SPEAKER ABSTRACTS

DAY 1 | October, 24 | 2022

SESSION 1 | Motor neuron disease | PLENARY

9:05

Angela Genge | Director of the Clinical Research Unit | Montreal Neurological Institute

Refining clinical trials in Amyotrophic lateral sclerosis (ALS)

This presentation will cover all current considerations in clinical trial design in ALS/MND from Phase 1 FIH to Phase 3 pivotal. The use of biomarkers in various programs including biological e.g. neurofilament light, electrophysiological e.g. CMAP, SDTC, imaging will be included. Also the effective use of adaptive designs to shorten the development period will be reviewed. Finally a number of current programs will be discussed to illustrate each of these points

9:45

Eneida Mioshi | Professor | School of Health Sciences, Norwich Medical School, University of East Anglia

Managing behavioural symptoms in MND: the MiNDToolkit for families and healthcare professionals

Cognitive and behavioural symptoms in MND have been well recognised, with various clinical assessments available for detection in clinical and research settings. Many of these symptoms overlap with those observed in FTD, such as apathy, disinhibition, rigidity, deficits in social cognition and lack of insight. As such, people with MND and/or FTD may not be fully aware of the behavioural changes they are presenting with, leading to challenging situations for family members, as well as issues in clinical decision making.

Despite recognition of such difficult symptoms, no standardised approaches in managing these exist in MND. Not surprisingly, questions about 'what should I do?' constantly arise from families and healthcare professionals.

MiNDToolkit, a novel psychoeducational intervention for carers, is currently being tested in a randomised feasibility trial in the UK. MiNDToolkit is hybrid; the intervention is delivered via the online platform as well as through trained healthcare professionals. For this reason, MiNDToolkit has its own bespoke online platform that brings together carers, healthcare professionals and researchers.

In this talk you will hear about the development, content, and preliminary findings of the MiNDToolkit randomised feasibility trial.

SPEAKER ABSTRACTS

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SESSION 2 | Movement disorders | PLENARY

10:25

Emma Devenney | NHMRC post-doctoral fellow | BMC, The University of Sydney

Hallucinations in non–Parkinson's disease neurodegeneration - evidence from cognition, genetics and neuroimaging

Objective: To explore the rate and underlying cognitive, behavioural and neural associations of hallucination development in non-Parkinson's neurodegeneration

Methods: Patients were recruited sequentially to this study and underwent a clinical examination to determine the presence of hallucinations, a battery of neuropsychological tests and MRI. A well-characterised homogenous group of patients with MND-FTD and well characterized hallucinations were genetically and demographically matched to a group without hallucinations and a healthy control cohort. Data was analysed according to 3 levels; 1) the relationship between neural structures, cognition, behaviour and hallucinations and 2) the impact of the C9orf72 expansion and 3) hallucination subtype on expression of hallucinations.

Results: From a transdiagnostic perspective, hallucinations were present in 55 of 449 patients (12.2%) across the spectrum of disorders. Of these, 60% were visual in nature only, 40% were auditory with 40% a combination of both. Specifically within the diagnostic categories, hallucinations were present in 22% of MND-FTD cases, 7% of SD cases, 11% of CBS cases, 14% of AD cases, 11% of lvPPA cases and 9% of PCA cases. There were no hallucinations in any of 35 cases of nfv PPA or in 21 cases of PSP. Attentional and working memory measures differed between groups (all $p<0.02$) with hallucinators making more frequent attentional and processing speed errors with evidence of structural changes centred on the prefrontal cortex, caudate and cerebellum ($p<0.001$). Attentional processes were also implicated in C9orf72 carriers with hallucinations as well as visual functions ($p<0.05$) while structural changes were focused on the thalamus ($p<0.001$). Patients with visual hallucinations in isolation showed a similar pattern with emphasis on cerebellar atrophy. A predictive model suggested that attention and working memory deficits were the best predictors of hallucination status ($p<0.05$)

Conclusion: Attentional and working memory subsystems and related distributed brain structures are implicated in the generation of hallucinations in MND-FTD that dissociate across C9orf72, sporadic MND-FTD and for the visual subtype of hallucinations.

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SESSION 2 | Movement disorders | PLENARY

11:15

Michele Hu | Professor of Clinical Neuroscience | Consultant Neurologist Nuffield Department of Clinical Neurosciences

From go to woe: Using idiopathic rapid-eye movement sleep behavior disorder (iRBD) to better understand and treat Lewy Body Disease

Perhaps the primary health challenge of the 21st Century is achieving a cure for neurodegenerative disorders including Alzheimer's and Parkinson's disease. The numbers of people living with Parkinson's globally are projected to double from 2015 to 2040, and we are already seeing effects of this worldwide expansion for which we are ill prepared. Since 1989 billions of dollars have been invested by the pharmaceutical industry in the search for a Parkinson's cure, with 16 drug compounds all testing negative in completed large-scale trials. These studies focused on patients with an established diagnosis, based according to current criteria on the presence of clinical motor features. We need to take stock and consider the reasons for this failure, as it may be that efforts have been made too late in the neurodegenerative cascade. In the search for a cure or effective disease modification, focus has therefore increasingly shifted to studying earlier stages with calls for a new research framework encompassing clinical features, pathological findings, genetics and molecular mechanisms to redefine Parkinson's. My talk focuses on iRBD, a prodromal form of both Parkinson's and Dementia with Lewy Bodies, providing a much earlier disease phase for targeted intervention with higher densities of salvageable brain neurons, but without the confounding placebo/nocebo effects of symptomatic therapies. My vision is to help researchers improve stratified iRBD participant selection for clinical trials, and to provide an outcome measure that is sensitive to change, quick to administer and cost effective; allowing participants to be assessed in clinic and at home.

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SESSION 2 | Movement disorders | PLENARY

12

Paula Loveland | Geriatrician at The Royal Melbourne Hospital | PhD candidate at the Walter and Eliza Hall Institute of Medical Research, Melbourne

Establishing robust biomarkers for DLB

Timely and accurate diagnosis of Lewy body dementia is challenging, and it remains an under-recognised and often misdiagnosed form of dementia. Therefore, biomarkers that provide objective evidence of pathological change early in the disease course are of considerable interest to patients and clinicians. Unfortunately, several of the currently recognised 'supportive' diagnostic biomarkers are not available in Australia or are only in highly resourced research settings.

Recent developments towards novel biomarkers for Lewy body dementia offer improved understanding of disease pathogenesis, identification of new therapeutic targets, and support for trials of disease-modifying therapies. Promising strategies include imaging and biofluid analysis, including peripheral blood. This talk will discuss current and emerging biomarkers for Lewy body dementia, and the challenges that must be addressed to translate candidate biomarkers into the clinic

SESSION 3 | Motor neuron disease | ForeFront

1:45

Amr Abdeen | PhD candidate | BMC, The University of Sydney

Does wild-type SOD1 proteinopathy cause dopamine cell loss?

Our group previously reported abnormal misfolding and deposition of wildtype SOD1 in the Parkinson's disease substantia nigra pars compacta (SNc), associated with a significant reduction in regional copper levels. We hypothesized that SOD1 proteinopathy contributes to dopamine neuron loss in this disorder, and thus developed and characterized a novel murine model (hSOD1WT/mCtr1+/-) expressing wildtype human SOD1 and brain copper deficiency to test this idea. Density of tyrosine hydroxylase (TH)+-dopamine neurons in the SNc did not differ between our mouse model and relevant control lines, including wildtype mice at six weeks and 3 months of age, however dopamine neuron density was reduced by 18% reduction in hSOD1WT/mCtr1+/- at 6 months of age compared with wildtype mice. At 12 months of age, a significant decrease in dopamine neuron density was observed between hSOD1WT/mCtr1+/- mice compared with both wildtype (22%, $p=0.0003$) and hSOD1WT (17%, $p=0.049$) control mice, while Ctr1+/- control mice of this age exhibited a 16% decrease in dopamine neuron density ($p=0.062$). Marked motor deficits, measured using rotarod performance, were exhibited by hSOD1WT/mCtr1+/- mice, compared with wildtype mice at both 6 and 12 months of age. Immunofluorescent dual-labelling of misfolded SOD1 and TH demonstrated an abundance of aggregated SOD1 protein inside and outside TH+-dopamine neurons within the SNc of 6- and 12-month hSOD1WT/mCtr1+/-, but not in wildtype mice. These data support our hypothesis that wildtype SOD1 is prone to misfolding in a cellular environment of copper deficiency and that resultant SOD1 proteinopathy contributes to the SNc dopamine neuron death.

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SESSION 3 | Motor neuron disease | ForeFront

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Shu Yang | Post-doctoral Reseach Fellow | Centre for MND Research, Macquarie University

The role of CHCHD10 in MND

In 2014, novel mutations were found in the gene encoding the mitochondria coiled-coil-helix-coiled-coil-helix domain containing 10 protein (CHCHD10) in patients with MND/FTD spectrum of neurological disorders, demonstrating a mitochondria origin of disease [1]. We have shown that CHCHD10 was significantly downregulated in MND and FTD patient brain and spinal cord tissues [2]. However, the exact molecular mechanism of CHCHD10 in MND pathogenesis is not well understood. In this study, we aim to determine whether CHCHD10 mutation causes mitochondria abnormality and whether it changes the behaviour of the major MND disease protein TDP-43. We co-transfected the wild type or an MND-linked CHCHD10 mutation (CHCHD10S59L) together with a wild type or TDP-43 with regulatable nuclear localisation signal (rNLS-TDP-43) in HEK293 cells and examined mitochondria morphology and TDP-43 localisation using immunocytochemistry. We found that CHCHD10S59L led to significantly reduced mitochondria branching length and number of mitochondria branching networks. The CHCHD10 mutation also led to increased TDP-43 mitochondria accumulation, a known hallmark MND pathology. Additionally, we have found that overexpression of wild type CHCHD10 is beneficial at reducing pathological TDP-43 burden. In conclusion, we have shown that CHCHD10 mutation led to unwanted TDP-43 mitochondria entry. This could be due to mitochondria damage caused by CHCHD10S59L as well as aberrant interactions between CHCHD10S59L and TDP-43. Our results suggest that CHCHD10 plays roles in regulating TDP-43 mitochondria entry and regulating the level of CHCHD10 may be beneficial in treating MND.

2:15

Sicong Tu | NHMRC Early Career Development Fellow - CJ Martin-Overseas Biomedical Fellowship | BMC, The University of Sydney

The neuroimaging signature of cortical hyperexcitability in ALS

Glutamate-induced excitotoxicity is a primary mechanism driving motor neuron death in ALS. In-vivo quantification of motor-associated glutamate concentration, however, has yet to identify a consistent pattern of abnormality. Existing MR spectroscopy (^{1}H-MRS) studies have reported varying patterns of elevated, reduced, or no significant change in glutamate concentrations in patients. We hypothesized that variability in glutamate concentration is mediated by the severity of underlying upper motor neuron (UMN) dysfunction. Specifically, presence of cortical hyperexcitability drives abnormal elevation in glutamate concentration. We examined whether clinical phenotyping of sub-clinical UMN dysfunction, as defined by a reduction or absence of short-interval intracortical inhibition (SICI), can account for ^{1}H-MRS quantification of in-vivo glutamate concentration in ALS. Findings indicate elevated Glx/NAA is a consistent signature of cortical hyperexcitability in ALS patients and divergent trajectory of longitudinal metabolite change. TMS clinical phenotyping of UMN dysfunction improves consistency and interpretability of imaging markers of motor pathology and presents a novel avenue for validation as clinical biomarkers in ALS

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SESSION 3 | Motor neuron disease | ForeFront

2:30

Annika van Hummel | Postdoctoral Researcher | Dementia Research Centre (DRC), Macquarie University

New Mouse models of MND/FTD

Motor Neuron Disease (MND) and Frontotemporal Dementia (FTD) are multi-factorial diseases with distinct but overlapping symptoms and pathology. Unfortunately, no disease-modifying drugs are available for either disease in part due to the complexity of underlying mechanisms. While clinical findings from patient cohorts shed light on many aspects of disease, full characterisation of early stages of disease, and the separation of individual causative or risk factors is difficult. Conversely, cell models can provide insight into individual mechanisms, but can only reproduce some functions of an in vivo system. Mouse models therefore provide the possibility of studying individual mechanisms or factors within a fully integrated system. Using state-of-the-art genetic technology and full characterisation of symptoms and pathology throughout disease progression, mouse models provide a reliable method of recapitulating and understanding disease mechanisms, and developing new, targeted therapies targeting these pathways. This presentation will provide an update of the characterisation of new mouse models of MND/FTD being used in the DRC.

SESSION 4 | Movement disorders | ForeFront

3:15

Elie Matar | Neurologist and Sleep Medicine Fellow | Woolcock Institute of Medical Research, The University of Sydney

Dynamic network impairments underlie fluctuations in Lewy body dementia

Cognitive fluctuations are a characteristic and distressing disturbance of attention and consciousness seen in patients with Dementia with Lewy bodies and Parkinson's disease dementia. It has been proposed that fluctuations result from disruption of key neuromodulatory systems supporting states of attention and wakefulness which are normally characterized by temporally variable and highly integrated functional network architectures. In this study, patients with DLB (n=25) and age-matched controls(n=49) were assessed using dynamic resting state fMRI. A dynamic network signature of reduced temporal variability and integration was identified in DLB patients compared to controls. Reduced temporal variability correlated significantly with fluctuation-related measures using a sustained attention task. A less integrated (more segregated) functional network architecture was seen in DLB patients compared to the control group, with regions of reduced integration observed across dorsal and ventral attention, sensorimotor, visual, cingulo-opercular and cingulo-parietal networks. Reduced network integration correlated positively with subjective and objective measures of fluctuations. Regions of reduced integration and unstable regional assignments significantly matched areas of expression of specific classes of noradrenergic and cholinergic receptors across the cerebral cortex. Correlating topological measures with maps of neurotransmitter/neuromodulator receptor gene expression, we found that regions of reduced integration and unstable modular assignments correlated significantly with the pattern of expression of subclasses of noradrenergic and cholinergic receptors across the cerebral cortex. Altogether, these findings demonstrate that cognitive fluctuations are associated with an imaging signature of dynamic network impairment linked to specific neurotransmitters/neuromodulators within the ascending arousal system, highlighting novel potential diagnostic and therapeutic approaches for this troubling symptom.

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SESSION 4 | Movement disorders | ForeFront

3:30

Laura Hughes | PhD candidate | BMC, The University of Sydney

Effect of LRRK2 protein and activity on stimulated cytokines in human monocytes and macrophages

Genetic variation in leucine-rich repeat kinase 2 (LRRK2) is strongly implicated in the risk of developing Parkinson's disease (PD) and this gene constitutes a potential therapeutic target. High expression of LRRK2 is observed in peripheral immune cells and evidence indicates a role for LRRK2 in immune cell function and the regulation of inflammatory pathways. However, the biological function of LRRK2 and mechanisms by which it may promote PD pathogenesis remains unclear. Therefore, this study sought to determine how LRRK2 protein levels and activity modulate inflammatory cytokines in human immune cells. Isogenic induced pluripotent stem cells (iPSC) with the LRRK2-activaing G2019S mutation, wild-type LRRK2, and LRRK2 knock-out were differentiated to monocytes and macrophages and stimulated with inflammatory toll-like receptor agonists. It was found that the LRRK2 G2019S mutation potentiated inflammation as shown by significantly higher levels of cytokines in tissue culture media following innate immune pathway stimulation, thereby supporting the emerging concept that peripheral immune dysfunction may contribute to PD.

3:45

Claire O'Callaghan | NHMRC Early Career Fellow | BMC, The University of Sydney | Behavioural and Clinical Neuroscience Institute, University of Cambridge

Translating noradrenergic drugs to neurodegenerative diseases

The locus coeruleus–noradrenaline system plays an extensive role in cognition and behaviour. It is among the earliest and most prominent sites of pathology in neurodegenerative diseases of ageing, including Alzheimer's and Parkinson's disease. Improving our ability to detect changes in this system in vivo has implications for early diagnosis and for tracking treatment interventions. My talk will focus on the locus coeruleus–noradrenaline system in Parkinson's disease – in particular, the role it plays in neuropsychiatric and cognitive symptoms. Using a combined approach, we characterised the locus coeruleus using 7T MRI and probed the system in a pharmacological study with the noradrenergic reuptake inhibitor atomoxetine. Together, these findings advance ideas around noradrenergic therapy in Parkinson's disease and hopefully provide some new insights into how the locus coeruleus–noradrenaline system orchestrates human behaviour.

4

Adahir Labrador Garrido | Research fellow | BMC, The University of Sydney

High content imaging of lysosomal phenotypes in iPSC-derived dopamine neurons

The Autophagy-Lysosome Pathway (ALP), one of the two main ways cytosolic and misfolded proteins are degraded, has been linked with neurodegenerative diseases and specifically with Parkinson's Disease. In this protocol we describe the use of a high-content imaging system and it's imaging software to analyse live and fixed neuronal cultures for the measurement and characterization of lysosomal phenotypes. The aim of this protocol is to create an automated analysis pipeline that can be used to process large volumes of data for any cell culture for the measurement of lysosomal and autophagosomal phenotypes under different treatment conditions.

SPEAKER ABSTRACTS

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SESSION 5 | Frontotemporal dementia | PLENARY

9:20

Patricia Lillo | Associate Professor | Departamento de Neurología Sur/Neurociencia, Facultad de Medicina, Universidad de Chile & Geroscience Center for Brain Health and Metabolism

South American perspective on frontotemporal dementia and ALS

This presentation will cover all current considerations in clinical trial design in ALS/MND from Phase 1 FIH to Phase 3 pivotal. The use of biomarkers in various programs including biological e.g. neurofilament light, electrophysiological e.g. CMAP, SDTC, imaging will be included. Also the effective use of adaptive designs to shorten the development period will be reviewed. Finally a number of current programs will be discussed to illustrate each of these points

9:55

Sharon Savage | Lecturer | School of Psychological Sciences, The University of Newcastle

Language retraining interventions in FTD

Cognitive and behavioural symptoms in MND have been well recognised, with various clinical assessments available for detection in clinical and research settings. Many of these symptoms overlap with those observed in FTD, such as apathy, disinhibition, rigidity, deficits in social cognition and lack of insight. As such, people with MND and/or FTD may not be fully aware of the behavioural changes they are presenting with, leading to challenging situations for family members, as well as issues in clinical decision making.

Despite recognition of such difficult symptoms, no standardised approaches in managing these exist in MND. Not surprisingly, questions about 'what should I do?' constantly arise from families and healthcare professionals.

MiNDToolkit, a novel psychoeducational intervention for carers, is currently being tested in a randomised feasibility trial in the UK. MiNDToolkit is hybrid; the intervention is delivered via the online platform as well as through trained healthcare professionals. For this reason, MiNDToolkit has its own bespoke online platform that brings together carers, healthcare professionals and researchers.

In this talk you will hear about the development, content, and preliminary findings of the MiNDToolkit randomised feasibility trial.

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SESSION 6 | Dementia | PLENARY

11

Michael Hornberger | Professor of Applied Dementia Research | Norwich Medical School University of East Anglia

Citizen science in dementia

This presentation will cover all current considerations in clinical trial design in ALS/MND from Phase 1 FIH to Phase 3 pivotal. The use of biomarkers in various programs including biological e.g. neurofilament light, electrophysiological e.g. CMAP, SDTC, imaging will be included. Also the effective use of adaptive designs to shorten the development period will be reviewed. Finally a number of current programs will be discussed to illustrate each of these points

11:30

Claire O'Connor | Research fellow | Conjoint Lecturer | Centre for Positive Ageing, HammondCare

Non-pharmacological interventions to support behaviour change, everyday functioning and wellbeing in dementia

The impacts of dementia are broad, leading to changes in behaviour and everyday functioning for the person with dementia, and wellbeing for both the person with dementia and their family carers. While no cure exists, non-pharmacological interventions to support people living with dementia are a vital approach recommended in clinical practice guidelines. There are many non-pharmacological interventions described in the research, however, this is not reflected in the real-world options available to people living with dementia in the community. For example, our survey of n=68 families living with younger onset dementia identified a need for better access to behaviour support services. In response to this need, we have been investigating the use of Positive Behaviour Support (PBS) for families living with dementia. In parallel with this work to support behaviour change in dementia, work is being done to bring interventions aimed at promoting wellbeing and maximising everyday functioning from research into the real-world. Specifically, two separate projects are currently using implementation science to evaluate Arts on Prescription at Home (AoP@Home) and reablement for people living with dementia in the community. These projects focusing on various non-pharmacological approaches will be described, with future directions discussed.

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SESSION 6 | Dementia | PLENARY

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Amy Brodtmann | Professor of Neurology | Department of Neurosciences, Central Clinical School, Monash University

Nuns and orthodoxies: charting vascular neurodegeneration

The prevailing dementia research orthodoxy of the latter half of the twentieth century was that neurodegeneration must arise from toxic brain proteins. There is now compelling evidence that vascular health is the greatest determinant of late-life cognition, including from community-based post-mortem studies (Nun study) finding that vascular brain burden determines cognitive profiles. Brain atrophy precedes and predicts cognitive decline in many neurodegenerative syndromes, but the trajectories of brain volume loss and cognitive impairment in stroke survivors are poorly understood. Brodtmann has introduced the concept of vascular neurodegeneration via her findings from the Cognition And Neocortical Volume After Stroke (CANVAS) study. She has demonstrated that stroke survivors have greater predicted brain age, greater signs of structural brain aging, extensive white and grey matter degeneration, and accelerated brain volume loss associated with cognitive changes. The use of imaging biomarkers in dementia intervention trials has several advantages over more traditionally used cognitive assessments, as atrophy rates are not as dependent on language or post-code. Describing the trajectories of brain volume loss in people with vascular contributions to their cognitive profile has increased our mechanistic understanding of neurodegeneration in high-risk populations and informed trial design to prevent post-stroke and vascular cognitive impairment.

SPEAKER ABSTRACTS

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SESSION 7 | Frontotemporal dementia | ForeFront

1:30

Fiona Kumfor | Associate Professor, NHMRC Career Development Fellow
Clinical Neuropsychologist | BMC,CPC, The University of Sydney

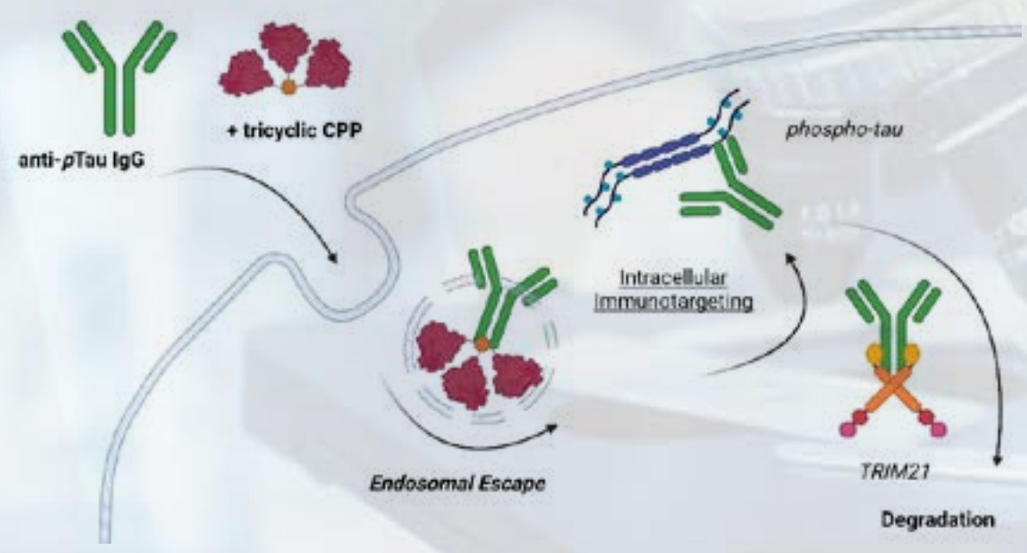
Antisocial/criminal, risk behaviours in FTD

Behavioural-variant frontotemporal dementia (bvFTD) and semantic dementia (SD) are characterised by impaired social cognition and behavioural changes. In some cases, patients may also show behaviours which may be considered antisocial or criminal. The few studies examining this phenomenon, however, have used retrospective case reviews, or have comprised relatively small samples. We developed a novel, purposefully designed tool - the Misdemeanours and Transgressions Screener (MATS) – to examine the propensity for criminal risk behaviours in FTD. Sixty-four bvFTD, 30 SD, 13 right-SD, 8 progressive nonfluent aphasia, 37 Alzheimer's disease (AD) patients and 53 demographically-matched controls were recruited. The MATS measured behaviour across 10 domains: traffic violations, theft, avoiding payments, verbal abuse, physical abuse, inappropriate sexual behaviour, public indecency, property damage, illegal drugs, and financial or professional recklessness. Irrespective of diagnosis, 46% of participants reported at least 1 criminal risk behaviour, with the most common behaviours being verbal abuse (n=38), financial/professional transgressions (n=31), traffic violations (n=20) and inappropriate sexual behaviours (n=15). In 21.4% of cases, this behaviour led to involvement of the police/authority figures. Logistic regression showed that a diagnosis of bvFTD and longer disease duration predicted the presence of criminal risk behaviours. These data suggest that criminal risk behaviours are much more common than previously thought. Future research is needed to understand why these behaviours develop, as well as how to educate police and the criminal justice system about the management of criminal risk behaviours in people with dementia.

1:45

Ole Tietz | Postdoctoral Research Fellow | Dementia Research Centre, Macquarie University

Towards Intraneuronal Immunotherapy



The intraneuronal environment hosts the vast majority of toxic tau filaments that characterise neurodegenerative diseases. The development of small-molecule drugs for tau remains very challenging, due to its naturally unfolded 3D structure; however, efforts to develop active and passive immunotherapies against tau aggregates are promising but have yet to yield a clinically approved treatment. A major obstacle in the development of tau immunotherapies is their poor central nervous system (CNS) bioavailability and inability to access the intraneuronal environment.

We developed an approach to delivering antibodies and antibody fragments into the cytosol and nucleus of cells using trimeric cell-penetrating peptides (CPPs). Our studies identify a tricyclic Tat peptide construct that enables intracellular delivery of functional immunoglobulin-G antibodies and Fab fragments via non-toxic, endocytic mechanisms at effective concentrations as low as 1 µM. We demonstrate successful delivery in live primary neuronal cells, as well as human brain organoids. This delivery system enables functional interaction of antibodies with cytosolic and nuclear proteins and is important step towards the development of intraneuronal immunotherapies to treat neurodegenerative diseases characterised by intraneuronal deposits of tau filaments.

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SESSION 7 | Frontotemporal dementia | ForeFront

2

David Foxe | Senior Research Officer | Clinical Neuropsychologist | Frontier, BMC, The University of Sydney

Improving the diagnostic accuracy and management of primary progressive aphasia

The Addenbrooke's Cognitive Examination-III (ACE-III) is a widely used cognitive screening tool for dementia. Here, we investigated how the ACE-III could differentiate the primary progressive aphasia (PPA) variants based on item-by-item performances and created an interactive diagnostic calculator which predicts the PPA variant based on a patient's individual ACE-III profile. Overall, our ACE-III PPA calculator demonstrates sound accuracy in differentiating the PPA variants, with sensitivity, specificity, and precision rates ranging between 79.9% and 100%. Verification of the calculator in a separate, neuropathologically confirmed PPA sample further revealed high classification accuracy in the semantic variant PPA and promising trends in the logopenic and non-fluent variant PPAs. We have now implemented its use in the FRONTIER Research Clinic. Promisingly and based on the findings from this study, we have engaged with SAP Digital Analytics to build other sophisticated data-driven clinical tools which hope to i) detect PPA from other dementia syndromes and ii) predict the disease trajectories of individual patients. Future directions and caveats of this prospective project will be discussed.

2:15

Samantha Knott | Research Assistant | Dementia Research Centre, Macquarie University

Expanding the spectrum of glial-predominant disorders: globular glial tauopathy

Expanding the spectrum of glial-predominant disorders: globular glial tauopathy

Background: Globular glial tauopathies (GGT) belong to the group of frontotemporal lobar degenerations and have overlapping clinical, genetic and pathological features to other neurodegenerative disorders. To date, co-existing proteinopathies have only been reported in a small proportion of GGT cases.

Methodology: An international multicentric study was initiated to collect and evaluate GGT cases. This study focused on the prevalence and type of co-existing proteinopathies including Aβ, TDP-43 and α-synuclein, which were examined in multiple brain regions.

Results: The cohort comprises 73 pathologically confirmed GGT cases collected from 17 centres as part of the GGT consortium. 36 (49%) cases had Aβ plaques, which included Thal phases 1 or 2 (n=16), phases 3 or 4 (n=14), and phase 5 (n=6). Cerebral amyloid angiopathy was found in 16 cases (22%). TDP-43 pathology was observed in 22 cases (30%). Limbic predominant age-related TDP-43 encephalopathy (LATE) neuropathological change was observed in 17 cases (23%; stage 1=3 cases, stage 2=10 cases, stage 3=4 cases). An additional 5 cases had an unusual constellation of neuronal and non-neuronal TDP-43 pathology that could not be classified. Lewy bodies were found in 12 cases (16%), which included one case with amygdala-predominant, four cases with brainstem-predominant, five cases with limbic-predominant, one case with neocortical-predominant Lewy bodies, and one case that could not be classified into current criteria.

Conclusion: This study highlights the spectrum of co-existing proteinopathies in GGT. Evaluating mixed pathologies has implications for biomarker and therapy development and for determining clinicopathological correlations

SPEAKER ABSTRACTS

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SESSION 8 | Dementia | ForeFront

3

Laura Dewitte| Postdoctoral researcher | Faculty of Psychology and Educational Sciences, KU Leuven | BMC, The University of Sydney

Understanding quality of life in dementia: a network analysis comparing self and informant reports

Quality of life (QOL) refers to the global evaluation of a person's emotional, social and physical well-being and their daily functioning. QOL scales used in dementia research typically capture a wide range of life domains, such as affect, cognition, relationship quality, health, living circumstances, etc. While these domains are often aggregated into one overarching QOL score, it seems unlikely that a single latent variable can account for the complexity of QOL in dementia. Further, the reliance on composite scores can mask important information regarding the experiences of people with dementia.

In the present study, we approached QOL in dementia as a multi-dimensional construct emerging from the complex interplay between its different elements. Using a widely used QOL scale (the Quality of Life in Alzheimer's Disease scale; QOL-AD; Logsdon et al., 1999), we employed network analysis to examine the underlying structure of self-rated (n = 118) and informant-rated (n = 127) QOL-AD scores, as rated by a transdiagnostic group of patients with dementia and their carers (e.g., spouse, child). More specifically, we estimated a regularized partial correlation network for each group using the graphical LASSO procedure. Results suggest important differences in terms of the structure and relationships between different QOL elements, suggesting the experience of QOL differs depending on the viewpoint of the patient and carer. Our findings will be discussed in relation to understanding and improving the well-being of people living with dementia and their carers.

3:15

Clement Loy | Professor of Clinical Epidemiology | Public Health, School of Public Health, The University of Sydney

RNA Therapy for Neurodegeneration: reflections on the Huntington Disease Trials

Clement is a cognitive neurologist with research interests in molecular genetics and clinical epidemiology. He has had the privilege of caring for families with Huntington Disease since 2000, with a special focus in clinical trials. He serves the wider community as a member of the Pharmaceutical Benefits Advisory Committee.

In his talk Clement will discuss about the first Anti-Sense Oligonucleotide trials for people with Huntington disease, which were carried out in the late 2010s, and halted in 2021. He will summarise the preliminary findings from these trials and reflect on their implications.

SPEAKER ABSTRACTS

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SESSION 8 | Dementia | ForeFront

3:30

Gabriel Wainstein | PhD candidate | BMC, The University of Sydney

The role of the locus coeruleus in shaping adaptive cortical melodies

Neural dynamics are shaped and constrained by the projections of a small nucleus in the pons: the noradrenergic locus coeruleus (LC). Much like a bow to the brain's violin, activity in the LC lacks content specificity, but instead dynamically shapes the excitability and receptivity of neurons across the brain. In this talk, I will explain how the style of the LC technique, which is analogous to different firing modes in the LC, affects distinct activity patterns in the rest of the brain. Through this analogical lens, we provide intuitive insights into how the complex activity of the LC acts to coordinate adaptive neural dynamics both in health and disease

3:45

Sam Lane | PhD candidate | Drug Discovery Lab, The University of Sydney

Development of vascularised human brain models to improve translation in Alzheimer's disease drug discovery

As classical cell culturing techniques falter in their ability to produce safe and effective therapies for central nervous system (CNS) diseases, modern techniques such as 3D culturing, induced pluripotent stem cells and bioprinters can expand translational capacity. Endothelial dysfunction is a hallmark of many diseases of the CNS, yet current research efforts are often performed in less-relevant cell types (e.g. immortalized cell lines or non-human cell lines/animal models) and in 2D culture systems which fail to recapitulate the physicochemical complexities of the native 3D environment. The Rastrum is a novel 3D bioprinter developed by Inventia Life Science, which reproducibly seeds cells in functionalized polyethylene glycol (PEG) hydrogels. Using iPSC-derived brain microvascular endothelial cells (iBMECs), we show that standard media capable of maintaining these cells in 2D is insufficient to support viability and morphological development in this 3D bioprinted PEG hydrogel. We show that iBMEC viability is better supported by a more richly supplemented media, and by extended or tapered ROCK inhibition. Our optimised media composition can support the long-term culture of iBMECs, including development of typical vascular network structures that express cell-type specific proteins. This in-vivo-relevant model serves as a foundation for continued study into CNS and vascular pathologies, with the potential for addition of other relevant cell types, and scalability for drug discovery applications.