for cell count, proliferation, and cell death were generated via in vitro assays. Additionally, the possibility of a near-infrared photo-activation-induced cytotoxic activity was tested. In most cases, conjugating the TKIs to an HMCD enhanced their cytotoxic activity, with some showing up to a 200-fold increase in potency (nanomolar EC50 values) compared to their parent HMCDs or TKIs. We also have data showing that 6 hr of near-infrared light activation of a lead HMCD-TKI compound could double the cytotoxic activity compared to the control (no-light condition). HMCDs are a promising molecule for improving TKI cytotoxicity in GBM cells and show photo-activation properties that could further enhance their potencies and effectiveness. Therefore, investigating the potential of HMCD conjugation with light activation could provide novel approaches to developing GBM treatments.

5.13

A low-cost method for high-throughput DiI labelling of neurons

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DiI is a fluorescent carbocyanine dye commonly used to label neurons for visualising dendritic spine morphology in brain tissue. While DiI is exceptionally versatile and can be applied using numerous delivery techniques in many different forms, so far, only the DiOlistic labelling technique enables high-throughput neuronal labelling, but it is often inaccessible to many researchers as it requires an expensive gene gun setup. Therefore, we present an alternative low-cost DiI labelling method that uses only a paintbrush, the lid of a 12-well plate, ethanol, and DiI crystals to provide high-throughput neuronal labelling. Our method provides the much-desired dense yet distributed pattern of neuronal labelling that is characteristic of DiOlistics but without the high costs that accompany it. In addition, we demonstrate immersion fixation of tissue sections produced by a custom 3-D printed brain slicer is a simple alternative to traditional tissue preparation by perfusion fixation and vibratome sectioning. Despite this creating thicker tissue sections, we also provide an inexpensive modified tissue mounting method to achieve a similar depth of coverage to existing methods. Lastly, we showcase the high-quality confocal imaging data of dendritic spines and 3-D morphological reconstructions obtained from our proposed method. Taken together, our proposed method allows high-throughput DiI labelling of neurons to be easily implemented across laboratories at a low cost with minimal preparation and equipment.

5.14

Behavioural effects of high doses of psilocybin in female rats

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Depression and anxiety disorders are pervasive mental health conditions that exert a profound impact on populations worldwide. These disorders not only impose considerable disability on affected individuals but also bear substantial economic implications. Current estimates by the World Health Organization suggest that 3.8% of the world's population experiences depression, and anxiety disorders affect approximately 0.4% to 3.6% of individuals. Psychedelic compounds, including Psilocybin, a fungal secondary metabolite found in psilocybin mushrooms, have exhibited promising results in clinical trials, demonstrating long-lasting positive effects. However, the neurobiological mechanisms underlying these effects, particularly in female subjects, remain poorly understood due to a lack of preclinical research. This study aims to investigate the effects of psilocybin on depression and anxiety-like symptoms. To induce symptomatology, female Sprague-Dawley rats were submitted to the Early Maternal Separation paradigm. They were then tested in the Affective Disorders Test before and after a single injection of high doses of psilocybin (8 or 16 mg/kg). Data analysis of the 15 measures of interest generally did not demonstrate a statistically significant effect of the doses administered in the behaviour of the subjects. Nevertheless, this research contributes to the growing body of literature on the therapeutic potential of psilocybin for depression and anxiety disorders and provides valuable insights for future clinical studies in both animal and human models.

5.15

Microglial and astrocytic responses in the human midcingulate cortex in Huntington's disease

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Huntington's disease (HD) is a neurodegenerative disorder that can cause motor, mood, and cognitive symptoms. Neuronal death in the cingulate cortex correlates with mood symptomatology. Neuronal loss is also linked to accumulation of mutant huntingtin protein (mHTT), a known trigger of neuroinflammation. Neuroinflammation involves protein and morphology changes in microglia and astrocytes. However, the contribution of these glial changes to HD pathology and presentation is not well understood and is necessary to discern whether these changes might be of therapeutic potential. Using immunohistochemistry, post-mortem midcingulate cortex (MCC) tissue from HD and control cases were stained with fluorescent markers for mHTT (1C2), microglia (Iba-1, HLA-DP/DQ/DR), and astrocyte proteins: Connexin 43 (Cx43) and excitatory amino acid transporter 2 (EAAT2). Glial marker and mHTT density, alongside microglia morphology were quantified. The results show microglia do not proliferate in HD, but transition from ramified states into activated morphologies in HD compared to controls ($p=0.001$). Activated microglia display close contacts with mHTT aggregates and the proportion of activated microglia positively correlate with mHTT burden ($p=0.001$). Astrocytes labelled with EAAT2 show decreased density ($p=0.0012$), size ($p=0.0054$), and percent area coverage ($p=0.0015$) in HD cases, particularly those associated with mood symptoms. This data demonstrates the presence of glial changes and their association with both mHTT burden in the MCC and the presentation of symptomatology in HD. These findings are significant as they highlight the importance of glia in the presentation of HD, which can inform research into therapeutics addressing symptom management.

5.16

The caudate nucleus is more susceptible to gliosis in X-linked Dystonia Parkinsonism

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X-linked Dystonia Parkinsonism (XDP) is a hereditary neurodegenerative disorder originally discovered in Panay, Philippines. XDP presents as an amalgamation of dystonic and Parkinsonian symptoms. XDP neuropathology is characterised by neuronal loss in the striatum, the primary region of interest. However, the contribution of non-neuronal cells to disease pathogenesis, including glia, is not well understood. A unique international collaboration between NZ-USA-Philippines allowed this study to investigate and characterise glial protein changes in clinically and neuropathologically documented XDP cases. The utilisation of antibodies to GFAP, HLA-DR, and IBA-1 to immunolabel glial proteins was implemented with ensuing automated analysis in 12 XDP post-mortem human brains compared with 5 neurologically normal control cases to profile gliosis-associated-pathology within the caudate nucleus (CN), and putamen of the striatum. Quantitative analysis of the XDP striatum demonstrated that variable glial protein changes are occurring in the XDP striatum. Investigations into the sub-compartments revealed the CN is more susceptible to gliosis, presenting with an increase in GFAP+ and HLA-DR+ immunoreactivity. On the other hand, the putamen appeared relatively spared from gliosis. Interestingly, IBA-1+ expression was preserved in the XDP striatum. However, within the CN, IBA-1+ immunoreactivity was more heavily concentrated in cells along the ventricular edge. These findings further extend our current understanding of XDP pathogenesis and the contribution of striatal degeneration to this relatively new disease. Furthermore, this study reinforces the increased vulnerability of the CN in XDP relative to control, ultimately advancing our understanding of the pathological basis of the unique clinical symptomatology of this disease.

5.17

Novel kappa opioid receptor agonists attenuate chemotherapy-induced neuropathic pain

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Chronic pain is a growing global issue that lacks effective treatment options. In New Zealand, one in five people suffers from chronic pain, with a higher prevalence seen in Māori, elderly and lower socioeconomic groups. Mu opioid receptor (MOR) agonists including oxycodone, morphine and tramadol are commonly prescribed to treat chronic pain, however, long-term use of MOR agonists can lead to tolerance, and drug dependency as well as effects on respiratory depression which can be lethal. Kappa opioid receptor (KOR) agonists are being considered as an alternative therapeutic drug target due to their anti-nociceptive properties without inducing reward or respiratory depression. However, the development of KOR agonists to date has been limited due to side effects such as sedation, aversion, and dysphoria. Evidence suggests that anti-nociceptive and anti-pruritic effects are mediated through the G-protein signalling pathways, whereas the dysphoric effects are mediated through β-arrestin-2 signalling pathways. This study shows that the novel KOR agonists LDK-267 and compound X possess antinociceptive effects in mice. In the paclitaxel-induced neuropathic pain model in mice, LDK-267 and compound X reduced both mechanical and thermal allodynia, and unlike morphine, did not produce tolerance when administered daily for 23 days. Moreover, LDK-276 did not induce sedative and anxiogenic effects in open-field and elevated plus maze tests. This data supports the therapeutic development of KOR agonists as non-addictive pain medications with reduced tolerance.

5.18

Investigation of pathology presentation within the human olfactory system

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Olfactory dysfunction is one of the most common symptoms of Alzheimer's (AD) and Parkinson's (PD) disease, occurring 5 to 10 years before other symptoms. Another early indication of AD and PD is an accumulation of the pathological proteins phosphorylated tau (AD) and phosphorylated a-synuclein (PD) in the olfactory bulb. Glomeruli in the olfactory bulb receive input from axons of olfactory sensory neurons located in the olfactory epithelium (located in the superior aspect of the nasal epithelium) where they detect odorants in the environment. This olfactory projection is a direct connection between the external environment and the brain. The olfactory vector hypothesis states that a toxin or pathogen can trigger pathogenesis in the brain by first entering the olfactory mucosa and the olfactory bulb, leading to neurodegenerative disease onset. My project investigates pathological aggregates' accumulation and distribution patterns within the human olfactory epithelium and olfactory bulb. Sections containing human olfactory mucosa and bulbs from 13 deceased individuals were stained with Hoechst and three morphological markers, phosphorylated tau, and phosphorylated a-synuclein, and were imaged using the VSlide Scanner. The analysis method visualizes the distribution of pathological aggregates and morphological markers. I found that pathological aggregates were present in most cases but were higher in non-neurologically normal cases. In some cases, pathological aggregates in the olfactory epithelium correlated with accumulations in the olfactory bulb. Understanding and predicting patterns of pathological aggregations within the human olfactory epithelium might be useful to aid the early diagnosis of AD and PD.

5.19

Meningeal explants as a responsive model for drug discovery: investigating inflammatory stimuli and potential therapeutic applications

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Meningeal tissues play a crucial role in the pathophysiology of neuroinflammatory conditions, making them an attractive target for drug discovery. This study aimed to investigate the responsiveness of meningeal explants to inflammatory stimuli and assess their potential as a model system for evaluating novel therapeutic agents. Meningeal explants were obtained from human post-mortem tissues and cultured ex vivo. The explants were exposed to various inflammatory stimuli such as interleukin-1 beta (IL-1β), tumour necrosis factor alpha (TNFα), interferon gamma (IFNγ) and lipopolysaccharides (LPS). Cytokine secretions were measured using cytometric bead arrays and proteome profiler cytokine array kits. Our results demonstrated that meningeal explants exhibited a robust and specific response to inflammatory stimuli. The explants displayed increased secretion of pro-inflammatory cytokines in response to inflammatory stimuli such as IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1) and interferon gamma-induced protein 10 (IP-10). The ability of these explants to exhibit cellular activation and cytokine secretion makes them a promising tool for drug discovery and therapeutic development. It also offers a platform for screening and evaluating potential therapeutic agents targeting meningeal inflammation. In conclusion, this study establishes meningeal explants as a responsive model for studying the inflammatory processes associated with neuroinflammatory conditions and serves as a valuable model system for drug discovery. Such agents could include anti-inflammatory drugs or compounds that modulate key inflammatory signalling pathways. Further research utilizing this model system can provide valuable insights into the mechanisms underlying meningeal inflammation and aid in the identification of novel therapeutic interventions.

5.20

Increased expression of Kir4.1, AQP-4 and GLT-1 in the Alzheimer's disease human brain

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Alzheimer's disease (AD) is a neurodegenerative condition with no cure. Astrocytes are thought to contribute to AD and in disease these cells undergo changes related to inflammation and loss of homeostasis. Previous in vitro and human transcriptomic studies in tissue have revealed astrocytic changes that are associated with AD progression. This study aimed to investigate the significance of key astroglial changes at the protein level in the middle temporal gyrus of the AD human brain. Immunohistochemistry (IHC) was performed on human brain tissue microarrays (TMAs) that contain up to 60 tissue core samples from neurologically normal and AD donors. IHC labelling with astrocytic antibodies was used to investigate protein expression of interest - glial fibrillary acidic protein (GFAP), inwardly rectifying potassium channel 4.1 (Kir4.1), aquaporin-4 (AQP-4) and glutamate transporter-1 (GLT-1). Images were acquired using the V-slide automated scanning microscope, and the software MetaMorph was used to assess cell count and protein expression. Increased expression of GFAP, Kir4.1, AQP-4 and GLT-1 was observed in the AD human brain compared to controls. Kir4.1 expression showed a redistribution from astrocyte cell bodies towards the processes in AD compared to control brains. These astrocytic changes were more closely associated with tau pathology than amyloid-beta pathology and were not associated with age or post-mortem delay. Our results, alongside previous studies, suggest that increased expression of astrocyte channels and transporters may indicate a neuroprotective role for astrocytes in AD and presents potential therapeutic avenues targeting this important cell type.

5.21

High-definition transcranial grey noise stimulation (HD-tGNS) as an intervention for generalized anxiety disorder: A pilot randomised sham-controlled trial

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Generalised Anxiety disorder (GAD), characterized by excessive fear/worry, poses a significant burden on healthcare systems. Neuroimaging studies investigating anxiety have implicated pathophysiological activity in amygdala, dorsal and subgenual anterior cingulate cortex, insula, orbitofrontal cortex, and parahippocampus brain regions, resulting in emotional dysregulation and somatic health issues. Targeting these key regions with neuromodulation might produce clinical benefits. The aim of this double-blinded randomized sham-controlled pilot trial was to evaluate the safety and acceptability of a novel brain stimulation technique [high-definition transcranial gray noise stimulation (HD-tGNS)] targeting key hubs of anxiety network and to explore its effects on clinical outcomes. Participants diagnosed with GAD were randomised to HD-tGNS or Sham stimulation group (n=7 per group). Treatment was applied three times a week for a total of three weeks. Clinical measures included GAD-7, Hospital Anxiety and Depression Scale (HADS), and State trait anxiety inventory (STAI) collected at baseline, and immediately post-intervention. No serious adverse events were reported following HD-tGNS, and participants perceived it as a highly acceptable intervention. Mann Whitney tests demonstrated no significant between-group differences in clinical outcomes. However, preliminary within-group t-test analyses demonstrate significant reductions in clinical outcomes in the HD-tGNS group [Mean Difference(MD): GAD-7 (-4.6±4.6, p=0.038), STAI-Y2 (-6.3±4.1, p=0.006), HADS (-3.7±3.9, p=0.043)] when compared to sham stimulation group [MD: GAD-7 (-2.9±5.3, p=0.232), STAI-Y2 (-5.6±10.9, p=0.371), and HADS (-3.7±5.4, p=0.117)]. HD-tGNS is a safe and acceptable treatment approach for GAD and demonstrates a positive trend of effect on clinical outcomes. A future fully powered trial is warranted.

5.22

A novel role for the central amygdala in the processing and transfer of recently acquired information

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Research into decision making has traditionally focused on regions in the frontal cortex and associated structures. There have been significant advances in determining the mechanisms behind action selection, but these studies typically obscure rapid transitions in behaviour that are indicative of sudden acquisition of understanding about a task by examining aggregate behaviour. In these studies, we combine a novel statistical approach to quantify this abrupt change in behaviour during a classical conditioning task with immunohistochemistry and electrophysiology in the central amygdala. We find changes in ERK expression and local field potentials that correlate with behaviour that signal a clear role for the central amygdala in the acquisition of understanding, unveiling a novel role for amygdala, and insight into the heretofore obscure mechanism through which task understanding is encoded.

5.23

Music-evoked versus visual-evoked autobiographical memories: An fMRI study in older adults with neurodegeneration and cognitive impairment

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Previous findings have demonstrated that preserved neural networks and structures in Alzheimer's disease pathology overlap with musical memory, emotions, and autobiographical memory associations. Music has the capacity to elicit positive memories, increased recollection of autobiographical memories, retrieval speed, and vividness. Music also holds the powerful potential to enhance overall cognitive performance. Prior research from our group demonstrated reduced activity in key nodes of musical networks, significant longitudinal effects on functional and structural brain measures, and improvement in memory sub-score of the Montreal Cognitive Assessment. The aim of the current study is to examine the potential benefits of daily exposure to long-known, autobiographical music compared to visual materials in older adults with cognitive impairment. Furthermore, the study intends to develop a deeper understanding of how functional network activity, and changes associated with the intervention, may differ in the brain during autobiographically-salient auditory (music) versus visual (i.e., photographs, videos) tasks. Participants aged 65 years and older will be recruited from St Michael's Hospital Memory Clinic. Individuals will be randomised into music (n = 10) versus visual (n = 10) conditions. Data acquisition includes MRI protocols at baseline and pre- and post-intervention period (4 weeks), and cognitive testing. Results from the current study are expected to provide empirical support for music as a short and meaningful treatment. Changes associated with daily exposure to music could potentially alter functional neural networks – contributing objective evidence for implementation of music-related therapies and interventions in neurodegenerative diseases.

5.24

Investigating the mechanism of action of promotion of remyelination by kappa opioid receptor agonists

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Multiple sclerosis (MS) is an autoimmune demyelinating disease. Progressive degeneration of the myelin sheath impairs saltatory conduction, causing symptoms such as muscle weakness, vision loss, and eventual paralysis, depending on lesion location. Current medications target the immune system but cannot induce repair or recovery. In MS, mature myelinating oligodendrocytes (OL) are lost and immature oligodendrocyte precursor cells (OPCs) fail to replace these. Identification of drug targets that induce differentiation of endogenous OPCs into myelinating OL is a promising therapeutic approach to enable repair and recovery in demyelinating diseases including MS. We have previously shown that kappa opioid receptor (KOR) agonists promote OPC differentiation, demonstrating therapeutic potential. However, many traditional KOR agonists have side effects attributed to activation of β-arrestin signalling pathways. This study aimed to determine whether KOR-mediated remyelination is controlled by the GPCR pathway or is β-arrestin dependent, and to elucidate the cell signalling pathways required for KOR-induced OPC differentiation. We utilised mixed glial cell cultures from wild type (WT) and β-arrestin KO C57BL6 mice and in vitro screening assays to evaluate promotion of OPC differentiation. The effect of KOR agonists in each culture was quantified by counting the total number of oligodendrocyte lineage cells (SOX10+) and the number of mature OL (MBP+) using immunohistochemistry and high-throughput confocal microscopy. We identified KOR-dependent signalling pathways that modulate oligodendrocyte maturation and show GPCR signalling via ERK1/2 pathways is required for OPC differentiation. This protocol has potential future use for screening KOR agonists to identify the best drug candidates for remyelination-based therapies.

5.25

Parcels or voxels? Better methods for predicting cognition from task-based fMRI

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One of the main goals of cognitive neuroscience is to predict individual differences in cognitive abilities from brain data. Recently our lab group has demonstrated relatively good performance of task-based functional MRI (fMRI) during working memory in predicting persons' cognitive abilities. There, during pre-processing, the fMRI data in voxels were grouped into parcellated regions based on a brain atlas before being used in machine-learning modelling. This parcellation process is standard for fMRI predictive modelling, but it requires researchers to choose an atlas and a method for parcellation. However, choosing an atlas and a parcellation method is arbitrary and does not have clear criteria to base on. Accordingly, this study aims to avoid parcellation by reducing the dimension of task-based fMRI voxels directly via Partial Least Squares (PLS). To test our approach, we used large-scale task-based fMRI data from over 800 individuals during a working memory task from the Human Connectome Project - Young Adult (HPC-YA). We first applied a general linear model to compute contrasts of task-based fMRI during working memory, resulting in contrast images that reflect higher (compared to lower) working-memory load. We then applied PLS to predict participants' cognitive abilities, collected outside of the scanner, from these task-based fMRI voxels. We found out-of-sample predictive performance from our approach to be on par with those from predictive models with parcellated data: R2=.12, Pearson's r=.4 and MAE=10.74. Accordingly, we provide an approach to avoid parcellation for predictive models of task-based fMRI.

5.26

The Hugh Green Biobank: a facility for the isolation, study, and testing of primary human brain cells for advancing brain research and therapeutic development

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The complexity and heterogeneity of the human brain has made neurological disease research incredibly challenging. To address this, we established the Hugh Green Biobank, focusing on the preservation and provision of primary human brain cultures. In collaboration with the Neurological Foundation Human Brain Bank, the Department of Neurosurgery at Auckland City Hospital and the Neurosurgery Research Unit, we have optimized protocols for tissue collection, processing, and cell culture maintenance. The biobank currently houses primary patient-derived human brain cell cultures obtained from 333 consenting donors with a range of brain disorders and cancers, including Alzheimer's, Parkinson's, Huntington's, Motor neuron disease, Epilepsy, and a range of CNS tumours, mainly Glioblastoma and Meningioma. These cultures are currently being used in studies such as understanding the contributions of neuroinflammation and aberrant signalling pathways to neurological disease, case-to-case variations of cellular phenotype and composition, and drug discovery. The use of primary human samples paves the way for personalized medicine through elucidating patient-specific responses to various drug compounds. Overall, the Hugh Green Biobank highlights the importance of biobanking within brain research and aims to continue broadening the horizons of discovery and therapeutic development.

5.27

In vitro models of brain macrophages: A comparative study

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The central nervous system (CNS) comprises various populations of macrophages, including parenchymal microglia and border-associated macrophages. These brain macrophages (BM's) play crucial roles in homeostasis and disease. Different in vitro BM models have been established, including primary human and rodent cells, induced pluripotent stem cells, and immortalised cell lines. However, no study has compared these models to assess their suitability in recapitulating human BM's. Therefore, our study aimed to characterise commonly utilised in vitro BM models. We compared three established BM models: primary human BM's, primary mouse BM's, and the HMC3 cell line. Human brain pericytes served as a negative control. Myeloid and mural cell-marker expression were assessed via immunocytochemistry. To compare functional characteristics, secretome analysis and phagocytosis assays were conducted. Mouse and human BM's stained positive for myeloid-cell markers (CD45, PU.1, Iba1), while HMC3 cells stained positive only for mural-cell markers (PDGFRβ, NG2). Distinct secretomes were observed in all four cell types, both basally and in response to inflammatory treatment. Notably, nitric oxide was secreted by mouse but not human BM's. Although phagocytic capacity was exhibited by all cell types, human and mouse BM's displayed significantly higher levels of phagocytosis. Comparative analysis revealed significant differences between mouse BM's, HMC3 cells, and human BM's. Such differences should be considered when using these models to study human neurological diseases, including neurodegenerative disorders and CNS cancers. Experimental findings obtained from mouse models or cell lines should be validated using primary human BM's to ensure translatability to human pathophysiology.

5.28

ADAM10/17 mediation of Group I mGluR-dependent synaptic plasticity

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Group I metabotropic glutamate receptor (mGluR) stimulation can result in enhanced long-term potentiation (LTP) or depression (LTD) of synaptic transmission. Critically, these effects require protein synthesis and cascades of enzyme activation, such as protein kinases. Soluble amyloid precursor protein-alpha (sAPPa), which also enhances LTP in a protein-synthesis manner, is a candidate intermediary signal for mGluR-mediated plasticity. mGluR stimulation generates sAPPa production by activating a-secretases, such as a disintegrin and metalloproteinases 10 and 17 (ADAM10/17). We hypothesized that the a-secretases ADAM10/17 are required for the protein synthesis-dependent components of mGluR-dependent synaptic plasticity. Field EPSPs were evoked in stratum radiatum of CA1 of hippocampal slices prepared from 6-8 week old Sprague-Dawley rats. Slices were incubated with either the broad-spectrum ADAM10/17 inhibitor, TNF-alpha protease inhibitor I (TAPI-1; 20 µM, 40 min), or the specific ADAM10 inhibitor, GI254023X (20 µM, 40 min), before and during bath application of the Group I mGluR agonist, DHPG (20 µM or 100 µM, 10 min), to test ADAM10/17 function in mGluR-dependent LTD. We subsequently applied high-frequency electrical stimulation to test ADAM10/17 contribution to mGluR-facilitated LTP. TAPI-1 reduced the magnitude of long-term DHPG-induced synaptic depression. GI254023X had no effect on DHPG-induced depression. DHPG enhanced synaptic paired-pulse facilitation but this was unaffected by co-treatment with TAPI-1 or GI254023X. TAPI-1 abolished DHPG-facilitated LTP. These results suggest that ADAM17 is necessary for the expression of postsynaptically mediated and protein synthesis-dependent, mGluR-regulated long-term synaptic plasticity. Whether the effects are mediated by sAPPa or cleavage products of other ADAM17 substrates remains to be determined.

5.29

Developing a relevant model of cannabinoid receptor signalling using human iPSC-derived neurons

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G protein-coupled receptor (GPCR) signalling research has conventionally been conducted using in vitro non-neuronal transformed cell lines. However, authentic insights into cannabinoid receptor 1 (CB1) signalling necessitates a neuronal model. Recently, human induced pluripotent stem cells (iPSCs) have shown promise as a more physiologically relevant alternative to rodent primary cultures and immortalised human cell lines. Following established iPSC differentiation procedures, we aim to evaluate the suitability of cortical glutamatergic i3 neurons (i3N) as a model for in-depth neuronal CB1 investigation. We present data delineating the endocannabinoid system within i3N. The expression of critical genes and proteins will be confirmed through RT-qPCR and immunocytochemistry (ICC). Preliminary results from our initial RT-qPCR replicate indicate similar expression levels of CB1 and the reference gene CYC1, absence of CB2 expression, and promising expression of endocannabinoid degradation enzymes MAGL and FAAH. ICC corroborates the presence of pluripotent markers OCT4 and SSEA4 in iPSCs, and successful differentiation into glutamatergic cortical neurons expressing MAP2 and VGLUT1. If substantiated by further data, these findings will underpin the i3N model's suitability for optimization in real-time BRET signalling assays. These assays will measure the physiological responses to a range of endogenous, synthetic, and phytocannabinoids. Successful deployment of the i3N model could facilitate a more nuanced understanding of CB1R signalling and trafficking in response to cannabinoid ligands, enriching our knowledge of the physiological effects of drugs and neurotransmitters within the brain's endocannabinoid system

5.30

Can you predict which neuropathy patients have CANVAS?

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CANAS syndrome is a neurodegenerative condition defined by the co-occurrence of ataxia, neuropathy and vestibular failure. It is caused by an intronic pentanucleotide expansion in the RFC1 gene. In New Zealand most people with CANVAS are identified when they presented with ataxia and the additional features have been looked for. However, internationally it is claimed that up to 30% of patients with sensory neuropathy have the RFC1 expansion and that often this finding occurs in isolation. Sensory neuropathy is a common finding on nerve conduction tests so we aimed to see whether, in a group of patients with sensory neuropathy, there were other clinical features that predicted a positive RFC1 gene test. Patients were identified from Auckland City Hospital EMG records between Jan 2015 - Dec 2021 and included if they had a sensory predominant neuropathy without other obvious cause. Four independent batteries of tests were performed on consenting patients: neurological exam including bedside head impulse test and autonomic testing, formal vestibular examination, nerve ultrasound, and a repeat nerve conduction designed to look for evidence of a dorsal root ganglionopathy. Forty-nine patients have been enrolled. Of the first 25 patients 3 had positive RFC1 tests - the first patients in New Zealand with CANVAS diagnosed on the basis of a neuropathy presentation. The full cohort will be presented in this poster. This study will indicate whether neuropathy occurs on its own, or whether other clinical features are present and predict RFC1 gene positivity.

5.31

Exploring the predictive association between mental health and cognition in older adults from the UK Biobank cohort

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Research shows that, after the age of 70, the co-occurrence of cognitive impairment and depression doubles every five years, and, after the age of 85, one in four people will have both conditions. This may point to the presence of a link between mental health and cognition across the lifespan. However, most of the data on the association between mental disorders and cognitive deficits are obtained from small sample sizes and from a limited number of measures for mental health and cognition. Thus these studies may not represent the general population and provide a poor representation of complex cognitive phenomena. To overcome these limitations, we developed a machine learning model that predicts cognitive abilities from 46 mental health measures in 31,148 UK Biobank participants (40-69 years old). First, we obtained a general factor of cognitive abilities, 'g', using 5 cognitive measures: fluid intelligence, reaction time, numeric memory, visual memory, and prospective memory. Next, we examined the extent to which these cognitive abilities were predicted by the 46 mental health measures, using Partial Least Squares (PLS). Out-of-sample prediction of our PLS model was r=0.21, explaining 4.5% of the variation in the target variable, 'g'. Replacing 'g' with four components derived from the exploratory factor analysis resulted in a similar performance at r ranging from 0.14 to 0.2. Thus, we are able to predict, though with somewhat limited performance, older adults' cognitive abilities based on their mental health. Accordingly, we found a, somewhat weak, link between mental health and cognition among older adults.

5.32

Why are two X's better than one? Modifying X inactivation for the treatment of X-linked neurological disorders

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Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, incurable neurological disorder characterised by degeneration of motor neurons. Mutations in the UBQLN2 gene can cause X-linked ALS, however, heterozygous biological females carrying the mutation show attenuated disease manifestation compared to males due to X chromosome inactivation (XCI). Furthermore, skewed expression towards the wildtype allele, and away from the mutant allele correlates to reduced disease severity between females in other X-linked disorders and provides an as-yet untapped therapeutic strategy. We plan to harness XCI skew as a novel therapeutic approach through 3 aims. First, we developed an allele-selective qPCR assay to quantify the ratio of mutant and wildtype UBQLN2 expression before and after therapy. Second, we are developing an iPSC-derived disease model from heterozygous carriers of an ALS-causing UBQLN2 mutation. Finally, we will artificially silence mutant UBQLN2 expression and activate wildtype UBQLN2 expression in this model, using a methylation-based dCas-linked epigenetic modifier resembling XCI. Our allele-selective qPCR assay produced efficient and selective amplification of the UBQLN2 alleles from plasmid DNA, and a proof-of-concept standard curve was generated to find allelic ratio in relevant cell lines. Fibroblasts from heterozygous carriers were differentiated into clonal iPSC lines, and their allelic skew quantified by allele-selective qPCR, and Illumina and Sanger sequencing. Delivery of the dCas epigenetic modifier was also validated and UBQLN2-specific guide RNAs were tested. This project is investigating how epigenetic modifiers that artificially recapitulate XCI skew can provide therapeutic protection for males and females, not only for UBQLN2-linked ALS, but all X-linked diseases.

5.33

Pūnaha Io – the New Zealand NeuroGenetic Registry & Biobank Update

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Pūnaha Io - the New Zealand Neuro-Genetic Registry & Biobank is intended to be an accessible repository of clinical data linked to biological samples donated from patients with rare neurogenetic disorders. It provides infrastructure aimed at translational research and is designed to facilitate and expedite the conduct of all stages of research in rare neuro-genetic disorders, from basic science and pre-clinical work through to clinical trial recruitment and post-market monitoring. Pūnaha Io has partnered with Te Ira Kāwai and the Neurological Foundation Human Brain Bank. Other key stakeholders include the study population, which comprises participants with neuromuscular diseases in childhood and adult life such as muscular dystrophies (n = 329), spinal muscular atrophies (n = 62), hereditary neuropathies (n = 175), congenital myopathies, myasthenias, myotonic syndromes (n = 228), metabolic myopathies, inflammatory myopathies; and also predominantly central nervous genetic diseases such as Huntington's disease (n = 220), inherited ataxias (n = 124), inherited movement disorders, and hereditary spastic paraparesis (n = 39). Sample collection, storage as well as governance of the collection is according to Te Ira Kāwai's established procedures. Sample collection commenced in 2022. To date samples from 48 participants with rare neurogenetic disease including Huntington's disease, myotonic dystrophy, friedreich's ataxia, and spinocerebellar ataxia have been stored. Disease-specific datasets for disorders that are primarily brain disorders include items that link with The Neurological Foundation Human Brain Bank, potentially enabling longitudinal analysis of clinical and bio-data spanning the progression of disease.

5.34

Modulation of axonal action potential conduction with bipolar disorder therapeutics

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Bipolar disorder (BD) is a chronic and debilitating neuropsychiatric illness characterized by emotional lability, but to date, no causal mechanism has been identified. Neuron-glia interactions have been suggested as a possible pathological mechanism in BD, with abnormalities in brain myelination (white matter) being one of the most consistent neuroimaging findings in BD. A strong relationship between functional network connectivity and myeloarchitecture has been established, and disturbances in both are found in BD. Lithium is the first-line therapeutic for BD, with alternatives including anti-epileptic ion channel modulator drugs such as carbamazepine, valproate, and lamotrigine. Our electrophysiological research investigates how lithium and anti-epileptics used to treat BD, alter action potential (AP) conduction down the axon. This data is collected using a novel in vitro preparation of the lateral olfactory tract (containing both central myelinated and unmyelinated fibres) from Swiss Webster mice. Two recording sites separated by ~1.5mm allowed the change in AP waveform along a length of the axon to be quantified. The parameters measured are depolarization and repolarization slopes, event duration, amplitude, and conduction velocity. Treatment with pharmacological substances enhanced the normal AP broadening seen during repetitive stimulation. This suggests lithium, too, may influence ion channel currents to modulate neuronal membrane excitability, including adaptive changes in AP duration during repetitive activity. Increased AP duration results in increased Ca2+ influx in the presynaptic terminal and increased neurotransmitter release and may therefore affect functional connectivity and plasticity in brain networks.

5.35

Cross hemisphere dysfunction of the anterior thalamic nuclei does not impair spatial working memory in rats

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The anterior thalamic nuclei (ATN) send almost exclusively ipsilateral connections to prefrontal cortex and subicular cortex. Loss of these projections may explain severe spatial working memory deficits associated with ATN dysfunction. We examined a delayed (60-sec) spatial win-shift radial-arm maze task in male PVGc rats and compared the effects of neurotoxic bilateral ATN lesions with a bilateral dysfunction caused by unilateral optogenetic inhibition of ATN terminals in prefrontal cortex and dorsal subiculum added to an ATN lesion in the contralateral hemisphere. With no optogenetic stimulation, bilateral ATN lesions (N=7) impaired accuracy compared to unilateral ATN lesions and sham lesions (ATN + inhibitory opsin in the contralateral ATN, N=9; ATN + opsin control, N=6; Sham + inhibitory opsin, N=7; Group, $F_{3,25}=13.57$, $p<0.001$). However, orange-light inhibition of the two ATN-terminal regions in rats with a contralateral ATN lesion had no effect (No stimulation vs Orange stimulation $p>0.8$; Group x Light x Day interaction, $F_{6,50}=0.51$, $p=0.79$). Unexpectedly, orange-light stimulation, visible in the fibre probes on the head, further impaired performance in rats with bilateral ATN lesions only (no opsin present, only optic fibres; Group by Light interaction, $F_{6,50}=2.94$, $p=0.01$); errors were increased compared to no stimulation ($p=0.01$) or blue light ($p=0.01$). Localised optogenetic inhibition of ATN terminals in the prefrontal cortex and subiculum in one hemisphere, combined with a contralateral ATN lesion, is unable to mimic a bilateral ATN lesion effect on spatial working memory. Bilateral ATN lesions render rats more susceptible to bright visual distraction, which may exacerbate their memory deficits.

5.36

Investigating the neurosteroid withdrawal hypothesis of pericatamenial epilepsy using visual long term potentiation

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Fluctuations in sex steroids across the menstrual cycle are associated with cyclic functional brain changes in health and disease. The withdrawal of progesterone, and its neuroprotective metabolite allopregnanolone, around menstrual onset is thought to be implicated in seizure exacerbation in 40% of females with epilepsy, a disorder termed pericatamenial epilepsy (PCE). This study aims to investigate changes in progesterone-related inhibition versus oestradiol-related excitation via examining changes in visually induced long-term potentiation (LTP) across the menstrual cycle. Visually induced LTP was recorded using electroencephalography in 25 healthy females during the perimenstrual, mid-follicular, and mid-luteal phases. This cohort will later form the comparison group of the main analysis between females with epilepsy with and without catamenial exacerbation. Visual LTP was assessed as changes in visual evoked potential (VEP) amplitude after high-frequency stimulation (tetanus). LTP occurred in the P2 VEP component in the late post-tetanus condition ($p = 1.38x10^{-6}$ FWE-c). P2 modulation was greater during the mid-follicular phase, where sex steroid levels are the lowest, than the perimenstrual phase, which also has low sex steroid levels but is associated with neurosteroid withdrawal. Lower LTP modulation during the perimenstrual phase could be attributed to dominating effects of allopregnanolone-related GABAergic inhibition. Rodent literature suggests PCE might be driven by reduced GABAergic inhibition. Thus, we expect the opposite change in LTP in the PCE cohort, where LTP modulation will be greater during the perimenstrual phase than the mid-follicular and/or mid-luteal. This will be the first direct investigation of the neurosteroid withdrawal theory of PCE in humans.

5.37

Tracking down PINK1 Parkinsonism in Aotearoa

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We have found that PINK1:L347P, a pathogenic variant that is rare to non-existent in European, African, Chinese and Latino populations, is not so rare in populations of people from different parts of the Pacific. Homozygous PINK1:L347P causes early-onset Parkinson's disease and/or dopamine-responsive dystonia. We have undertaken a study to determine the extent to which PINK1 gene variants cause early-onset parkinsonism (<55 years) in NZ Māori and well as people from maritime South East Asia or Pacific countries living in Aotearoa. In Auckland, patients were identified via their consulting neurologist. In Waikato, a systematic audit of patient records was undertaken. Patients were consented before clinical genetic testing (8 exons of the PINK1 gene). In Auckland, neurologists identified 39 patients for genetic testing; of the 28 consented for testing, 17 have tested positive for homozygous PINK1 L347P and 1 compound heterozygous for PINK1 L347P:R492*. PINK1 positive patients average age-of-onset is 35 years (range 12-54). PINK1 negative patients average age-of-onset is 45 (range 26-60). In Waikato, 8 patients have been identified for genetic testing; 3 have been consented for testing. The single person that has been tested to date is homozygous for PINK1 L347P. In conclusion genetic testing is usually indicated if the likelihood of a gene positive test result is >10%. In our cohorts we have tested 29 people, yielding 19 PINK1 positive results (66%). All PINK1 positive patients had Western Polynesian ancestry. Early-onset parkinsonism is less prevalent in NZ Māori; of the 5 Māori patients identified with EOPD, 2 have been tested and both were PINK1 negative.

5.38

Effects of cannabidiol (CBD) in an animal model of Alzheimer's disease induced by streptozotocin

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Alzheimer's disease (AD) is a multifactorial, irreversible neurological disorder, showing amyloid-beta plaques (Aβ), hyperphosphorylated tau, neuroinflammation, described by glial reactivity, leading to neuronal death and cognitive decline. Previously studies have shown improvement in the reduction of astrogliosis and microgliosis in animal models through treatment with cannabis-derived compounds. Cannabidiol (CBD) have shown promising effects of in reducing amyloid plaque deposition and neuroinflammation. Hence, in this study we further investigated the effects of CBD against glial reactivity. Sporadic AD was induced by streptozotocin (STZ) injections (3 mg/kg, i.c.v.) into the lateral ventricle of 6-month-old male Wistar rats (n = 80) followed by cannabidiol treatment (10 mg/kg, i.p.) for 14 days, compared to their sham or no treatment controls. Behavioural testing, including olfactory discrimination (OD), open field (OF), novel object recognition (NOR), sucrose preference, water and sucrose consumption, and spontaneous alternation was carried out. The brains were collected for immunohistochemistry for Aβ, Iba-1+ microglia, GFAP+ astrocytes, and oxidative stress parameters. STZ treated animals showed weight loss during the treatment ($p = 0.048$). While STZ-CBD treated rats showed increased consumption of liquids ($p < 0.001$). STZ treated rats were not able to discriminate chambers in the OD and CBD was able to reverse olfactory deficits ($p = 0.006$). In the NOR test, the STZ treated group were not able to discriminate novel objects however CBD was able to reverse short-term memory deficits ($p = 0.002$). Based on our findings of the effects of CBD, it may be a candidate in improvement of memory and olfactory AD deficits.

5.39

Investigating the relationship between L-type calcium channels and neuronal excitability in the P301S (PS19) tauopathy model of Frontotemporal Dementia

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Frontotemporal dementia (FTD) is a progressive neurodegenerative disease with no cure. Many cases are characterised by hyperphosphorylated tau protein and, in turn, reduced binding of tau to microtubules. PS19 mice, expressing FTD-related P301S human mutant tau, have been used to investigate FTD and related tauopathies characterised by hyperphosphorylated tau aggregates and neuronal degeneration. Synaptic dysfunction and changes in neuronal excitability have also been implicated in early FTD pathology, and age-related dysregulation of calcium homeostasis has been implicated in the progression of FTD and other neurodegenerative diseases. We investigated the link between tau and L-type voltage-gated calcium channels (L-VGCCs) using the L-VGCC agonist BAYK8644 (20 µM) to assess changes in population-spike amplitude (PSA) recorded from the dentate gyrus of 2-3- and 6-9-month-old PS19 and wild-type (WT) male and female mice. Both PS19 and WT slices from 6-9-month-old animals demonstrated an increase in PSA following one-hour application of BAYK8644. However, the increase in PSA was significantly greater in WT compared to PS19 mice. Conversely, preliminary results from the 2-3-month-old mice suggested a genotype-specific increase in PSA only in PS19 tissue following BAYK8644 application. These data indicate that there are genotype, and potential age-related, differences in the L-VGCC up-regulation of excitability of dentate granule cells. Further preliminary treatment of 2-3-month-old PS19 and WT tissue with the microtubule stabiliser Taxol (100 nM) indicated that the genotypic increase in PSA cannot be entirely due to microtubule destabilisation, providing potential evidence for early direct effects of mutant tau on L-VGCCs that culminate in altered neuronal excitability.

5.40

Reflex tears to target alpha-synuclein in Parkinson's disease

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Neurotoxic alpha synuclein (α-syn) aggregation is the key molecular signature in Parkinson's disease (PD). α-syn oligomers in the eyes' reflex tears may yield a link between neuropathology and disease status. Real-time quaking-induced conversion accelerates aggregation of monomeric α-syn protein by seeding with α-syn oligomers. Reflex tears from people with PD may include sufficient oligomeric α-syn to seed laboratory-prepared concentrations of purified recombinant monomeric α-syn, thereby shortening aggregation half-time. We describe a ThioflavinT-based seeded-aggregation assay to test reflex tears. Initial methodology used systematic variations with laboratory-produced α-syn oligomers and then tear fluids from five healthy controls. This compared non-seeded monomeric α-syn and tears, to samples in which pre-prepared oligomers were introduced. Based on four replicates per person, the mean half-time range for seeded tear samples showed clear differences to unseeded samples (seeded: half-time range = 19.2-24.1 h, mean 22.1 h; unseeded: half-time range = 33.4-40.9 h, mean = 35.7 h; mean within-subject difference = 13.5 h, SD = 5.5 h, $p<0.003$). We will next verify if there is accelerated seeding, and the oligomeric α-syn structural characteristics (transmission electron microscopy), in reflex tears of PD patients, relative to age-matched controls. We plan to assess the relationship between oligomeric α-syn in tears and disease status using measures of (a) cognition, (b) motor impairment, (c) rapid eye movement sleep behaviour disorder and (d) brain integrity where MRI is available. These findings may establish a readily accessible biomarker to evaluate PD clinical/genetic status and progression, comparison with other synucleinopathies, and, in future, disease-modifying treatments.

5.41

Connexin 43 hemichannels — a potential therapeutic target for attenuating preterm inflammation-related brain injury

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Brain injury and neurological deficits in preterm infants are highly associated with exposure to infections/inflammation after birth. We observed brain dysmaturation in the white matter and cerebral cortex of very immature rats with neonatal inflammation. We also found upregulation and abnormal opening of astrocytic connexin 43 (Cx43) hemichannels contributes to hypoxia-ischemia induced neonatal brain injury, which was alleviated by blockade of Cx43 hemichannels. In this study we hypothesized that inflammation in neonatal rats causes upregulation and abnormal opening of astrocytic Cx43 hemichannels in the white matter and cerebral cortex which leads to astrocyte activation and subsequent brain injury. Sprague-Dawley rat pups received single daily intraperitoneal injections of saline or lipopolysaccharide (LPS; 0.3 mg/kg/day) on postnatal day (PND) 1–3. Brain tissues were collected on PND4 and stained for Cx43 and astrocytes (GFAP) or used for Droplet Digital PCR (ddPCR) to detect the expression level of Cx43, P2X4 and P2X7 receptors, GFAP and Iba1. LPS-induced inflammation was associated with increased density of total and astrocytic Cx43 but not astrocytic processes in the white matter of the rat brains. While inflammation increased Cx43 and GFAP expression in the white matter and the cerebral cortex, it did not significantly change the expression of Iba1 and the P2X receptors. Inflammation in neonatal rats may lead to increased astrocytic Cx43 in the white matter and the cerebral cortex triggering astrocyte activation and brain injury. Therefore, blockade of Cx43 hemichannels may be an effective strategy to prevent inflammation-related brain injury in preterm infants.

6.1

Olfactory processing in thalamocortical circuits in monkeys

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The olfactory system, as opposed to the other sensory systems, does not have a primary thalamic relay. However, the mediodorsal thalamus receives inputs from different primary olfactory areas including the piriform cortex and has strong reciprocal connection with the orbitofrontal cortex, a secondary olfactory area. The mediodorsal thalamus has been shown to be involved in some olfactory processing in mammals however only few studies detailed the encoding of olfactory information in this structure, especially in monkeys. In addition, given the strong relationship between the mediodorsal thalamus and the orbitofrontal cortex, it is essential to compare the odour responses in both structures and determine how they interact during odour presentation. To do so, we recorded neural signals (single units as well as local field potentials) from both structures simultaneously in four male rhesus macaque monkeys during repeated presentations of various olfactory stimuli including monomolecular odorants as well as biological odorants (i.e., female urine). Both mediodorsal thalamus and orbitofrontal cortex contained single unit responses that responded to one or more of the four odours presented in each session, indicating that both structures are involved in processing odour information in primates.

6.2

Targeted brain delivery of therapeutics using focused ultrasound in a sheep model of Parkinson's disease

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Disruption of the basal ganglia network connectivity forms the basis for several movement disorders, including Parkinson's disease (PD). Although various drug approaches exist for treating PD, these can lose effectiveness with time, with only a subset of people eligible for surgical intervention to improve function. Focused ultrasound, a novel, safe and non-invasive approach, coupled with intravenous liposomes to target neurological agents to the site of action, could become a therapeutic tool for drug delivery in patients with neurodegenerative disorders and brain tumours. After obtaining proof-of-concept in a PD rat model, five female Romdale sheep underwent two surgeries, four weeks apart. At the first surgery, a hemi-parkinsonian lesion was induced by intracranial injection of 6-OHDA into the left hemisphere of the SNpc to deplete dopamine unilaterally. At the second, an ultrasound transducer was fitted outside the skull, targeting the ipsilateral striatum. The dopamine receptor agonist apomorphine injected subcutaneously demonstrated the effectiveness of the hemi-parkinsonian lesion, confirmed post mortem by immunohistochemistry and HPLC. Motor parameters, including drug-induced rotation and distance travelled, were measured to examine the effectiveness of dopamine agonist release from intravenous liposomes. Short-duration pulses of focused ultrasound targeting the striatum released dopamine agonists from circulating liposomes at physiological timing (seconds). Replacement of dopamine using our novel smart drug delivery technology at physiological timing should maintain effectiveness of dopamine therapy long-term, by restoring phasic receptor activation punctuated by low tonic levels. Our combinatorial approach overcomes current delivery strategies' limitations, potentially providing a novel means to treat PD.

6.3

Changes in pre-attentive auditory processing in depression using the roving-MMN EEG task

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Depression has been commonly associated with disordered predictive coding. One task that investigates predictive coding in humans is the mismatch negativity (MMN), which measures the brain's pre-attentive response to unexpected sensory changes and is characterized by a voltage decrease occurring 100-250ms after a deviant stimulus. Various MMN paradigms have been employed in depression studies, yielding inconsistent findings. The roving-MMN paradigm, which incorporates changing the standard auditory stimuli to match the deviant stimuli, is considered a good predictive updating model and has not yet been utilized to compare depressed and healthy individuals. Our study investigates pre-attentive differences between depressed individuals and healthy controls using the roving-MMN task. Fifteen participants with Major Depressive Disorder (MDD) and nine healthy controls were recruited. Electroencephalography was recorded while participants completed the roving-MMN task. Difference waves for the MMN were calculated by subtracting the standard tone from the deviant tone for each individual and compared between groups. There was a significant difference between the healthy and depressed cohort (FWE-corrected p=0.045) with the depressed group having a greater negativity at 125ms. This finding reinforces that there is a difference in pre-attentive auditory processing between healthy and depressed individuals. This paradigm should be utilised in the future as consistent results in this task would discern if the difference is due to predictive coding errors. This result adds to the inconsistencies seen for MMN in depression, future research could shift focus to the underlying reasons for this unpredictable variability such as differences in cohorts, or subtypes of depression.

6.4

Handle incompatibility, cup size, and contents influence finger trajectories during pointing movements

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Although appropriate use of objects requires an appreciation of properties such as shape, size, and orientation, the visual pathways responsible for pointing and grasping can be separate and dissociable. Indeed, objects could potentially generate confusion if their perceptual features (e.g. shape) are irrelevant during a simple pointing task. To examine interference caused by object properties when performing simple pointing movements a 2x2x2 experiment varied Cup Contents by Size by Handle Orientation. Twenty participants placed their index finger in the centre of a touch screen and dragged a cursor to the left or right towards images of full or empty coffee cups that varied in size, and direction of handle (leftwards, rightwards). A cup's handle was "compatible" for grasping when oriented left for rightwards cursor movements (or oriented right for leftwards movements). Cursor coordinates were sampled at 200Hz, filtered at 8Hz and double differentiated to produce velocity and acceleration functions from which peak velocity, acceleration and deceleration were determined. Response latencies were greater for larger cups, implying that these movements required more advance preparation. Participants undershot their movement endpoints when the cup handle was compatible with grasping, and overshot when the cup handle was not compatible with grasping. Movements seemed to be faster to the bigger handle, and slower to the smaller handle. Participants aimed closer to the cup centre when cups were big and full. Kinematic analysis indicated object orientation influenced movement trajectory, but object contents influenced aiming points, and is relevant to an understanding of apraxia.

7.1

Ka mua, ka muri. Walking backwards into the future

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People living with Parkinson's disease are offered drug and deep brain stimulation treatments to reduce symptoms. Biomedical researchers propose that more selective treatments will offer greater symptom relief with fewer side effects. However, at the early stages of medical device development, accessibility and equitable outcomes for diverse target populations are rarely considered. An implantable optogenetic stimulation device has been developed, and commercialised, to investigate brain mechanism controlling movements, and as a potential future treatment for models of Parkinson's disease. However, further translation of this device would produce inequitable outcomes for Māori and older people. Community consultation highlighted that holistic approaches for health and wellbeing were needed to delay the onset of Parkinson's disease and/or slow symptom progression.

7.2

From the lab to the lounge: Engaging with Māori communities is critical to achieve equity in outcomes for whānau living with mate wareware

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The beliefs and values of both patients and health care providers contribute to health disparities. We know that the acceptance and effectiveness of the management of a health condition is largely dependent on a person's worldview. Current dementia services available for whānau living with mate wareware are embedded in western methodologies. That is, the diagnosis, treatment and management of such services are largely exclusive of a Māori worldview. Māori cultural identity is at the centre of Māori health and wellbeing, and it is within a mātauranga Māori knowledge base that appropriate and acceptable practices for the management of mate wareware services for Māori, can be found and integrated into existing services. As researchers we have a moral responsibility to engage with the Maori community, listen to their needs and learn from them. Not to do so, risks the diminishment of our credibility as scientists. This presentation will look at the engagement processes researchers of mate wareware have undertaken with Maori communities and how we continue to work toward building a trusting relationship with iwi and hapū. Our actions are guided by the principles of the Treaty of Waitangi and our responsibility as New Zealanders to contribute to equitable health outcomes for Māori.

7.3

From test tubes to TV: A story of HDYO-NZ

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Huntington's disease (HD) is a genetic neurodegenerative disorder characterised by variable motor impairment (chorea), psychiatric and cognitive symptoms. HD rangatahi (youth), have a 50% chance of inheriting the condition from a gene positive parent, with symptoms presenting in midlife. For more than a decade, my PhD and post-doctoral research has focused on elucidating the contribution of cellular degeneration and pathogenic protein deposition to better understand the symptom heterogeneity of HD. In 2013, after presenting work detailing neuronal loss patterns in post-mortem HD tissue samples at an HD community conference, it became apparent that while we (the researchers) were focused on understanding the disease post-mortem, we need to do more to support those living with HD. In this presentation, I will share my journey in partnership with the HD community to advocate, educate and support youth impacted by HD through the creation of the Huntington's disease youth organisation of New Zealand (HDYO-NZ), a registered charitable trust. This presentation will discuss the value and significance of researcher engagement with the community, for the communities we are trying to serve, which in turn underpins the wider impact of our neuroscientific contribution to society. This presentation will also discuss how early career researchers can harness science communication practices to raise the local and global profile of their research.

7.4

'Ma te kahukura, ka rere te manu – Adorn the bird with feathers so it may fly'
Engagement for the future influencing system-wide change

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Health services have been traditionally developed using Western health models, without consideration of more holistic health and wellbeing needs. Dr Julie Wharewera-Mika, a senior Clinical Psychologist and Kaupapa Māori researcher, has challenged the delivery of health services for Māori. Prioritising whanaungatanga (relationship building) to ensure genuine and intentional engagement with whānau, hāpori with lived experience, providers and practitioners was fundamental to her research practice, to maximise impact, and to address inequity to promote system-level transformation. Dr Wharewera-Mika will share her advocacy journey, informed by whānau lived experience and community-led responses to reduce health & wellbeing inequities promoting holistic wellbeing. Grounded in te ao Māori values, she will highlight the value of engagement with Māori whānau, hāpori and hapū and those affected by neurological conditions, and display how this can drive research, and provide practical advice for those wanting to strengthen their own systems advocacy and engagement journey.

8.1

Functional neuronal hyaluronidase enzymes regulate the extracellular matrix in association with neurite outgrowth in vitro

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Neurons and glia are surrounded by an intricate array of proteins and sugars. This brain extracellular matrix (ECM) regulates many neural functions, ranging from early development to plasticity, with ECM components dysregulated in developmental and degenerative neurological diseases. Despite its significance to brain health, the cellular mechanisms regulating ECM metabolism remain unresolved, with glia considered the major drivers. We recently established that neurons can synthesise hyaluronan, a long-chain sugar and principal component of the matrix. This study aims to characterise neuronal capacity for hyaluronan depolymerisation. Using dissociated hippocampal cultures (from embryonic day 18 rats, prior to gliogenesis), we resolved neuron-specific expression of the hyaluronidase enzymes, HYAL2—3, CEMIP and TMEM2 from the earliest stages of development. These enzymes were localised on soma, emerging neurites and growthcones—pivotal structures involved in guiding neurite outgrowth. When seeded on substrates coated with synthetic sodium hyaluronate, the immature neurons also showed functional hyaluronidase activity, particularly in association with growthcones. Pharmacological inhibition of these enzymes (Vcpal 10-50µM) led to a dose-dependent decrease of hyaluronate breakdown (area of degradation quantified using cytochemistry and automated image analysis). Interestingly, the effects of Vcpal also correlated with dysregulated neurite outgrowth. While lengths were retracted, the number of neurites emerging from the soma was increased. The data shines a new spotlight on neurons, with functional hyaluronidase enzymes, as independent regulators of their surrounding ECM. Further, without neuronal hyaluronidase activity, the excessive retention of ECM hyaluronan disrupts neurite development, with implications for disorders showing dysregulated nerve circuitry.

8.2

An unbiased de novo network analysis uncovering the developmental intersection between autism and co-occurring traits

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Autism is a complex neurodevelopmental condition that manifests in various ways. It is often accompanied by other neurological disorders, such as ADHD and anxiety, which can complicate diagnosis and management. The roles of specific genes in autism have been investigated but their relationship with co-occurring traits is not fully understood. In this study, we integrated genetic information at various levels (expression quantitative trait loci [eQTLs], genes, and proteins) to investigate the connectivity between autism and co-occurring traits. We discovered that the 17q21.31 locus contributes to the intersection between autism and other neurological traits and conditions in fetal cortical tissue. We also identified a cluster of co-occurring traits, including cognition and worry, linked to genetic loci at 3p21.1. These distinct genetic loci had developmental windows (e.g. fetal development) in which they had the potential to influence trait combinations. Completing an epidemiological study on New Zealand health records found an overlap in co-occurring conditions with what we had identified in our network analysis. Next, we conducted a two-sample Mendelian Randomisation analysis and identified four genes located at the 17q21.31 locus that are causally linked to autism in fetal cortical tissue (i.e. LINC02210, LRRC37A4P, RP11-259G18.1, RP11-798G7.6). Our results support the hypothesis that an individual's autism phenotype is partially determined by their genetic risk for co-occurring conditions. Overall, our findings provide insights into the relationship between autism and co-occurring traits, which could be used to develop predictive models for better clinical management.

8.3

Long-term impacts of cannabis on resting state functional networks: are there any?

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Cannabis is the most widely used illicit drug in New Zealand, and is known to impact learning, attention, and memory. We have previously shown focal differences in hippocampal and amygdala grey matter volumes in cannabis users relative to non-users, but no further differences in grey matter, white matter, or perfusion. However, other studies suggest cannabis-related changes in functional connectivity. In a subset of the Christchurch Health and Development Study's (CHDS) longitudinal birth cohort, now in their 40's, we explored the impacts of past heavy cannabis exposure on brain functional connectivity using fMRI. Between cannabis users (n=35) and non-using controls (n=34, matched for sex and tobacco use, and corrected for multiple comparisons), only small regions of the sensorimotor and frontal executive networks exhibited altered connectivity, suggesting relatively intact resting state brain networks. Previously reported alterations of connectivity in the literature may reflect acute, but not necessarily chronic, effects of cannabis.

8.4

The role of the dopamine D1 receptor in the anticipation of and engagement in social play

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Social play is of upmost importance for social, cognitive, emotional and sensorimotor development, and is one of the most rewarding activities for juvenile rats to engage in. The present study explores the effects of a genetic reduction in the dopamine D1R on the anticipation of and engagement in social play. Subjects, DAD1-/- mutants and wildtype controls, were isolated from their cage mates for 3.5 hours to induce motivation for social play. After isolation, subjects were placed into individual anticipation boxes for ten minutes and then both animals were placed in the play arena for 10 minutes. This procedure was repeated for a total of seven days, so the subjects learn that the anticipation box was followed by the opportunity to engage in social play, thus inducing anticipatory behaviour. We used a comprehensive method of analysis for play including the frequency and sequence of play behaviours (chasing, pinning, wrestling, pouncing, non-active), along with 50 kHz vocalisations. Overall, DAD1-/- mutants mostly engaged in a similar initiation, amount, and structure of social play relative to wildtypes. The pharmacological literature is contradictory on whether the dopamine D1R is involved in social play and/or its motivational aspect. Our results with a genetic manipulation suggest that the dopamine D1R might have a minor role in social play but is likely not the main regulator of play behaviour. In terms of anticipation, the DAD1-/- mutants' lack of anticipatory behaviour supports a prominent role of the D1 receptor in anticipatory pleasure.

9.1

The effect of fruits and vegetables on children's mental and cognitive health: A systematic review of intervention studies and perspective for future research

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Background: Childhood is a critical period to promote and protect mental well-being. Observational evidence suggests that higher fruit and vegetable (FV) intake could benefit children's mental and cognitive health, but comparatively little is known from intervention studies about the causative effects. We therefore conducted a systematic review of FV intervention studies that investigated mental and/or cognitive health outcomes in children aged 10 years or younger, both to understand the current evidence base and inform future intervention trial design. Systematic Review Methods and Results: A systematic search of the Cochrane, Embase, PubMed, and CINAHL databases was conducted for articles published before August 2022. A total of 4686 articles were identified, with only 7 of the 17 full texts screened included in the final review. Included studies used either a cross-over (n=4) or parallel (n=3) design, with sample sizes ranging from n of 14 to 54. Six of the 7 studies were conducted in the UK by the same research group using a drink made from fresh or freeze-dried blueberries as the intervention, the other study was conducted in Thailand and used a drink made from mulberry powder as the intervention. The majority of studies were acute interventions with outcomes measured in a 2–3-hour postprandial window (n=6, 85.7%). Positive Affect increased 2 hours after blueberry consumption (sample size=52), though longer-term effects were not found with daily supplementation for four weeks (sample size=15). Measures of Executive Function were sensitive to the effects of mulberry and blueberry interventions, with improvements observed in both acute and longer-term interventions and particularly with more cognitive demanding tasks. Future Research perspectives. Despite a strong theoretical basis for mental and cognitive health benefits of increased FV intake, the closest available intervention evidence was for studies providing supplemental doses of vitamins and polyphenols through beverages made of fresh or freeze-dried blueberries and mulberries. The benefits of increasing FV in the diet are undisputed and therefore highly suitable to improve childhood mental health at a population level, yet intervention studies are needed to confirm causation and efficacy. Acknowledging the challenges of conducting rigorous trials of this nature in children, we will discuss future research opportunities to advance this critical field of research.

9.2

Parkinson's disease and nutrition: what is the link?

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Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease and affects 1% of people over the age of 60 years in industrialised countries. In New Zealand, the number has increased from ~ 7,000 in 2006 to ~11,000 in 2020. Whilst the lowest rate is in Māori, given that the life expectancy of Māori is increasing at a greater rate than that of non-Māori, the prevalence of Parkinson's among Māori will increase faster than others in the New Zealand population. Parkinson's is heterogeneous in nature and results in a spectrum of motor and non-motor symptoms which include issues related to adverse nutritional status. Diet is often overlooked despite being an important factor in the management of the disease, and people with Parkinson's (PwP) face many issues which can negatively impact their nutritional status. Poor nutritional status is multifactorial and different symptoms can occur over the course of Parkinson's which vary in the degree to which they impact adversely on quality of life. These symptoms include anosmia, dysgeusia, dysphagia, orofacial issues, gastrointestinal dysfunction, cognitive effects, poor bone health, and an increased risk of sarcopenia. Each of these symptoms can individually or together impair dietary intake, negatively impact nutritional status and importantly, impair quality of life in PwP.

9.3

Linking the Gut Microbiome to Neurocognitive Development in Bangladesh Malnourished Infants

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Malnutrition is a significant global health issue that affects millions of infants every year. Malnutrition has serious implications on cognitive and neurological development, leading to long-term deficits in learning, memory, and behaviour1. While much is known about these implications, there remains a crucial need to understand the mechanism by which they arise. To this end, we trained AI Random Forest classification models with a combination of gut microbiome species and functional profiles, serum metabolites, and neurological electroencephalogram (EEG) metrics from 1-year-old infants with Moderate Acute Malnutrition (n = 70) and healthy infants (n = 70) to predict brain development; specifically to classify high and low quantiles of Expressive Communication (EC) score. Data were obtained as part of the M4EFaD trial, run in Dhaka, Bangladesh (NCT05629624). The models predict EC effectively (AUCROC = 0.71). By interpreting these models, serum metabolites had the highest proportion of highly predictive features. Interestingly, presence of Bifidobacterium species in the gut and their fermentation pathways were strong predictors of high EC (SHAP score = 0.20). Through co-abundant network analysis, Bifidobacterium species were correlated with serum fatty acids and EEG measurements forming a distinct cluster involved in the breakdown of cholesterol esters and sugars for sphingomyelin biosynthesis - an essential precursor for cognitive maturation2. Depletion of this cluster was predictive of malnutrition. The intricate and non-overlapping connections among gut microbiome composition, nutritional status, and behaviour highlight the significance of targeted interventions in addressing both the short and long-term impacts of malnutrition.

9.4

The effect of milk fat globule membrane supplementation on cognitive and psychological outcomes in adults

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Polar lipids are present in abundance in the nervous system and are essential for the maintenance of membrane integrity, neuronal membrane health, and signalling capacity. Milk fat globule membranes (MFGM) are a rich source of complex lipids and membrane proteins. Pre-clinical studies demonstrate that phospholipid supplementation can mitigate age-related cognitive decline and alter the hypothalamic pituitary adrenal axis function. Polar lipids for improvement of cognitive and psychological health in humans has not been widely investigated. We aimed to test the effect of two doses of MFGM supplementation on stress, cortisol response and cognitive performance. One-hundred-and-twenty-two healthy adults were enrolled in a randomized, double blind placebo controlled trial. Participants received MFGM 600mg, MFGM 1200mg, or placebo daily for 12 weeks. At baseline, 6, and 12 weeks, salivary cortisol, cognitive test performance, and psychological outcomes were assessed. Participants supplemented with MFGM had significantly lower stress (p=0.002) and anxiety (p=0.06) scores than the placebo group after 12 weeks. No group differences in cortisol or cognitive test performance were detected. Evidence suggests MFGM supplementation can improve psychological health.

9.5

Effects of intermittent access to high-fat, high-sugar diets on behaviour and gut microbiota

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Studies in humans and animal models show that consuming foods high in fat and sugar (HFHS) can impair cognition and alter composition of the gut microbiota. However, HFHS foods are rarely eaten exclusively, and more commonly form part of diverse diets that vary in composition over the short- and long-term. The cognitive effects of HFHS foods eaten under these conditions are less well understood. Here we tested whether HFHS diet-induced cognitive impairments were sensitive to (a) diet withdrawal; (b) intermittent or (c) time-restricted access; and (d) individual differences in consumption of HFHS foods. Adult male Sprague-Dawley rats were fed a 'cafeteria-style' diet comprised of palatable sweet and savoury HFHS foods and 10% sucrose solution, provided in addition to standard chow and water. Short-term memory was assessed via hippocampal-dependent place recognition and perirhinal cortex-dependent object recognition tests; faecal microbiota diversity was analysed via 16S rRNA gene amplicon sequencing. The HFHS diet-induced place memory impairment was ameliorated by withdrawing the HFHS diet for 11 but not 4 days. Place memory and microbiota diversity were progressively altered by intermittent access to HFHS diets, and were still evident when HFHS diet access was time-restricted (8h/day). Changes in cognition were associated with microbiota beta diversity but were not reliably predicted by the proportion of energy derived from fat or sugar, nor by total caloric intake. Results demonstrate that even intermittent or limited intake of HFHS foods may lead to changes in cognitive function.

10.1

Nalfurafine alleviates neuroinflammation by promoting an anti-inflammatory microglia phenotype in preclinical models of multiple sclerosis

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Demyelination is a pathological feature of multiple sclerosis, and no current therapeutics induce remyelination or promote repair and recovery. New therapeutics targeting remyelination are urgently needed. Astrocytes and microglia play important roles in maintaining myelin health, clearing debris and promoting anti-inflammatory cytokine release. The kappa opioid receptor (KOR) has been identified as a potential target for the development of remyelinating pharmacotherapies. This study investigated nalfurafine, a clinically available KOR agonist, in cuprizone toxin-induced preclinical models of demyelination. There was an increase in glial cell infiltration ($p<0.05$) following demyelination, and nalfurafine treatment alleviated astrocyte infiltration but failed to reduce microglia activation, as assessed through both cell number and morphology. The expression of KOR on both astrocytes and microglia was analysed following demyelination. Fewer than 5% of astrocytes expressed KOR in healthy mice, and expression of KOR was unaltered by nalfurafine treatment. Approximately 30% of microglia express KOR and there is a region-specific increase in KOR expression following nalfurafine treatment ($p<0.05$). The inflammatory phenotype of microglia following demyelination and treatment with nalfurafine was assessed using immunohistochemistry for the pro-inflammatory markers CD74 and CD68 and the anti-inflammatory marker CD206. Demyelination caused a significant increase in CD74 and CD68 positive microglia and a significant reduction in CD206 positive microglia compared to healthy control animals ($p<0.05$). Furthermore, following demyelination nalfurafine alleviated both CD74 and CD68 expression and increased CD206 expression compared to vehicle control animals ($p<0.05$). Our results show nalfurafine changes the functional phenotype of microglia enabling remyelination in preclinical model.

10.2

Exploring chronic low-grade inflammation-associated white matter alterations in major depressive disorder

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Chronic low-grade inflammation is thought to play a role in worsening the symptoms of major depressive disorder (MDD) and hampering the response to antidepressant treatments. Diffusion kurtosis imaging (DKI) has been shown to provide sensitive measures of the inflammation inside the brain and be lowered in MDD compared to controls. This pilot study examines differences in DKI metrics in the white matter of a cohort of individuals with major depressive disorder, stratified by chronic low-grade inflammation, and healthy controls. Ten patients with MDD and CRP≤1 mg/L (low-inflammation group), four with MDD and CRP ≥3mg/L (high-inflammation group), and nine healthy controls with CRP ≤1mg/L underwent DKI. DKI metrics in white matter tracts were analysed using tract-based spatial statistics. A one-way ANOVA test was applied across the three groups to reveal clusters of significant group effects. Clusters of significant group effects for radial and mean kurtosis were identified in areas including the left anterior corona radiata and left inferior fronto-occipital fasciculus. Post-hoc t-tests indicated that within these areas, there was lower radial kurtosis in the high-inflammation MDD group compared to the low-inflammation MDD group. This study highlights the role of DKI as a marker of the effects of chronic low-grade inflammation on the brain in MDD. These findings warrant further investigation in larger cohorts to assess their clinical implications; DKI metrics like mean kurtosis and radial kurtosis may potentially be able to identify patient subgroups and target those who may benefit from anti-inflammatory treatment in MDD.

10.3

Using EEG to assess neural effects of Estradiol: Progesterone ratio in females with and without epilepsy

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Catamenial epilepsy is a menstrual cycle-specific exacerbation of seizures in epilepsy. Literature suggests changes in the ratio of sex steroids across the menstrual cycle may affect seizure frequency. Visual gamma (VG) has previously been found to vary in frequency across the menstrual cycle in healthy women (HC), reflecting changes to GABA-related inhibition. GABAergic inhibition is protective against seizures. This study aims to measure visually induced gamma as a reflection of changes in GABAergic inhibition, demonstrating role of sex steroids altering neural signalling across the menstrual cycle in females with and without epilepsy. Electroencephalography recorded induced VG oscillations in HC (n=49) and a pilot sample (n=12) of females with epilepsy (EC). Absolute sex steroid concentration in blood samples of participants across mid-luteal, mid-follicular and peri-menstrual phases were also collected. Mean estradiol (E2) was relatively similar in HC (M=297.48, SD=216.01, range 60-1169 pmol/L) compared to EC (M=352.86, SD=277.01, range 92-1088 pmol/L). As was progesterone (P4) absolute concentrations in EC (M=12.74, S=15.93, range 0.2-45.9 nmol/L) compared to HC (M=15.01, SD= 19.83, range 0.2-116 nmol/L). However, mean ratio of E2:P4 is much higher in EC (426.08) compared to HC (170.35). E2 has excitatory neural effects and allopregnanolone (metabolite of P4), enhances GABAergic inhibition. The higher ratio of E2:P4 in EC may reflect a difference in excitatory to inhibitory balance in the brain. Analysis of visual gamma in part 2 of this study aims to show concurrent changes in GABA-driven inhibition. Knowledge provided by this research will help uncover the pathophysiology of catamenial seizures.

10.4

Ginkgolic acid restores ferritinophagy in a Parkinson's disease cell model

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Iron accumulation and lysosomal impairment are pathogenic features of Parkinson's disease (PD). The autophagy-lysosomal pathway regulates the iron storage protein ferritin through degradation and iron redistribution (ferritinophagy). Evidently, α-synuclein compromises autophagy by impairing autophagosome and lysosome fusion. Ginkgolic acid (GA) potently stimulates autophagy in vitro and thus, our work expands upon this to target iron accumulation within a cellular PD model. SH-SY5Y neuroblastoma cells were depolarised with potassium chloride to instigate calcium-dependant pathogenesis and were monitored after 48, 72, and 96hrs. Trimethadione was used to inhibited calcium channels that open during membrane depolarisation events. Samples were imaged as Z-stacks on the Nikon A1R+ confocal microscope and analysed in 3D using ImageJ. After 72hrs, cultures were treated with various GA concentrations either with or without the autophagy inhibitor, chloroquine, for a further 24hrs. Resultantly, α-synuclein aggregation and ferritin accumulation occurred in a time-dependant manner following depolarisation. However, trimethadione attenuated both pathologies further illustrating calcium-dependence. After 96hrs, ferritin observably composited into vesicle-like structures, significantly co-localising with the autophagosome marker LC3. All GA concentrations cleared the accumulated ferritin and its associated LC3, indicating autophagy restoration. Chloroquine prevented GA from enhancing autophagy regardless of its concentration. Thus, GA seemingly enhances autophagy upstream of lysosome acidification, yet sufficiently overcome α-synuclein aggregation-derived impairments. The present work indicates GA as a pharmacological candidate for developing future PD therapies. Furthermore, the work illustrates the multifaceted benefit of targeting autophagy for attenuating disease pathogenesis.

10.5

Identification of six new monoamine oxidase (MAO) inhibitors from tobacco smoke and their biochemical characterisation

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Smoking is supposed to be the most difficult addiction to quit, yet nicotine, the main addictive component in tobacco smoke, has only moderate potential for addiction. Surprisingly, positron emission tomography (PET) scans have shown that smokers have lowered levels of brain MAO A (28%) and MAO B (40%) activity relative to non-smokers. Nicotine does not exhibit any MAO inhibitory activity, but non-nicotinic components in tobacco smoke inhibit MAO, a key enzyme responsible for the metabolism of neurotransmitters such as dopamine, serotonin, and norepinephrine. It has been hypothesized that, because MAO metabolises neurotransmitters in the brain, MAO inhibitors in tobacco smoke may increase the lifetime of neurotransmitters and enhance the reinforcing properties of nicotine. We have identified six new MAO inhibitors on tobacco smoke in amounts likely to be significant. Of particular interest are the "slow acting" MAO inhibitors identified, since it has long been proposed that tobacco smoke results in irreversible MAO inhibition. Bioassay-directed the isolation of the six new MAO inhibitors, identification of these inhibitors, in vitro MAO inhibitory activity, and kinetic and molecular docking studies are described. Previously we demonstrated that two known inhibitors, harman and norharman only made up 5-10% of the total MAO inhibitory activity in cigarette smoke. New data suggests that the six new MAO inhibitors from tobacco smoke may make significant contributions to MAO inhibitory effect of cigarette smoke. These MAO inhibitors may also have pharmaceutical possibilities, in smoking cessation, or in relief of anxiety or depression or in Parkinson's and Alzheimer disease.

10.6

Region-specific activation of protein tyrosine kinase 2 (Pyk2) in temporal lobe epilepsy

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Mesial temporal lobe epilepsy (MTLE) is one of the most common forms of drug-resistant epilepsy and its precise aetiology is still unknown. Thus it is vital to investigate the therapeutic targets and signalling pathways for its treatment. Previous studies have demonstrated the activation of Pyk2 in stress mediated pathways in the brain. We thus hypothesized that the activation of Pyk2 might be a contributing factor in its pathogenesis. For this purpose we analysed the mRNA levels of Pyk2 and protein levels of p-Pyk2Tyr402 in the hippocampus, anterior temporal lobe and cortex of pilocarpine model of TLE and also visualized its cell specific expression using immunofluorescence assay. Further to investigate the role of calcium in its activation we performed a calcium assay using flow cytometry. The results obtained revealed a significant upregulation of pPyk2Tyr402 in the hippocampus and ATL region of the TLE model which was positively correlated with calcium levels. The clinical correlation of Pyk2 activation was further obtained in epileptic patient samples. Our study for the first time showed a region specific activation of Pyk2 in TLE emphasizing its role in the generation of independent epileptogenic networks and epileptogenesis.

11.1

Autophagy decreases in the ageing mouse brain in a sex dependent manner

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Ageing is the most important risk factor for neurodegenerative diseases that cause dementia such as Alzheimer's disease. Alzheimer's disease is also genetically linked to an intracellular process called autophagy, which is responsible for suppressing hallmarks of biological ageing such as the build-up of protein aggregates. Previous research has shown decreases in brain autophagy proteins with ageing, indicative of an age-related decrease in autophagy. Despite this, no study has directly measured flux of waste material through the autophagy-lysosomal pathway and related this to ageing in the mammalian brain. To address this gap, we used the tandem-fluorescent-LC3 reporter mouse (tf-LC3) that expresses a ratiometric fluorescent probe to measure autophagic flux in the brain. As ageing, sex, and obesity all impact the risk of developing dementia in humans, we analysed autophagic flux in mouse brains at 6-, 12-, and 18-months of age, in both male and female mice, and with or without diet-induced obesity. We found an age-related decrease in autophagy in the brain in male mice only. Female mice did not display the same relationship between autophagic flux and age in the brain. Despite detecting obesity-related changes in autophagy in the heart, we did not find significant obesity-related changes in autophagy in the brain. These results show that maintaining autophagy in the brain with ageing could be of benefit. However, our results show that autophagy's relationship with brain ageing appears to be sex-dependent and this will likely impact its use as a therapeutic target relevant to neurodegeneration.

11.2

Investigating the impact of tobacco particulate matter and selected components on monoamine oxidase activity, protein expression, and gene expression in brain SH-SY5Y cells

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Smoking addiction is an alarming issue that demands high attention due to the widespread prevalence of smoking and the millions of lives lost as a result. Several studies have indicated the role of non-nicotinic components, such as monoamine oxidase inhibitors (MAOIs), in smoking addiction. Our group has identified six previously unidentified candidate MAOIs in tobacco smoke. We exposed an SH-SY5Y cell line to different regimens of ethanol (control), nicotine, tobacco particulate matter (TPM), and a cocktail of MAOIs, to understand the impact of these candidate MAOIs. Nicotine was used at a final concentration of 0.2 µM, and the candidate MAOIs were used at concentrations relative to that found in TPM. An MAO activity assay was performed to determine the optimal exposure period that produced maximal MAO inhibition. Nicotine did not show any significant MAO inhibitory effect. However, TPM and the cocktail of MAOIs reduced MAO activity by about 43% and 53%, respectively. Additionally, an MTT assay confirmed that the exposure treatments did not have any overt cytotoxic effects. The exposure treatments did not induce any change in MAO A and MAO B protein and gene expression. However, we identified several genes with altered expression after exposure to TPM and the MAOIs cocktail, which were associated with smoking-related diseases and addiction. These results suggest that the candidate MAOIs identified by our group are key contributors to the MAO inhibitory properties exhibited by cigarette smoke, providing valuable insights into the mechanisms underlying smoking addiction and its associated health conditions.

11.3

Deciphering the role of lncRNAs in lysosome and neuron health

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In healthy neurons, lysosomes, the cell's recycling centres, are trafficked up and down neuronal projection highways, recycling and degrading cellular waste, and transporting cargo. Lysosomes have been reported to facilitate transport of RNA molecules, and modulate neuronal synaptic activity. Long non-coding RNAs (lncRNAs), transcripts greater than 200 nucleotides in length that don't code for proteins, function by regulating a plethora of cellular functions including gene expression, mRNA degradation, protein trafficking, protein translation, and microRNA sponging. In neurodegenerative disorders lncRNAs have been associated with the dysregulation of autophagy, which converges with the fusion of autophagosomes with lysosomes. These intricate processes are stringently regulated, and when defective, lead to neuron dysfunction in neurodegenerative diseases. In a childhood form of neurodegeneration, Batten Disease, mutations in a single lysosomal protein, CLN5, lead to lysosomal dysfunction, a build-up of cellular waste, and ultimately cell death. Here we have performed transcriptomic analysis of human iPSC-derived CLN5-deficient cortical neurons to identify differentially expressed lncRNAs. Using bioinformatic analysis and expression databases I have generated an inclusion/exclusion criteria to select lncRNAs based on gene level and transcript level expression for lncRNAs expressed in cortical neurons. I have identified a pool of 10 differentially expressed lncRNAs to screen for lysosome dysfunction. In the remainder of my project I aim to explore how these lncRNAs can modulate lysosome function to maintain neuronal homeostasis. Our study reveals new potential therapeutic targets for the treatment of neurodegenerative disorders.

11.4

Study of molecular interactions of TREM2 in Alzheimer's disease

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Globally, Alzheimer's disease (AD) is the leading cause of dementia. One of the hallmarks of Alzheimer's disease (AD) is the extracellular aggregation of amyloid beta (Aβ) protein into amyloid plaques in the brain. Triggering receptor expressed on myeloid cells-2 (TREM2) is a key protein that mediates inflammatory response in AD. Mutations in TREM2 have been linked to a three-fold increase in the risk of AD. Among the many ligands of TREM2, its interactions with Aβ are pivotal for understanding the microglial response in AD. In addition, individual interactions of TREM2 and Aβ with glycosaminoglycans (GAGs) have been reported to mediate the pathology of AD. We hypothesize that cell-surface GAGs such as heparan-sulfate interact with TREM2, mediating its interaction with Aβ. Mutations in TREM2, adversely affect these interactions leading to insufficient microglial response. We aim to decipher the role of these ternary TREM2-Aβ-GAG interactions in AD. We are approaching this in vitro by using isolated, purified proteins and employing various biochemical techniques, such as aggregation-kinetics assays, solution NMR, and electron microscopy. Here, we present some of our preliminary data. Considering heparin as a model GAG, we show that it doesn't interact with monomeric Aβ, but potentially interacts with Aβ fibrils. We find that TREM2 strongly inhibits Aβ aggregation, whereas heparin blocks this effect, potentially by binding to the same site as Aβ on TREM2. We believe that our study will provide a detailed understanding of key interactions of TREM2 underlying AD and may help in developing therapeutic strategies in future.

11.5

A human functional genomics approach to investigate inflammation in dementia

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Alzheimer's disease (AD) affects around 10% of people over 65 worldwide, with significantly reduced quality of life and substantial whānau, societal and economic burden. Our understanding of AD pathogenesis is incomplete, however accumulating evidence suggests microglia play a key role in disease causation and progression. Microglia importantly communicate with astrocytes and these glial cells have both beneficial and detrimental functions in AD. Our research group aims to define disease-associated glial phenotypes to identify protein and functional changes in microglia and astrocytes that may represent novel drug targets. We previously generated a large single-nuclei transcriptomic dataset of AD and control microglia and astrocytes. Differential expression revealed significant gene changes, and co-expression analysis identified putative functions of these dysregulated genes. Based on these findings we have defined disease-associated glial gene sets to investigate at the protein and functional level. We found up-regulation of a core set of microglial and astrocyte proteins using immunohistochemistry in human brain tissue. The microglial protein GPNMB shows a particularly large up-regulation in AD, strongly correlates with amyloid-beta and tau pathology, and is co-expressed with microglial activation/dysfunction markers. GPNMB is expressed in human microglia cultured in vitro, and up-regulated by exposure to amyloid-beta and AD-related soluble molecules. GPNMB gene co-expression suggests a role in lipid homeostasis and ongoing work is investigating this function, as well as associated astrocytic changes. GPNMB expression in microglia signifies a human microglial disease phenotype and deciphering its role, and associated astrocyte changes, will further enable us to target glia for AD treatment.

12.1

Causative variant discovery in motor neuron disease

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New Zealand has among the highest incidence and mortality rates of motor neuron disease (MND) globally, but it is uncertain whether this relates to environmental or genetic risk factors. Contributing to this uncertainty, New Zealanders with MND have poor access to clinical genetic testing. We sought to conduct genetic testing in New Zealanders to identify known and novel genetic contributors to MND risk, and to test the pathogenicity of identified variants of uncertain significance (VOUS). Blood DNA was collected from 13 controls, 138 people with MND (121 sporadic, 17 familial) and 29 people at genetic risk. DNA was tested for variants in C9orf72, SOD1, FUS, TARDBP, UNC13A, and 41 other MND-associated genes. Dermal fibroblasts were cultured from 8 controls, 10 people with MND (2 sporadic, 8 familial) and 18 people at genetic risk. VOUS were tested for pathogenicity in silico using a suite of prediction tools, and in vitro using assays of RNA splicing (mini-genes, qPCR, RNA-seq) and protein quality (western blot, immunocytochemistry). We identified known pathogenic variants in C9orf72 (n=20, 11.1%) and SOD1 (n=9, 5.0%), and VOUS in 14 genes including ATP13A2 and DCTN1. In silico and in vitro pathogenicity testing suggested that the identified ATP13A2 and DCTN1 variants are pathogenic. This pipeline has enabled return of known pathogenic variant results to people with MND, and discovery and pathogenicity testing of VOUS. By characterising the range and frequency of genetic risk factors for MND in New Zealand, we hope to understand and reduce our high rates of the disease.

12.2

Development of iPSC-derived neuronal models to study Batten disease; a group of childhood dementias

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Batten disease is a group of 13 monogenic lysosomal diseases characterised by childhood dementia, blindness, ataxia, and premature death. While recent progress has been made in clinical treatment using intraventricular enzyme replacement and gene therapy, we still have minimal understanding of how mutations in these genes lead to Batten disease. The Hughes laboratory has a long-standing interest in Batten disease and has contributed to both gene therapy approaches and development of neural culture systems for studying disease development. In this talk, I will discuss recent progress in characterising lysosome-associated pathologies in induced pluripotent stem cell (iPSC) models of two forms of Batten disease, that allow us to compare and contrast disease forms and test therapies in high-throughput prior to in vivo testing. I will also discuss our 'omics approaches to uncover the function of the CLN5 form of Batten disease in human neurons, and recent work to test how glial cells contribute to pathology Batten disease. Understanding Batten disease will contribute to our understanding of lysosomal function in health, and neurodegenerative diseases in general, where lysosome dysfunction is also apparent.

12.3

Pūnaha Io – the New Zealand Neuro-Genetic Registry and BioBank – Lowering barriers to research in Aotearoa

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How was it that, on the 22 November 2023, the first person in the world to receive an antisense oligonucleotide to treat myotonic dystrophy received it in Tamaki Makaurau, Aotearoa? This talk will chart the development of Pūnaha Io – the New Zealand Neuro-Genetic Registry and BioBank and show how it has lowered the barriers for New Zealanders with neurogenetic and neuromuscular conditions to take part in such research with stunning success. Clinical trials are one thing, but the registry is useful for reducing barriers at other stages of research as well, so the talk will show how the University of Auckland CBR Neurogenetic Clinic has built on the Registry as its base to undertake epidemiological studies, natural history studies and hypothesis driven research. In 2020 the Registry was transformed by the addition of a BioBank in partnership with Te Ira Kāwai – the Auckland Regional Tissue bank. The BioBank is not just a collection of random samples from people with neurogenetic conditions but a deliberately and prospectively collected capturing of the clinical course of disease over the lifespan of the participant with each sample timestamped with the participants clinical status at that time. Most importantly, Pūnaha Io is not just for our own research. In fact, the vast majority of the over ninety studies that Pūnaha Io has helped recruit participants for are external studies – here in Aotearoa and overseas. You too will be invited to think how you could use Pūnaha Io's data or samples to do Neuro-Genetic research.

12.4

Balancing hope and reality: Clinical trials for Duchenne Muscular Dystrophy in Aotearoa

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Genetic diagnosis of neuromuscular disorders has rapidly improved, making them a major focus of therapeutic research. There are over 200 products in the therapeutic pipeline, however 90% of preclinical therapies never reach clinical trials. Of those in clinical trials, only 10% obtain marketing approval. Duchenne muscular dystrophy (DMD) is a severe progressive disorder affecting 1 in 3600 males. Progressive muscle weakness leads to loss of ambulation and ultimately death due to respiratory and cardiac involvement. For many patients and their families, hope lies in research and clinical trials that could potentially offer breakthrough treatments. The first targeted therapy for DMD was approved by the FDA in 2016. In 2023 the FDA narrowly approved gene therapy for DMD, however further trials are required to confirm clinical benefit. Despite these significant advances, the majority of boys with DMD are not able to access disease modifying therapies. Rare disease drug trials require multiple sites to recruit sufficient patients, working against challenges such as lack of regulatory harmonisation. This has enabled access to clinical trials for some New Zealand patients. Hopes and expectations of families are high, however, for the majority these are not realised because of restrictive trial inclusion criteria, carrying a high emotional impact. Currently no disease modifying therapies for DMD are funded in New Zealand. For patients with rare diseases, translation of drug development to widespread access is slow related to limited evidence of treatment effectiveness, high drug development costs, and reimbursement challenges in a system with competing priorities for healthcare budgets.

13.1

Unravelling molecular details of protein interactions in Alzheimer's disease

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Protein misfolding and aggregation are linked to a number of neurodegenerative diseases, including Alzheimer's disease. Fibrils formed by the protein amyloid-beta are the major component of extracellular deposits found in patients affected by Alzheimer's disease. Despite intensive research, Alzheimer's disease remains incurable, and there is an urgent need for increased basic understanding of disease mechanisms. In order to understand the role of amyloid-beta aggregation in disease progression, and to understand how we can interfere with this harmful process, we are investigating how certain proteins interact with amyloid-beta and alter its aggregation. Proteins secreted from immune cells in the brain, such as S100B and TREM2, have emerged as a potential link between protein aggregation and inflammation. Using purified proteins and an array of biophysical and biochemical methods including NMR spectroscopy, we are studying structural and mechanistic details of these interactions in order to understand how proteins can prevent amyloid toxicity. We have discovered that the astrocyte protein S100B directly interacts with monomeric amyloid-beta and suppresses its aggregation into fibrils. We propose that it acts as an extracellular chaperone, blocking harmful protein aggregation. Preliminary data on the interaction of the microglial protein TREM2 with amyloid-beta suggest a parallel role in blocking amyloid-beta protein aggregation. Overall, the ability of immune proteins to stabilise healthy forms of amyloid-beta and limit toxic forms highlights the important roles of these key links between immunity and protein aggregation, and our understanding of the molecular details of these interactions may open new avenues for disease intervention.

13.2

Early-phase amyloid PET as a cerebral perfusion surrogate in cognitively impaired Parkinson's disease

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Accurate diagnosis is crucial for effective treatment and care in neurodegenerative disorders. In vivo imaging of pathological proteins like amyloid beta (Aβ) are increasingly used for diagnostic assistance. Measuring cerebral blood flow, known as perfusion, also provides important diagnostic information. Evidence suggests that 'early-phase' PET images, taken immediately after radiotracer injection, may mirror perfusion information. This study aimed to investigate if 'early-phase' images of the Aβ PET tracer 18F-Florbetaben (FBB) can provide perfusion information and assess cognitive status in Parkinson's disease (PD). One-hundred-and-fifteen PD patients ranging from normal cognition, mild cognitive impairment to dementia underwent early-phase FBB (eFBB) and late-phase PET at 0-10 min and 90-110 min, respectively, after intravenous injection of 300 MBq ± 20% FBB. Additional scans included T1-weighted MPRAGE structural and arterial spin-labelling (ASL) perfusion MRI. eFBB images were co-registered to subject T1-weighted images and calculated for individual uptake (SUVR) using Centiloid Project-defined whole cerebellum as reference. Voxel-wise linear regression models investigated eFBB uptake associations with global cognitive ability, with age and sex as covariates, corrected for multiple comparisons. Regional SUVR and perfusion from the AAL3 atlas-defined ROIs were correlated for comparison. Early-phase PET images replicated the established PD pattern of hypoperfusion, with cognitive ability associated with uptake in parieto-occipital and prefrontal areas. Moreover, eFBB regional uptake correlated with perfusion across widespread cortical regions ($r=0.27$-0.51, $p<0.005$). The results indicate that early-phase PET uptake may be a suitable surrogate measure for cerebral perfusion, suggesting that a single 'dual-phase' PET scan may provide perfusion and pathological protein status.

13.3

Cybersickness prevention and alleviation via machine learning-guided high-definition transcranial direct current stimulation

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Cybersickness (CS) is a type of visually induced motion sickness experienced in Extended Reality (XR) environments. The condition causes debilitating nausea, disorientation, and oculomotor issues that hinders comfort and performance. Treatment for motion sickness involves drugs with sedative properties that impair task performance, which would be counter intuitive for enabling XR activity. We present a novel approach by predicting CS onset and preventing it via machine learning-guided cathodal high-definition transcranial direct current stimulation (HD-tDCS) with no known side effects. The study recruited healthy participants (n=19, 18-36 years). Electroencephalogram (EEG) was monitored at rest and fed as spatiotemporal inputs to a custom prediction algorithm which uses a spiking neural network architecture. This architecture previously identified Cz as key site for intervention. The identicality of the new EEG inputs was compared with a pretrained map of CS related brain activity. Immediately following positive prediction, either placebo, anodal or cathodal HD-tDCS was applied at Cz (10-10 electrode configuration) for 5-minutes at 1.5mA with 30s ramp-up/down, with subsequent 10-minute virtual reality immersion to record CS events. Cathodal stimulation yielded a significantly higher number of successful preventions compared to anodal (*p = 0.01) and placebo (***p = 0.00056), achieving a large effect size (>0.8) with a 47% reduction in the likelihood of CS. We hypothesized that the treatment worked through disruption of activity at the motor processing region under Cz. Thus the area appears to not only be a marker of susceptibility and a marker of ongoing CS but a contributor towards the condition.

13.4

Does extravascular water extraction rate differ in Alzheimer's disease compared to healthy aging?

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Converging evidence shows that the blood-brain barrier (BBB) is altered in Alzheimer's disease (AD). Our aim was to apply a new MRI technique that does not require contrast agents, to study the BBB in people living with AD. Arterial Spin Labelling (ASL) MRI is typically collected at relatively long inflow times, dominated by extravascular (EV) signal, to measure perfusion. Acquiring data at shorter inflow times, the ASL signal signature will contain both EV and intravascular (IV) components. As these components have different transverse relaxation (T2) times, measuring T2 decay can enable estimation of the EV fraction (fEV) of the total ASL signal. Greater fEV at a given time point implies faster water exchange across the BBB, reflecting permeability. Participants (n=17 with AD, n=23 controls) were recruited from the Dementia Prevention Research Clinics (New Zealand). Images were acquired at 3T using a custom multi-echo, multi delay ASL protocol. The fEV at two different inflow times (2100ms and 3100ms) was estimated by fitting a biexponential model to the ASL signal. Comparison of fEV between groups was made using a Mann-Whitney U test. The median fEV at the first inflow time was 0.78 (IQR=0.11) in controls, compared to 0.84 (IQR=0.19) in AD (W=265, p=0.06) and at the second inflow time 0.86 (IQR=0.22) and 0.88 (IQR=0.15) respectively (W=210, p=0.70). A higher tissue fraction of ASL signal at the earlier inflow time would indicate faster water transport across the blood-brain barrier and warrants further investigation in regions relevant to AD.

14.1

Scaling of avoidance behaviours by hypothalamic stress neural activity

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Real and perceived threats elicit avoidance behaviours to prioritise safety. These behaviours need to be flexible however and can be influenced by the environment, past experience, or competing motivations of the organism. How neural circuits consolidate these factors to program scalable outputs in avoidance behaviours remain poorly understood. Here, we demonstrate a role for hypothalamic corticotropin-releasing hormone (CRH) neurons in governing avoidance behaviours in an activity-level-dependent manner. A foraging task was developed, where mice can voluntarily leave their home area to explore a novel, and therefore potentially dangerous, open environment (foraging area) to obtain food. Through fibre photometry recordings of CRH neuron activity, we show that avoidance from the foraging area is immediately preceded by elevations in CRH neuron activity. However, as mice adapted to the open area, we observed gradual suppressions in CRH neuron activity, which correlated with reduced avoidance. Through chemogenetics, we found that artificially increasing CRH neuron activity was sufficient to increase avoidance behaviours, as indicated by reduced time in foraging area. We next tested whether CRH neuron activation can increase avoidance behaviours in the presence of a competing motivation (hunger) using fasted mice. In contrast to sated mice, CRH neuron activation did not increase avoidance behaviours in fasted mice. There was no differences in time spent foraging between fasted mice with and without artificial CRH neuron activation. Taken together, we demonstrate that CRH neuron activity induces avoidance behaviours in a scalable manner. However, rival motivations, such as hunger, can outcompete CRH neuron activity for behavioural selection.

14.2

Capability of multimodal MRI to capture cognitive abilities across the lifespan: Predictability, reliability and generalizability

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Across the lifespan, people differ in their cognitive abilities, and these individual differences may be indicative of neurological/psychiatric issues. Having a neuroimaging-based biomarker that can capture the individual differences in cognitive abilities may allow us to detect early or trace neurological/psychiatric issues. As with any robust biomarker, a neuroimaging-based biomarker needs to have good psychometric properties: predictability (i.e., predicting cognitive abilities of persons outside of the model-building processes), reliability (i.e., having stable ranks across time), and generalisability (i.e., predicting cognitive abilities across datasets). Here, we benchmarked these abilities for MRI of different types to capture cognitive abilities across the lifespan. We took three MRI databases (Human Connectome Project Young Adults (HCP-YA), Human Connectome Project Aging (HCP-A), Dunedin Study (DUD)), covering 2,131 people from 22 to almost 100 years old. Each database consists of multiple MRI types: structural, resting state and several tasks. We combined different MRI measures together using a stacking approach and Elastic Net to predict cognitive abilities. Stacking led to good prediction across datasets: HCP-YA (r = 0.61), HCP-A (r=0.61), DUD (r=0.55). Similarly, stacking also led to excellent test-retest reliability in HCP-YA (ICC = 0.81) and DUD (ICC= 0.84)., For generalisability, we could only combine non-task MRI types (i.e., structural MRI and resting state fMRI) together, given that different studies used different tasks. We found non-task stacking led to modest generalisability across datasets with raverage=0.20, compared to prediction within-datasets raverage=0.37. Thus, multimodal MRI could capture cognitive abilities with good predictability and reliability and modest generalisability.

14.3

Long-term recall of non-spatial memory and the thalamic reuniens

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The nucleus reuniens (RE) is situated in the midline thalamus and provides a key link between the hippocampus and prefrontal cortex. This anatomical relationship positions the Re as an ideal candidate to facilitate memory consolidation. Evidence is, however, lacking whether this role extends beyond spatial memory and contextual fear memory, both of which are strongly associated with hippocampal function. We therefore trained intact male Long-Evans rats on an arbitrary odour-trace-object paired-association task in which the explicit 10-second delay between paired items renders the task sensitive to hippocampal function. Neurons in the RE showed markedly increased activation, based on expression of the immediate early gene Zif268, when rats were re-tested for the previous non-spatial memory 25 days after reaching acquisition criterion (Remote memory; N = 8) relative to a group tested at 5-days post-training (Recent memory; N = 8), as well as a control group tested 25 days after acquisition but with a new pair of non-spatial stimuli (25-day New learning; N = 6), and 9 home cage controls ($F(3,25)=64.72$, $p<0.001$). The Remote recall group also showed increased Zif268 expression in the superficial layers of the medial prefrontal cortex (anterior cingulate cortex, Group by Layer interaction $F(6,54)=3.49$, $p=0.005$; and, prelimbic cortex, Group by Layer interaction $F(9,81)=7.13$, $p<0.001$). We conclude that the RE is also preferentially engaged during remote nonspatial recall, not just spatial memory and contextual fear memory. The comparative importance of the RE for memory consolidation and remote recall relative to other thalamic nuclei will also be discussed.

14.4

Oxytocin receptor activation in the basolateral amygdala complex enhances stimulus detection, and facilitates aversive, but not appetitive, learning

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Oxytocin is a neuropeptide that is known for its pro-social and anxiolytic effects in animals and people. Recent reports indicate that the effects of OT on social behaviour depend on the social context: increased pro-social effects in the absence of social threat, but increased defensive aggression when threats are present. We previously replicated this bi-directional effect of OT in a fear conditioning protocol, and identified qualitative changes in stimulus processing that underlie it. In the present series of experiments, the effects of OT receptor activation in the basolateral amygdala on stimulus-processing mechanisms were examined further using conditioning protocols that consist of changes in stimulus-outcome contingencies (i.e., extinction and reversal), and with stimuli paired with aversive (i.e., foot shock) and appetitive (i.e., sucrose) outcomes. It was revealed that the effects of OTR stimulation diverge for aversive and appetitive learning – enhancing the former but not the latter. However, across both types of learning, OTR stimulation enhanced the detection of conditioned stimuli. Overall, these results are consistent with an emerging view of OT's effects on stimulus salience; facilitating the detection of meaningful stimuli while reducing responding to those that are irrelevant.

14.5

The relationship between cortical thinning, grey matter atrophy, and cognitive performance in mild cognitive impairment

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Mild cognitive impairment (MCI) can be a transitory state between healthy aging and Alzheimer's disease. However, the complex relationships between brain structure and cognitive performance in MCI are still poorly understood. We utilised data from the Dementia Prevention Research Clinics (DPRCs) and partial least squares (PLS) techniques to investigate the relationship between cognitive measures and structural magnetic resonance imaging (MRI) measurements of cortical thickness and grey matter volume (GMV) in MCI and controls. Across a range of cognitive domains, results showed that the association between brain measures (GMV and cortical thickness) and cognitive performance was stronger for the MCI group relative to the control group. Memory measures correlated with GMV and cortical thickness in the temporal, frontal and inferior parietal lobes. Attention/Working Memory performance correlated with cortical thickness in the left frontal, occipital, and temporal regions. The Processing Speed domain showed significant correlations with cortical thickness across all lobes. Performance on Language/Semantic subtests correlated with GMV in the bilateral temporal and occipital lobes. Within the Visuospatial domain, performance correlated with cortical thickness in the posterior brain regions and with GMV in the bilateral frontal, parietal, and right temporal lobes. The Executive Function domain exhibited widespread correlations with cortical thickness and GMV across all brain lobes. Understanding the relationship between atrophy and cognitive performance in MCI may aid early detection and intervention of individuals at increased risk of progressing to Alzheimer's disease.

14.6

Expanding our understanding of tobacco dependence

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Tobacco dependence is driven by nicotine but, although smoking is highly addictive, in the laboratory nicotine appears only mildly addictive. To test the hypothesis that monoamine oxidase (MAO) inhibitory activity in tobacco smoke can enhance nicotine's abuse potential, we first identified 6 new significant MAO inhibitors, using bioassay-directed purification. Two are reversible inhibitors of both MAO-A and -B, as shown by kinetic and in silico studies. In contrast, four others appear to be irreversible inhibitors. We have looked at the interaction of the mixed inhibitors with cultured cells, where the data obtained supports the hypothesis that direct inhibition by these inhibitors can explain the effects of the tobacco smoke preparation on MAO activity. Behavioural studies in rats (using nicotine self-administration, and conditioned place preference) strongly suggest that these inhibitors enhance the addictive properties of nicotine. Consideration of our results has suggested a model for smoking dependence which incorporates MAO inhibition caused by smoking, as well as direct responses to nicotine. While much remains to be done, the potential implications of this model are far-reaching for understanding smoking's effects.

15.1

The novel HS-mimetic, Tet-29, regulates immune cell trafficking across CNS barriers

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Disruption of the extracellular matrix (ECM) at the blood brain barrier (BBB) underpins neuroinflammation in multiple sclerosis (MS). The degradation of ECM components, such as heparan sulfate (HS) proteoglycans, can be prevented by inhibiting the enzyme, heparanase, which is the only enzyme able to cleave HS. Inhibiting heparanase with natural HS or HS-mimetics has been investigated for cancer treatments to inhibit metastases, but their efficacy in neuroinflammatory diseases has not yet been realised. This study investigates the use of a novel HS-mimetic Tet-29 in an animal model of MS, experimental autoimmune encephalomyelitis (EAE). We found that when Tet-29 was administered before or after the onset of disease, it significantly reduced lymphocyte accumulation in the central nervous system which, in turn, decreased disease severity in EAE. Tet-29's disease-modifying effect was associated with a rescue of BBB integrity as well as inhibition of activated lymphocyte migration across the BBB and choroid plexus in trans-well models with CD4+ and CD8+ T cells being the greatest affected by Tet-29. Under in vivo or in vitro homeostatic conditions, Tet-29 did not significantly affect steady state trafficking in contrast to the MS therapeutic natalizumab, an anti-VLA-4 monoclonal antibody. Together these results suggest that Tet-29 modulates, rather than abolishes, trafficking across CNS barriers.

15.2

The role of regulatory T cells in remyelination, following kappa opioid receptor agonist treatment

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Multiple sclerosis (MS), a demyelinating disease of the central nervous system, is increasing in prevalence in New Zealand. Currently, treatment options are limited to immunomodulatory agents and generalised symptom management. Kappa opioid receptor (KOR) agonists, like nalfurafine and U50, 488, have been shown to promote remyelination in experimental autoimmune encephalomyelitis (EAE), an animal model of demyelination. This has been correlated with a regression in demyelinating disease. However, the mechanisms governing this remyelination are still largely unknown. Our research suggests that FoxP3+ regulatory T cells are required for kappa opioid receptor agonist promotion of remyelination. We have demonstrated that in vivo neutralisation of regulatory T cell function with anti-CD25 antibody treatment abolished nalfurafine- and U50,488-mediated recovery from disease and spinal cord remyelination and led to an increased disease-associated mortality in all groups. Furthermore, selective genetic deletion of the kappa opioid receptor on regulatory T cells significantly impaired nalfurafine-mediated remyelination and recovery from disease compared to wild-type, nalfurafine-treated controls and led to an increased rate of disease relapse. These preliminary findings suggest regulatory T cells are crucial for nalfurafine-mediated remyelination and recovery from EAE, and that this protective effect is mediated through the kappa opioid receptor on regulatory T cells specifically. This research contributes to the understanding and development of therapeutics targeted at promoting remyelination within the central nervous system, which would directly address the cause of disability in MS – demyelination.

15.3

Texture analysis as a biomarker for Alzheimer's disease

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This review aims to assess the current state of texture analysis (TA) research in Alzheimer's disease (AD) and evaluate its potential benefits, limitations, and implications in diagnosing AD. A structured review was conducted using the Web of Science core collection and PubMed databases, employing search terms related to AD, MRI, MCI, and texture analysis. Notably, the Alzheimer's Disease Neuroimaging Initiative (ADNI) database was commonly used for participant recruitment, with the hippocampus and whole brain frequently chosen as regions of interest (ROIs) and the Gray-level co-occurrence matrix (GLCM) as the primary texture analysis method. Review findings indicate that texture analysis holds promise in AD classification and prediction, effectively distinguishing AD dementia from other dementia types such as Lewy body dementia. Consistent findings suggest that changes in hippocampal texture serve as a more sensitive biomarker for AD compared to hippocampal volume, as they capture different pathological markers. Moreover, incorporating texture analysis into predictive models along with other clinical information such as MMSE, gender, volume, and age improves the ability to predict the conversion from mild cognitive impairment (MCI) to AD, making texture analysis a valuable tool for early prediction of MCI to AD conversion. However, there is considerable heterogeneity among studies in terms of objectives, participant demographics, ROI selection, texture analysis methods, and classification techniques, all of which influence the findings. However, despite these variations, accurate AD prediction through texture analysis may facilitate targeted resource allocation, addressing the increasing disease burden. Thus, continued TA research is crucial for mitigating AD's impact.

15.4

Unique Alpha-synuclein strains enable the exploration of novel targets associated with Parkinson's disease risk genes

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Parkinson's disease (PD), the world's fastest growing neurodegenerative condition, affects around 10 million people, underscoring an immediate need for enhanced diagnostic and therapeutic methods. PD is marked by the accumulation of alpha-synuclein, resulting in dopaminergic neuron death causing a variety of motor and non-motor symptoms. This disease's heterogeneity, attributed to conformationally-distinct alpha-synuclein aggregates of varying pathogenicity, complicates the creation of disease-modifying treatments. While PD has traditionally been considered neuron-centric, recent research indicates non-neuronal cells, able to degrade alpha-synuclein, may play a pivotal role in disease progression. Building on this insight, our study hypothesises that investigating non-neuronal cells in a strain-specific manner could unveil novel therapeutic targets. We exposed human brain-derived pericytes to different alpha-synuclein strains and performed an RNAseq analysis, revealing distinct changes in gene expression, which were further validated using multiplex fluorescent immunohistochemistry. The expression of 48 proteins was assessed in human-derived pericytes, treated with alpha-synuclein and post-mortem brain tissue before quantifying successfully detected proteins using tissue microarrays. In vitro labelling revealed an increase in expression of BCL-XL, EBAG9 and PUM2 in treated cells. Co-localization analysis with cellular markers identified nine differentially expressed proteins in situ. Notably BCL-XL and ASAH1 are linked to PD risk genes. BCL-XL, an antiapoptotic protein associated with PINK1 mitophagy, exhibited increased microglial ($p=0.01$) and pericytic ($p=0.007$) load in PD. ASAH1, a lysosomal protein linked to GBA1, displayed an increased neuronal load ($p=0.02$) and a decreased vascular ($p=0.01$) load in PD. Ongoing investigation of these proteins could elucidate their association to PD-related genes and pathogenesis.

15.5

Nalfurafine facilitates recovery from cuprizone + rapamycin-induced demyelination

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The kappa opioid receptor (KOR) is a promising target for remyelinating therapies. Nalfurafine, a potent and selective KOR agonist, enhances recovery in both the experimental autoimmune encephalomyelitis (EAE) and cuprizone-induced demyelination mouse models. In the current study, we evaluated the effectiveness of nalfurafine utilising an extended demyelination model where rapamycin is administered alongside cuprizone to prevent spontaneous remyelination. Adult male C57BL/6J mice were administered 0.2% cuprizone mixed with powered chow and 10 mg/kg (i.p.) rapamycin once daily for 84 consecutive days. From days 85-126, mice received daily i.p. injections of nalfurafine (0.01 or 0.1 mg/kg), clemastine (10 mg/kg) or vehicle. At several time points throughout the procedure, animals were assessed on locomotor activity tests, horizontal bar tests, and on mouse motor skill sequence (MOSS) wheels. We also quantified axonal health (g-ratios) using transmission electron microscopy, overall myelin levels using BlackGold II histology, and oligodendrocyte numbers using immunofluorescence. Cuprizone + rapamycin treatment resulted in hyperlocomotion, poorer horizontal bar scores, and less distance travelled on the MOSS wheels. Partial recovery was observed on both the horizontal bar and MOSS wheel tests over time, which was facilitated by nalfurafine treatment. Cuprizone + rapamycin treatment also produced prolonged demyelination and poorer axonal health, which was accompanied by a loss of mature oligodendrocytes. Nalfurafine treatment enhanced remyelination, improved axonal health, and resulted in a greater number of mature oligodendrocytes. These data indicate that nalfurafine enhances recovery from cuprizone + rapamycin-induced demyelination and provides strong preclinical evidence for the efficacy of KOR agonists as remyelinating agents.

15.6

Potential role of deregulated Histone Deacetylase 4 (HDAC4) in the pathogenesis of temporal lobe epilepsy

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Temporal lobe epilepsy (TLE) is a neurological disorder characterized by recurrent seizures and cognitive deficits making it imperative to understand its molecular basis. HDAC4 dysregulation is associated with several neurological disorders but its role in TLE is poorly understood. We thus aimed to analyse HDAC4 expression and characterize its interaction with its substrate-serum response factor (SRF) in TLE. For this purpose we developed the pilocarpine model of TLE and analysed the mRNA and protein levels of HDAC4 and SRF along with their interaction in the hippocampus, anterior temporal lobe and cortex using qRT-PCR, western blotting and co-immunoprecipitation respectively. Cell specific HDAC4 expression was analysed using an immunofluorescence assay. Our results revealed a significant increase in HDAC4 and SRF levels in the TLE model hippocampus. Further a decrease in HDAC4-SRF interaction was found in the epileptic hippocampus suggesting TLE related HDAC4-SRF dysregulation. We also established a clinical correlation between these findings using epileptic patient samples. These results thus, provide an outlook into targeting HDAC4 as a potential therapeutic target in TLE.