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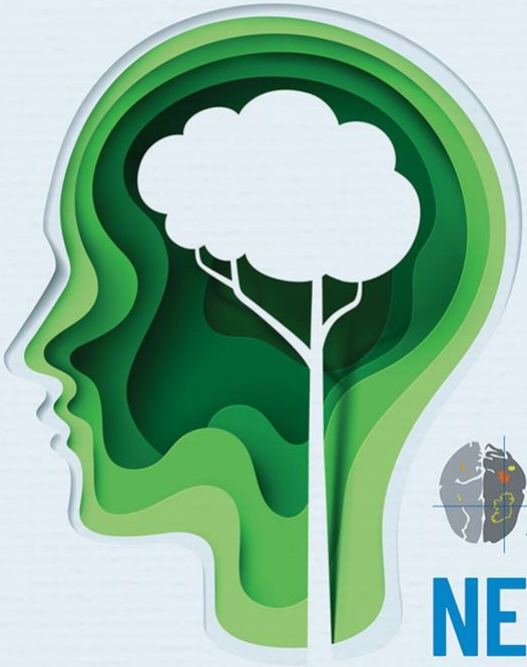

Neuroscience Ireland

NEUROSCIENCE IRELAND CONFERENCE 2023

RCSI, Dublin
29-30 AUG '23

ABSTRACT BOOK

SCAN FOR MORE INFORMATION OR VISIT bit.ly/3MVKh2C

RCSI LEADING THE WORLD TO BETTER HEALTH

Organising Committee

Dr Jennifer Dowling (Lead) – Royal College of Surgeons in Ireland

Dr Andreas Grabrucker – University of Limerick
Dr Cian O' Connor – Royal College of Surgeons in Ireland
Daniela AD Costa – University of Galway
Prof. Karen Doyle – University of Galway
Dr Niamh Connolly – Royal College of Surgeons in Ireland
Dr Niamh O' Sullivan – University College Dublin

Acknowledgements

The organization of this conference has been supported by many teams inside and outside of RCSI. We would like to acknowledge the support of all RCSI administrative and facilities staff, the Neuroscience Ireland council and all others who have helped make this event possible.

INDEX

WELCOME MESSAGE

Dear Colleagues,

Welcome to Neuroscience Ireland 2023 in the Royal College of Surgeons in Dublin! We are looking forward to a fantastic 2-days of Irish Neuroscience, showcasing national and international experts and early career researchers from across the island of Ireland.

This conference could not have happened without the local organising committee led by Dr Jennifer Dowling, The Dementia Research Network Ireland and The Alzheimer Society of Ireland - our partners at this event, our sponsors, speakers, poster presenters and all of our members. Thank you all!

We are looking forward to a great scientific and social programme and a wonderful opportunity to network and reconnect!

Professor Karen Doyle, President, Neuroscience Ireland

CONFERENCE GREEN INITIATIVES

As researchers we can all do our part to make our research activities more sustainable.

At the Neuroscience Ireland conference this year, we have made a number of efforts to reduce the climate impact of our activities:

- The programme and book of abstracts is solely available in digital format, without any printed copies.
- Fewer meat-based options for lunch and the banquet dinner enable us to reduce the carbon footprint associated with food. We were delighted that ~20% of attendees specified vegetarian/vegan on their registration forms.
- There are opportunities to refill your water bottle on site.
- Single-use coffee cups are no longer available in the RCSI canteens, and the use of single-use crockery/cutlery has been minimised.

We encourage all researchers to strive for Green Lab certification in their research labs. Speak to Niamh Connolly at RCSI (niamhmconnolly@rcsi.ie) for more information.

EARLY CAREER RESEARCH NETWORK (NSI-ECRN)

On the back of the 2020 Neuroscience Ireland Young Investigator Symposium, the NSI-ECRN was established as a virtual forum for Neuroscience Postgrads and Postdocs to discuss their research, share technical expertise, help foster collaboration, and grow the Neuroscience community across Ireland.

The ECRN strives to develop a community of like-minded students, researchers, and academics to create a platform for scientific knowledge exchange, communication, publication, and outreach.

Part of THE ECRN virtual landscape, every two years, we organise the Young Investigator Symposium. The next symposium will take place next year.
We also host the ***NeuroConnect* forum** – a monthly seminar series to facilitate advertisement, engagement, and knowledge exchange related to technical/informative topics. Interested?

- Register for the Zoom Link of future NeuroConnect Meetings
- Click here if you would like to participate in the 2024 Series!

You can also find us at the following platforms:

Sign up to our mailing list to make sure you don't miss any news!

SPONSORS

We would like to encourage all delegates to visit the trade exhibition area throughout the meeting. Get your exhibitor passport stamped by all exhibitors, write your name on the back and hand it in to event staff to be in with a chance to win a €100 gift voucher!

Neuroscience Ireland would like to thank the following sponsors for their support:

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PROGRAMME OUTLINE

Tuesday, 29th August

O' Flanagan Lecture Theatre, Ground Floor, 123 Stephens Green

09.30 - 10.10	*Registration & Welcome Coffee* *Exam Hall, Level 1, 123 St Stephens Green*
10.10 - 10.15	*RCSI Welcome Address – Prof. Fergal O'Brien, Deputy Vice Chancellor for Research & Innovation, RCSI*
10.15 - 10.20	*NSI Welcome Address – Prof. Karen Doyle, NSI President*

Session 1: Clinical & Translational Neuroscience

Sponsored by the Royal College of Surgeons in Ireland

Chair: *Dr Jennifer Dowling (RCSI)*

10.20 - 11.00	*Mechanisms underlying rule making and breaking: insights across psychiatry and neurology* Dr Jeffrey Glennon, University College Dublin, Ireland
11.00 - 11.20	*Developmental outcomes in babies born during the Covid-19 pandemic* Dr Susan Byrne, RCSI, Ireland
11.20 - 12.00	**Tea/Coffee, Posters & Trade Exhibitions** *Exam Hall, Level 1, 123 St Stephens Green*

Chairs: *Dr Radharani Benvenutti (RCSI) & Dr Olga Baron (UCD)*

12.00 - 12.20 *Assessing biomaterial microcarriers for sustained dopaminergic neurotrophin delivery in the context of enhancing cell-based brain repair in the Parkinsonian rat brain*
Kaushik Narasimhan, University of Galway

12.20 - 13.10 **Selected PhD Researcher Flash Talks**
[3 minutes each & 2 minutes questions]

Janelle Stanton (UL), Janeen Laabei (TCD), Elin Strachan (UCD), Oisín Joyce (TCD), Ciara Walsh (UCD), Cian Gavin (UCD), Donia Arafa (University of Edinburgh), Rie Matsuzaki (UCC), Tammy Strickland (RCSI)

13.10 - 14.30 **Lunch, Posters & Trade Exhibitions**
Exam Hall, Level 1, 123 St Stephens Green

Session 2: Integrative Systems

Chair: *Dr Andreas Grabrucker (UL)*

14.30 - 15.10 *AQP4 Antibody Biology and Treatment Decisions*
Dr Patrick Waters, Oxford University, UK

15.10 - 15.30 *Impact of endurance exercise on microglia metabolic adaptability and pathogen-induced neuroinflammation in C57BL/6J mice*
Dr Zsuzsanna Barad, Trinity College Dublin

15.30 - 15.50 *Gut Microbiota Regulates the Integration of Central Stress and Circadian Signals*
Gabriel Tofani Sousa e Silva, University College Cork

15.50 - 16.30	**Tea/Coffee, Posters & Trade Exhibitions** *Exam Hall, Level 1, 123 St Stephens Green*

Session 3: Molecular & Cellular Neuroscience

Sponsored by ThermoFisher Scientific

Chair: *Dr Niamh O' Sullivan (UCD)*

16.30 - 16.50	*Platelet-activating factor receptor (PAFR) modulation as potential strategy to reduce astrocyte pro-inflammatory signalling in Alzheimer's disease* Sakshi Hans, University of Limerick
16.50 - 17.10	*Alterations in gut microbiota induced by AAV-mediated overexpression of human α-synuclein in a 'brain-first' rat model of early-stage Parkinson's disease* Joan Omosefe Osayande, Univeristy College Cork
17.10 - 17.50	*Innate and adaptive immune mechanisms in myelin regeneration in the Central Nervous System* Dr Yvonne Dombrowski, Queen's University Belfast, UK
17.50 - 19.00	**Wine Reception, Posters & Trade Exhibition** *Exam Hall, Level 1, 123 St Stephens Green*
19.00 - 23.00	**Banquet Dinner (RCSI)** *College Hall, Ground Floor, 123 St Stephens Green*

Wednesday, 30th August

O' Flanagan Lecture Theatre, Ground Floor, 123 Stephens Green

09.00 - 09.30 *Welcome Coffee*
Exam Hall, Level 1, 123 St Stephens Green

Session 4: New Horizons in Alzheimer's

With Dementia Research Network Ireland & The Alzheimer Society of Ireland

Chair: *Prof. Karen Doyle (UoG)*

09.30 - 09.35 *Introduction Dementia Research Network Ireland*
Dr Vanessa Moore, DRNI

09.35 - 09.55 *DRNI & The ASI - in conversation with a Public Patient Involvement Panel Patient Advocates*

09.55 - 10.25 *New horizons in the diagnosis and treatment of Alzheimer's disease*
Prof. Sean Kennelly, Trinity College Dublin, Ireland

10.25 - 11.00 *Delirium: the collision of evolving dementia and acute illness*
Prof. Colm Cunningham, Trinity College Dublin, Ireland

11.00 - 11.40 **Tea/Coffee, Posters & Trade Exhibitions**
Exam Hall, Level 1, 123 St Stephens Green

Chair: *Dr Derek Costello (UCD)*

12.20 - 13.10 **Selected Researcher Flash Talks**
[8 minutes each & 2 minutes questions]

Dr Gloria Vegilante (TCD), Dr Cansu Sahin (UG), Yasmine Tadjine (TCD), Dr Jane Conway (UG)

Session 5: Advances in Technology & Computational Neuroscience

Sponsored by Laboratory Instruments & Supplies

Chair: *Dr Niamh Connolly (RCSI)*

12.20 - 13.00 *Single-cell Mendelian randomisation for target and biomarker discovery in human brain disease*
Prof Michael Johnson, Imperial College London, UK

13.00 - 13.20 *Advancing Brain-Computer Interfaces from bench to bedside for neurorehabilitation using TMS-Neurofeedback*
Dr Kathy Ruddy, Queen's University Belfast

13.20 - 14.20 **Lunch, Posters & Trade Exhibitions**
Exam Hall, Level 1, 123 St Stephens Green

Session 6: Behavioural & Cognitive Neuroscience

Chair: *Dr Dara Cannon (UoG)*

14.20 - 15.00 *Using population cohort data to investigate the relationship between stress and healthy brain ageing*
Dr Joanne Feeney, Trinity College Dublin, Ireland

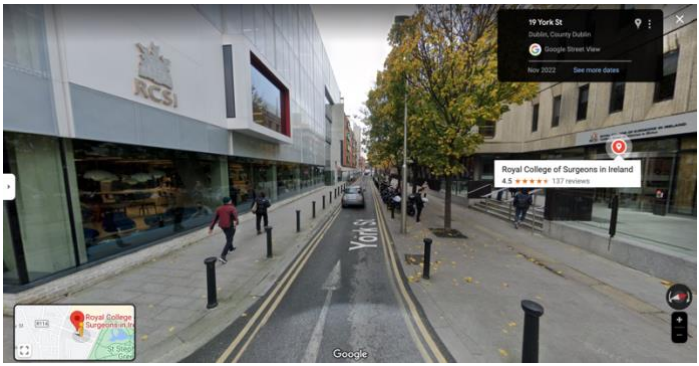
15.00 - 15.20 *The estrogen-immune axis: a key regulator of behavioural inflexibility*
Mairéad Sullivan, University College Dublin

15.20 - 15.40	*Early Career Researcher Award* Dr Roisin Mc Mackin, Trinity College Dublin, Ireland
15.40 - 16.00	*Tom O'Connor Distinguished Investigator Award* Prof Geraldine Boylan, University College Cork, Ireland
16.00 - 16.15	Prize giving
16.15 - 16.25	Closing Remarks – ***Prof. Karen Doyle, NSI President***

CONFERENCE VENUE

We will welcome you at Royal College of Surgeons in Ireland, Dublin; located at 123 St. Stephens Green.

Registration Desk:



Located on York Street entrance of 123 St. Stephens Green. The entrance is depicted on the right side of the picture.

You will find the Registration Desk directly at the lobby.

Main Conference Venue
O' Flanagan Lecture Theatre
(Ground Floor)

Conference Dinner
College Hall
(Ground Floor)

Poster Sessions, Coffee/Lunch Breaks & Trade Exhibitions
Exam Hall, Level 1

Toilets

Directly across from the Exam Hall on Level 1. There are also toilets directly passed the Porters Desk in the Lobby on the right-hand side.

Volunteers and RCSI staff will be on hand during the conference to provide directions for all delegates during the event.

PHOTOGRAPHY

Neuroscience Ireland attendees are advised that a photographer will be on site at various stages during the conference.

The materials will be used for publications, promotional materials, social media and online outlets. If **you do not wish** to be featured, kindly inform RCSI event staff or a member of the conference organising team.

For any queries, please contact Jennifer Dowling (jenniferdowling@rcsi.ie).

GUEST SPEAKERS

Session 1: Clinical & Translational Neuroscience

Chair: Dr Jennifer Dowling (RCSI)

Dr Jeffrey Glennon

University College Dublin, Ireland

TALK 1: *Mechanisms underlying rule making and breaking: insights across psychiatry and neurology.*

Jeffrey C. Glennon is an Assistant Professor (Ad Astra Fellow) focused on linking experimental psychology to biological mechanisms with a track record in industry and academic settings. His research is centred around rule making / rule breaking processes in the cingulate cortex that governs rational versus emotional decision making. As a translational neuroscientist, he seeks to implement basic and preclinical efforts into clinical practice relevant to patients. This work underlies current research into drug-able mechanisms in type I myotonic dystrophy, autism and insulin-signalling pathways in type II diabetes as new drug targets relevant to treatment-resistant obsessive compulsive disorder (OCD). It also underlies his interest in loss of inhibitory GABAergic prefrontal cortical control mechanisms in conduct and antisocial problems. As a neurophysiologist/pharmacologist with both academic and pharmaceutical industry experience (3 patents), he has received strong grant funding (3.9M euro) since his full-time return to academia in 2011.

Dr Susan Byrne
Royal College of Surgeons in Ireland, Ireland

TALK 2: *Developmental outcomes in babies born during the Covid-19 pandemic.*

Dr Susan Byrne is a Senior Lecturer in FutureNeuro/Department of Paediatrics in RCSI, and consultant paediatric neurologist in CHI at Crumlin. Dr Byrne graduated from medical school at Trinity College Dublin in 2005. Between 2009 and 2012 she completed her PhD in genetic epidemiology. Prior to her move back to Ireland in 2021, Dr Byrne worked as a paediatric Neurology consultant at the Evelina London Children's Hospital. During her time there, she specialized in neuroinflammatory disorders of childhood and paediatric stroke, as well as general paediatric neurology including neurogenetic conditions. Since completing her PhD, Dr Byrne has been interested in research and teaching. Her main area of interest is in genotype/phenotype correlation in the neurogenetic disorders of childhood. More recently she has been involved in describing the neurological features of PIMS-TS, which is the post- inflammatory disorder associated with Covid-19 in children.

Session 2: Integrative Systems

Chair: Dr Andreas Grabrucker (UL)

Dr Patrick Waters

Oxford University, UK

TALK 1: *AQP4 Antibody Biology and Treatment Decisions.*

Dr Waters BSc PhD CSci FIBMS FRCPath is the co-director of the autoimmune neurology diagnostic laboratory. His research focuses on antibody-mediated central nervous system diseases. He is interested in the discovery of new antibody targets, the optimisation of assays to detect antibodies in a patient's serum and cerebrospinal fluid, and understanding the mechanism through which the antibodies cause disease. Specifically, the autoimmune neurology diagnostic laboratory is principally focused on the detection of neurological autoantibodies in patients, and developing a better understanding of their causes and treatment. The main disease categories which they study are the many forms of Autoimmune Epilepsy / Encephalitis and Neuromyelitis Optica (NMO) with a focus on developing new autoantibody tests, understanding the mechanism of patient autoantibodies, appreciating which cells produce autoantibodies and how these cells are best targeted with medications.

Session 3: Molecular & Cellular Neuroscience

Chair: Dr Niamh O' Sullivan (UCD)

Dr Yvonne Dombrowski

Queen's University Belfast, UK

TALK 3: *Innate and adaptive immune mechanisms in myelin regeneration in the Central Nervous System.*

Dr Dombrowski's research focuses on immune mechanisms in tissue damage and repair. Tissue damage can occur in infectious (e.g. bacteria, viruses, fungi) or sterile settings (e.g. trauma, autoimmune attack). The Dombrowski group is primarily interested in the underlying immunological mechanisms that direct tissue repair and regeneration with the goal to identify novel therapeutic targets for immune-mediated diseases such as Multiple Sclerosis (MS). Current projects of the group investigate the function of inflammasomes during myelin damage and regeneration in the central nervous system (CNS) and the effects of IL-1 cytokines on oligodendrocytes in the CNS - the cells that produce myelin. Other projects in the group investigated the role of inflammasomes in regenerative inflammation after infectious tissue damage and the role of e-cigarette vapour as an inflammasome activator. Dr Dombrowski has published her work in high-impact journals (e.g. Nature Neuroscience) and her research has been recognized in prestigious awards including an Early Career Fellowship from The Leverhulme Trust, the MS Society Research of the Year award and the invitation to the 64th Lindau Nobel Laureate Meeting for Physiology and Medicine as one of ten UK representatives.

Session 4: New horizons in Alzheimer's

Chair: Prof Karen Doyle (NUIG)

Prof. Sean Kennelly

Trinity College Dublin, Ireland

TALK 2: *New horizons in the diagnosis and treatment of Alzheimer's disease.*

Professor Sean Kennelly MB BCh BAO PhD FRCP (Lond) FRCPI is a consultant physician in geriatric and stroke medicine at Tallaght University Hospital (TUH) and Clinical Associate Professor of Medical Gerontology at Trinity College Dublin. He is Director of the Institute for Memory and Cognition, and the Cognitive Clinical Trials Unit in Tallaght University Hospital, Dublin. He is the clinical director of the National Intellectual Disability Memory Service in TUH. He is a co-lead investigator on HRB-funded Dementia Trials Ireland, a national clinical trials network, and is the principle investigator on HRB-funded of Dementia Research Network Ireland (DRNI). A fellow of the Royal College of Physicians in London & Ireland, he has extensively published in his main research areas of Ageing, brain health, dementia, and Inflammaging. He has served as chief and principal investigator on several international clinical trials in early-stage Alzheimer's disease. He is the principle investigator and lead- clinical advisor on several industry collaborations investigating novel applications of digital gait and speech biomarkers in the detection of cognitive decline.

Dr Colm Cunningham
Trinity College Dublin, Ireland

TALK 3: *Delirium: the collision of evolving dementia and acute illness.*

Dr Colm Cunningham is an Associate Professor in Neuroscience, in the School of Biochemistry and Immunology in Trinity College Dublin (TCD) and is coordinator for the TCD Neuroscience degree. His main research interest is to develop and study animal models to understand the impact of inflammation, in particular systemic inflammation, on brain function and neurodegeneration. Dr Cunningham trained for a Ph.D. in the neurochemistry laboratory of Keith Tipton in TCD before spending 7 years working with Prof. Hugh Perry's CNS inflammation group in the University of Southampton, where he first described the phenomenon of microglial priming during chronic neurodegeneration. He was awarded a Wellcome Trust Career Development Fellowship in 2006 to establish the first animal models of delirium during dementia in Trinity College Dublin and, following this, he won a WT Senior Fellowship to further develop this work to pursue inflammatory mechanisms relevant to delirium. The interaction between prior neurodegenerative pathology and superimposed secondary insults in delirium and long-term cognitive decline is now the major focus of his work and his lab is currently supported by the US National Institute of Aging (NIA) and by Alzheimer's Research UK.

Session 5: Advances in Technology & Computational Neuroscience

Chair: Dr Niamh Connolly (RCSI)

Prof. Michael Johnson

Imperial College London, UK

TALK 1: *Single-cell Mendelian randomisation for target and biomarker discovery in human brain disease*

Prof Michael Johnson is the Professor of Neurology and Genomic Medicine in the Department of Brain Sciences, Imperial College London, and a previous Deputy Head of the Centre for Clinical Translation in the Division of Neurosciences. He is an Honorary Consultant Neurologist at Imperial College Healthcare NHS Trust. His research focuses on the use of computational biology and systems genetics to identify cell-type specific causal pathways and novel drug targets for human brain disease and behaviour. His lab aims to identify novel therapeutic opportunities which cannot be captured using traditional reductionist scientific methods. Additionally, Prof Johnson is a Fellow of the Royal College of Physicians (FRCP), Fellow of the Royal Australasian College of Physicians (FRACP), Fellow of the Royal Society of Medicine (RSM), Member of the UK Association of British Neurologists (ABN), Member of the British Medical Association (BMA) and Member of the International League Against Epilepsy (ILAE). His research has benefited from grants from the UK research councils, charity foundations, the EU and the pharmaceutical and biotech industries. I have a strong track record of successful commercial collaboration with extensive funding from Pharma including grants currently from UCB and Roche.

Session 6: Behavioural & Cognitive Neuroscience

Chair: Dr Dara Cannon (UoG)

Dr Joanne Feeney
Trinity College Dublin, Ireland

TALK 1: *Using population cohort data to investigate the relationship between stress and healthy brain ageing*

Joanne Feeney holds a PhD in Neuroscience from Trinity College Dublin and first joined TILDA in 2011 as a postdoctoral researcher in cognition. In 2014 she was awarded a Centre for Ageing Research and Development in Ireland (CARDI) Leadership in Ageing Research fellowship, based at Queen's University Belfast. Her project investigated the impact of stress on the cardiovascular and neurocognitive health of older adults on the island of Ireland and used data from TILDA and from the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA). In 2018 she took up the position of Research Fellow in Cognitive Neuroscience at TILDA and became a Senior Research Fellow in 2019. Her research centres around the risk and protective factors for cognitive decline and accelerated brain ageing. She is particularly interested in how psychosocial stress impacts brain health in later life and the physiological pathways through which this occurs. Dr Feeney leads the Cognitive Neuroscience group within TILDA and is also closely involved with the Health Cognitive Ageing Project (HCAP).

SELECTED ORAL PRESENTATIONS:

SHORT TALKS

PHD RESEARCHER FLASH TALKS

Chairs: Dr Radharani Benvenutti (RCSI) & Dr Olga Baron (UCD)

RESEARCHER FLASH TALKS

Chair: Dr Derek Costello (UCD)

Session 1: Clinical & Translational Neuroscience

SHORT TALK 3: Assessing biomaterial microcarriers for sustained dopaminergic neurotrophin delivery in the context of enhancing cell-based brain repair in the Parkinsonian rat brain

Kaushik Narasimhan
PhD Student at University of Galway

Cell replacement-based therapeutic approaches for Parkinson's disease has long faced hindrance by the poor cell survival post-transplantation, in part due to growth factor deprivation experienced in the adult, diseased brain relative to their pre-implantation levels in the embryonic brain (for primary cell transplants) or in tissue culture (for stem cell-derived transplants). In this context, we investigated the suitability of PEGDA-SPA cryogel microcarriers (MCs) (loaded with hGDNF or hBDNF) as potential biomaterial systems for neurotrophin (NT) delivery. Initial in vitro assessment of their morphology was done by microscopy, followed by their cytocompatibility using AlamarBlue® assay, and NT loading efficiency and kinetics of NT release (using ELISA). Preliminary early in vivo assessment of their biocompatibility, biodegradability and NT release & retention profiles was done (using IHC). In vitro assessment confirmed their spongy spherical structure, and their cytocompatibility with neurons (SH-SY5Y cell line), microglia (HMC3 cell line), and trophic effect in primary neural (E14 VM cell) cultures, as well as their capability for loading and sustained release of NTs. In vivo assessment confirmed their biocompatibility, and their intact presence in rat brains even at day 14 post-implantation, as well as their ability to have NTs retained within the MC structure, and released into the surroundings even at day 14 post-implantation. These findings offer promising potential of the MCs for sustained delivery of NTs to engrafted cells in the context of enhancing cell-based brain repair in PD.

PhD Researcher Flash Talks

POSTER 31: Suppression of mutant HTT acts on neurotransmission and protein clearance pathways to ameliorate symptoms in the R6/1 mouse model of Huntington's Disease

Cian Gavin
PhD Student at University College Dublin

Huntington's disease (HD) is a neurodegenerative disorder caused by a mutation in the HTT gene. This results in a devastating proteinopathy, characterised by severe motor, cognitive and behavioural symptoms. Lowering of mutant-HTT is a promising therapeutic approach, however efficacy in the clinic remains elusive. We aimed to test the effect of HTT-lowering in the R6/1 mouse model of HD, investigate whether earlier treatment was more effective, and to explore associated proteomic signatures. R6/1 mice were treated with antisense oligonucleotide (ASO) or vehicle via intracranial stereotaxic injection. Mice were subject to a battery of behavioural tests to explore disease phenotype and its potential rescue. Subsequent downstream proteomic analysis was performed via LC-MS/MS. Latency on the rotarod was increased in ASO-treated R6/1 mice ($p=0.0487$) and earlier treatment further improved motor coordination ($p=0.0184$). We show improved spatial memory on the Barnes maze, where the use of spatial strategy was increased in R6/1 mice treated early ($p=0.0113$) and late ($p=0.0183$). When reversal learning was tested, only mice treated earlier with ASO continued to use spatial strategy ($p=0.001$). We show rescue of recognition memory in novel object tests in mice treated early ($p=0.0015$) and late ($p<0.0001$). Differential protein expression results indicate that changes in dopaminergic, mitochondrial and synaptic structural proteins are responsible for observed behavioural improvements. Pathway enrichment analyses suggests protein trafficking/degradation and synaptic neurotransmission play key roles in pathogenesis. HTT suppression ameliorates neurodegenerative phenotype and earlier treatment is more effective. Proteomic analyses provides insight into pathways that could be targeted with combination therapy.

POSTER 32: Herbicides & The Microbiota-Gut-Brain Axis- Glyphosate Induces Behavioural Changes at Doses Relevant to Human Health

Rie Matsuzaki
PhD Student at University College Cork

The gut microbiota plays a vital role in maintaining the physical and mental well-being of the host. It is influenced by various factors, including xenobiotics such as pesticides. Glyphosate, a widely used herbicide, is believed to be harmless to humans because it targets the shikimate pathway, which is absent in animal cells. However, this belief is now being questioned as studies suggest that glyphosate may negatively affect the pathway in microorganisms residing in the gut, such as gut bacteria, which could have an impact on the host. Previous research has focused on either high dose exposure for toxicological effects or commercially available glyphosate-based herbicides. Indeed, the impact of glyphosate exposure at doses relevant to human health indicators are lacking e.g., Acceptable Daily Intake (ADI). In this study, adult C57BL/6 male mice were chronically exposed to glyphosate (0, 0.5 [ADI in Europe]), 5, 50 mg/kg/day) via drinking water. In week 5, behavioural analysis was initiated with a focus on anxiety, stress-coping, cognition, and sociability. Strikingly, glyphosate exposure increased anxiety in the open field test and diminished social novelty preference in the three chamber test in animals exposed to glyphosate in a dose independent manner. Future analysis will focus on understanding the potential mechanisms underlying these behavioural impairments. For this, we aim to analyse compositional and functional changes in the gut microbiome from pesticide exposure. Additionally, changes in the gut and brain will be explored with a focus on immune system, neuroplasticity and physiology.

POSTER 57: Does Moderate or High Intensity Exercise Influence Multisensory Integration in a Cohort of University Students: An Exploratory Study

Oisín Joyce
PhD Student at Trinity College Dublin

Exercise can affect cognitive abilities short- or long-term, with varied task performance outcomes based on modality and intensity. We evaluated moderate and high intensity exercise effects on the Sound-Induced Flash Illusion (SIFI) task, assessing multisensory integration of audio and visual input. The SIFI task's viability in pitch side assessment of sports-related concussion (SRC) depends on its resilience to exercise. 192 participants (88 Males, 104 Females) undertook two exercise protocols on separate days; a high-intensity, interval anaerobic protocol and a moderate-intensity, steady-state protocol. Subjects were assessed pre- and post-exercise on the SIFI neurocognitive test, blood lactate, and heart rate (HR). The effect of exercise on SIFI performance was analysed for statistical stability via test–retest reliability to assess the internal consistency of each SIFI condition. A significant difference in lactate ($p = 0.00$, effect size = -1.89) and HR ($p = 0.051$, effect size = -0.14) was observed between post-moderate and post-high intensity exercise, proving that each exercise protocol induced the desired physiological changes. Both reliability and internal consistency statistics were deemed 'excellent' for both moderate (ICC2k= 0.909; 95% CI [0.85-0.94]; $\alpha = 0.951$) and high intensity exercise (ICC2k= 0.907; 95% CI [0.84-0.94]; $\alpha = 0.955$) respectively and proven statistically significant ($p<0.000$ in each case). These results show that neither moderate nor high intensity exercise affected SIFI performance across the cohort. These data suggest the SIFI remains immune to exercise's impact on perceptual performance, making it a suitable tool to assess SRC and brain health in athletes.

POSTER 58: Optimization and characterization of a PLGA microparticle-embedded GelMA hydrogel as a therapeutic delivery system for potential spinal cord injury repair

Ciara Walsh
PhD Student at University College Dublin

Spinal cord injury (SCI) is a devastating condition with limited regeneration, and no curative therapy is currently available. We have previously demonstrated that cell-based delivery of the immunomodulatory cytokine interleukin(IL)-13, drives alternative immune cell activation and improves both functional and histopathological recovery after SCI in mice. However, from a translational perspective there are many caveats associated with cell-based delivery approaches, such as poor cell graft survival and localization. Therefore, we have developed an injectable biomaterial-based delivery system consisting of poly(lactic-co-glycolic acid) (PLGA) microparticles embedded in a photocrosslinkable gelatin methacrylate (GelMA) hydrogel for localized and sustained delivery of IL-13 in preclinical SCI. Recombinant IL-13 was successfully encapsulated in PLGA microparticles using the double emulsion synthesis method. The release of IL-13 from GelMA hydrogel, PLGA microparticles, or a combination of PLGA-in-GelMA was measured over 6 weeks in vitro. IL-13 bioactivity was assessed in vitro by demonstrating that released IL-13 increased Arginase-1 expression and decreased LPS-induced expression of TNF-α and iNOS in BV2 microglia. Finally, ongoing work focuses on investigating the therapeutic efficacy of this hydrogel system in vivo using a mouse contusion SCI model. Thus far, we have shown that the hydrogel is well tolerated in vivo and that encapsulated microparticles are distributed throughout the lesion site following hydrogel injection, demonstrating the potential for localised therapeutic delivery. Taken together, these results suggest the utility of our biomaterial-based delivery system for controlled therapeutic release which may have significant potential for SCI repair.

POSTER 89: Patient-derived cellular models as tools to elucidate the pathophysiology of Hao-Fountain syndrome

Janelle Stanton
PhD Student at University of Limerick

Synaptic plasticity (SP) plays a key role in the human ability to adapt to environmental input, along with learning and memory processes. Altered SP significantly contributes to neurological and psychiatric disorders, including Autism Spectrum Disorders (ASD). Furthermore, mutations in essential proteins facilitating SP have also been identified in human patients with intellectual disabilities. Recently, loss of function mutations in ubiquitin-specific protease 7 (USP7, also called herpes virus-associated ubiquitin-specific protease, HAUSP), have been identified as a disorder-causing variant, linked explicitly to Hao-Fountain syndrome, a neurodevelopmental disorder manifesting intellectual disability, ASD, and seizures. Located at chromosome 16p13.2, USP7 encodes a deubiquitinating proteolytic enzyme that cleaves multiple ubiquitin chain linkages. Previously, USP7 was shown to regulate the ubiquitination of proteins, including the MDM2-p53 pathway, which is vital for DNA repair, transcription, and cancer. However, the precise mechanisms of how USP7 mutation causes the clinical phenotype of Hao-Fountain syndrome on a cellular level are missing so far. In this collaborative project, using patient-derived human induced pluripotent stem cells in combination with omics approaches (proteomic and transcriptomic analysis) and targeted biochemical analyses (qrt-pcr and western blot analysis), we aim to understand the functions of USP7 in neuronal development and SP by recapitulating neurodevelopmental processes using in vitro model systems including 2D models from iPS cells to differentiated mature neurons along with 3D models systems such as cerebral organoids. Our studies have revealed several ASD and ID-linked protein dysregulations and, thereby, cellular pathways that will be validated and explored as future drug targets.

POSTER 90: NOX2-mediated regulation of microglial NLRP3 inflammasome in traumatic brain injury

Janeen Laabei
PhD Student at Trinity College Dublin

NADPH oxidase 2 (NOX2) is an enzyme complex responsible for reactive oxygen species (ROS) production in microglia. NOX2/ROS is a priming signal for NLRP3 inflammasome activation. GSK2795039 is a novel small molecule drug that inhibits NOX2. Here, we characterised GSK2795039 in models of microglial activation in vitro and translated findings to an experimental traumatic brain injury (TBI) model in mice. Immortalised Microglial (IMG) or primary microglia from p1 Wistar rats were pre-treated with GSK2795039 (1-40μM), or MCC950 (NLRP3 inhibitor; 0.5μM) and stimulated with lipopolysaccharide (LPS; 100ng/ml) and ATP (1mM)/Nigerecin (10μM) to induce NOX2/ROS and NLRP3 inflammasome activation. ROS production and cell viability were measured in cells. The conditioned media was analysed for IL-1β, IL-18 and TNF-α by ELISA, nitric oxide, and lactate dehydrogenase to measure pyroptosis. Protein expression of NLRP3, Caspase-1 and ASC were measured in cell lysates and supernatants by Western immunoblot. In LPS/ATP and LPS/Nigerecin models in IMG and primary microglia, GSK2795039 attenuated ROS, IL-1β, IL-18 release, and NLRP3 and cleaved-caspase-1 protein expression, which may be due to reduced NOX2/ROS signalling. Using a controlled cortical impact in adult male C57Bl/6J mice, flow cytometry studies demonstrated moderate-level TBI resulted in rapid infiltration of inflammatory monocytes with increased NOX2/ROS/Caspase-1/IL-1β+ expression and proliferation of resident microglia compared to control mice. Follow-up studies are assessing the therapeutic potential of post-injury GSK2795039 administered on TBI neuroimmunological, neurobehavioral and neuropathological outcomes. In conclusion, GSK2795039 may be a promising drug for mitigating NOX2-mediated neuroinflammation in microglia.

POSTER 91: Loss of Opa1 results in mitochondrial disruption and neurodegeneration in novel in vivo models of optic atrophy in zebrafish and fruit flies

Elin Strachan
PhD Student at University College Dublin

Optic atrophy (OA) is the most common form of inherited optic neuropathy, characterised by progressive and irreversible degeneration of retinal ganglion cells (RGCs), resulting in sight loss. Approximately 70% of OA patients carry mutations in the mitochondrial fusion protein OPA1. However, it is unclear why OPA1 mutations lead to RGC death and subsequent vision loss. Fruit fly and zebrafish models of OA were developed using CRISPR/Cas9 gene editing to create tissue-specific or whole animal knockouts (KO) of endogenous Opa1. qPCR validated Opa1 disruption in both models. In flies, survival and axonal mitochondrial morphology was monitored compared to control animals. In zebrafish larvae, visual behaviour was measured using optokinetic response (OKR) assays and a seahorse extracellular flux analyser measured metabolic changes. Mass spectrometry was used for proteomics analysis in zebrafish. Neuron-specific Opa1 KO flies demonstrate a significantly reduced median life expectancy. Axonal mitochondria in these Opa1 KOs are significantly smaller and more rounded, consistent with a fusion defect. Zebrafish Opa1 mutants display a significant loss of visual acuity compared to control siblings. Seahorse analysis demonstrates metabolic disruption in Opa1 KO larvae, including a reduction in both basal and maximal respiration. Proteomics analysis indicated differential expression of proteins involved in oxidative phosphorylation and stress response. I have generated novel models of OA by targeted loss of Opa1 in both zebrafish and fruit flies. Disrupted mitochondrial flux (organisation and function) and neurodegeneration (survival and visual function) are evident in both systems, indicating that highly conserved functions of Opa1 likely contribute to disease pathogenesis.

POSTER 92: Investigating mechanisms of demyelination and its consequences for axons

Donia Arafa
PhD Student at University of Edinburgh

The loss of myelin from axons, known as demyelination, is a hallmark feature of diseases such as Multiple Sclerosis and occurs throughout ageing. While the long-term consequences of myelin loss are known to be detrimental, little is understood about mechanisms driving the process of demyelination itself. Using two demyelination models, we have observed that myelin swelling, or vacuolation, precedes overt myelin loss, and is a common feature of myelin damage. While vacuolation always accompanied myelin loss, it did not always lead to demyelination and could even be reversed, suggesting there is a threshold of damage below which individual sheaths can recover. Furthermore, we found that increasing neuronal activity exacerbated myelin vacuolation, which could be slowed by suppressing action potential firing in zebrafish, suggesting that the normal physiological role of oligodendrocytes in ion buffering cannot be met in situations where the cell is damaged. Finally, we saw by live imaging that myelin vacuolation affects axonal structure, indicating that damage to axons occurs even before they have been demyelinated. Together these data suggest that demyelination itself may be a regulatable, cell biological process that can be manipulated, with immediate consequences for axonal structure.

POSTER 93: Microglial-specific knockdown of Bmal1 leads to behavioural changes, an increased susceptibility to seizures and an altered inflammatory profile in mice

Tammy Strickland
PhD Student at Royal College of Surgeons in Ireland

Neuroinflammation is a feature of epilepsy and contributes to seizure development. The inflammatory response is mediated by microglia, which are regulated by the circadian rhythms; the 24-hour variations in physiological function orchestrated by autoregulatory genes, including Bmal1. The disruption of circadian rhythms is associated with increased microglial activation. Here we explored the microglial-specific Bmal1 deletion impact on behaviour and seizure susceptibility in mice. Forty young adult Bmal1-Cx3CR1Cre-ER mice were injected with either tamoxifen (40mg/kg; IP/daily/10 days) to induce microglial-specific Bmal1 knock-down (Bmal1-KD) or vehicle. Two weeks after recombination, mice underwent behavioural tests. A subset of this cohort was implanted with electrodes for electroencephalographic (EEG) recordings and underwent the injection of a low dose of kainic-acid (KA;IP;15mg/kg) to test seizure susceptibility. Pro-inflammatory gene expression was assessed by qPCR in hippocampi and cortices from naïve and KA-treated mice. Bmal1-KD mice were significantly more active ($p<0.05$) than controls. No difference was observed in cognition. Bmal1-KDs had an increased susceptibility to develop acute seizures ($p<0.0001$) and significantly increased seizure severity measured by the total EEG power ($p<0.0002$) after KA administration. TNF-α was significantly reduced at baseline in Bmal1-KD mice and was significantly upregulated in Bmal1-KDs compared with controls following KA ($p<0.01$). Conclusions: Microglial-specific depletion of Bmal1 led to disrupted behaviour and higher propensity to develop seizures. Bmal1 reduction led to alterations in cytokine expression at baseline and following KA. Further studies will elucidate how Bmal1 disruption affects epileptogenesis.

Session 2: Integrative Systems

SHORT TALK 2: Impact of endurance exercise on microglia metabolic adaptability and pathogen-induced neuroinflammation in C57BL/6J mice

Zsuzsanna Barad
Postdoctoral researcher at Trinity College Dublin

There is compelling evidence that lifestyle factors, including physical activity dramatically influence the homeostatic functions of an organism at every level. Of the wide-ranging benefits, studies conducted in humans as well as animal models suggest that regular, moderate-to-vigorous intensity aerobic exercise confers neurotrophic, pro-cognitive, and anti-inflammatory effects, which may be partially mediated by various factors released from contracting skeletal muscle by way of inter-organ crosstalk, including direct muscle-brain communication. Recent evidence indicates the potential of exercise to modulate the metabolic states and function of microglia, the tissue resident macrophages of the central nervous system (CNS). Neuroinflammation and microglia activation have been characterized by a shift in metabolic pathways towards aerobic glycolysis, which critically determines the adaptive response of microglia to immunological challenge, regulating its immune functions such as cytokine release and phagocytosis. To characterize, here, we investigate the impact of 7 days of moderate intensity treadmill exercise on microglia metabolic phenotype and function in 3-4-month-old C57/BL6J mice, by assessing the bioenergetic phenotype of primary microglia in exercising and sedentary mice. Furthermore, microglia metabolic adaptations and immune functions are elucidated in exercising vs sedentary mice upon a peripheral immune challenge via subseptic dose of lipopolysaccharide (LPS). Our findings indicate that prior short-term exercise can moderately attune the bioenergetic and inflammatory changes induced by LPS. This provides a potential mechanism underlying the long-term effects of regular physical activity in developing resilience of brain tissue to injury and inflammatory insult.

SHORT TALK 3: Gut Microbiota Regulates the Integration of Central Stress and Circadian Signals

Gabriel Tofani Sousa e Silva
PhD Student at University College Cork

Stress and circadian systems are bidirectionally interconnected to maintain appropriate responses to external stimuli. The gut microbiota has been shown to modulate these systems independently, but its role in the regulation of the integration of stress and circadian signals remains unknown. With the modern environment involving increasing circadian disruption and stressor exposure, there is a need for a better understanding of how our responses to these constant changes are shaped, and more importantly, how they can be targeted to improve health. In this work, we provide compelling evidence that gut microbiota modulation of stress responsiveness exhibits diurnal rhythmicity. From a comprehensive bioinformatic analysis of transcriptomics and metabolomics, we demonstrate that the diurnal oscillations of the stress-relevant pathways are disrupted by modulating the gut microbiota in the suprachiasmatic nucleus, amygdala and hippocampus, key brain regions involved in both central circadian regulation and the behavioural stress response. This was coupled with alterations in the rhythmic profile of glucocorticoid secretion, impaired response to acute stress and altered stress-sensitive behaviours. Moreover, we perform faecal microbiota transfer and show that diurnal oscillations of gut microbes regulate glucocorticoid secretion and unmask the microbial underpinnings of such changes. Thus, the gut microbiota regulates diurnal oscillations of stress responsiveness and is necessary to respond adaptively to psychological stressors throughout the day, which paves the way to explore interventions that can target gut microbes to modulate circadian and stress-related manifestations at the same time.

Session 3: Molecular & Cellular Neuroscience

SHORT TALK 1: Platelet-activating factor receptor (PAFR) modulation as potential strategy to reduce astrocyte pro-inflammatory signalling in Alzheimer's disease

Sakshi Hans
PhD Student at University of Limerick

The platelet-activating factor (PAF) molecule is a pro-inflammatory phospholipid mediator that functions by binding its receptor PAFR (PAF receptor). PAF is a key player in the mechanism of chronic inflammation. The pathology of disorders such as cardiovascular disease, cancer, rheumatoid arthritis, but also neurodegenerative diseases has been linked to such chronic inflammation. PAF signalling has been associated with cardiovascular diseases. However, its role in neurodegenerative disorders is less clear. The amyloid-beta (Aβ) hypothesis of Alzheimer's disease (AD) suggests that neuroinflammation due to Aβ in the brain is a driving cause. Here, we investigate whether Aβ-driven PAF signalling has implications for AD. Our preliminary results show that PAFR expression is significantly upregulated after treatment with Aβ and lipopolysaccharide (LPS) (as positive control) both on gene and protein levels. Protein levels of PAFR are significantly decreased after inhibiting PAF receptors following treatment with Aβ. Inhibiting PAF receptors also significantly reduces levels of oxidative stress and the number of amyloid-beta aggregates, as determined by fluorescent staining. Additionally, inhibiting PAF receptors significantly decreases astrocyte activation on the protein level, as determined by Western blotting and staining with anti-GFAP, a marker for astrocyte activation. Thus, PAF signalling seems to control the majority of neuroinflammation in our in vitro model. Further assays will model AD pathology in neurons and analyse AD hallmarks in neurons treated with medium from astrocytes exposed to our treatment conditions. We conclude that PAFR inhibition is a strategy in AD and identified molecules with potent PAFR inhibitory activity.

SHORT TALK 2: Alterations in gut microbiota induced by AAV-mediated overexpression of human α-synuclein in a 'brain-first' rat model of early-stage Parkinson's disease

Joan Omosefe Osayande
PhD Student at University College Cork

Parkinson's disease (PD) leads to midbrain dopaminergic neuron degeneration and neuronal accumulation of alpha-synuclein (α-syn). A new 'brain-first vs body-first' hypothesis of PD has proposed that α-syn pathology starts in the brain, then spreads to gut, or conversely starts distally in the gut, then spreads to the brain through peripheral nervous system. The gut microbiota has been implicated in PD and early dysbiosis and accumulation of α-syn in the gut has been reported in 'body-first' PD, but it is unclear if these events also occur in 'brain-first' PD. Here we investigated whether alterations in gut microbiota and α-syn accumulation occur in the GI tract of a 'brain-first' rat model of PD. Adult female rats received a unilateral intranigral stereotactic injection of adeno-associated virus (AAV)-α-syn or AAV-null viral vectors. Faecal and tissue collection, microbiota profiling, HPLC, immunohistochemistry for tyrosine hydroxylase (TH), α-syn, phospho(P)α-syn and H&E staining were conducted at 24 weeks post-surgery. AAV-α-syn significantly reduced TH-positive striatal dopaminergic terminals and striatal dopamine. While there were no differences in alpha and beta diversity, taxonomic composition analysis found decreased abundance of several bacteria including Blautia, while increased abundance of Streptococcus in the α-syn group was noted. Furthermore, P-α-syn was detected in the proximal colon in the AAV-α-syn group. This study shows intranigral α-syn resulted in gut microbiota alterations and P-α-syn accumulation in the proximal colon of a rat model of 'brain-first' PD. This suggests that profiling gut microbiome alterations may be a useful early indicator of 'brain-first' PD.

Session 4: New horizons in Alzheimer's

Researcher Flash Talks

POSTER 33: Mechanisms linking traumatic brain injury to neurodegenerative disease: a focus on tau

Gloria Vegliante
Post-Doctoral Researcher at Trinity College Dublin

Traumatic brain injury (TBI) afflicts 55 million people worldwide. It represents a huge burden for the health system, and a leading cause of injury-related death and disability, with devastating impact on individuals and society. TBI is a complex disease characterised by dynamic pathophysiological adaptive and maladaptive processes that may predispose to chronic neurodegeneration and increase risk of dementia later in life including Alzheimer's disease (AD). However, the mechanisms driving the transition from the acute biomechanical impact to late neurodegeneration still need to be fully addressed. The development of progressive proteinopathies is a shared feature of dementia and TBI. Tau pathology has sparked our interest being a hallmark of AD and pathognomonic feature of chronic traumatic encephalopathy. In this study we document the presence of tau pathology in human brain contusion samples surgically removed after severe TBI in patients. We provide evidence that human TBI-induced tau (tauTBI) has self-templating properties and spreads throughout the brain causing a widespread tau pathology, associated with synaptic dysfunction and cognitive impairment. Moreover, we show that tauTBI can be horizontally transmitted to naïve mice by intracerebral inoculation, causing memory deficits. Thus, human tauTBI holds prion-like properties, suggesting a mechanism by which an acute biomechanical impact may predispose to neurodegeneration in patients. Finally, we exploit the C. elegans model to demonstrate that the bio-inspired hexapeptide Aβ1-6A2V(D), acting against amyloid β and tau, could represent an innovative pharmacological approach to counteract pathological aggregates formation and mitigate the progression of dementia and post-traumatic neurodegenerative processes.

POSTER 34: Multimedia methods for metacognition of concepts: A PPI pilot study demonstrating applications of creative technologies to understanding Bipolar I Disorder.

Jane Conway
Post-Doctoral Researcher at University of Galway

Bipolar I Disorder (BP-I) is a psychiatric disorder characterized by shifts in mood between periods of mania and depression. Mood episodes negatively affect psychosocial functioning and are associated with cognitive impairments in both social and non-social domains. One such impairment observed in BP-I is in metacognition - the capacity to assess the reliability of one's own mental representations and processes. However, how people select and use abstract concepts for understanding and decision-making is unclear because the literature specifically on Metacognition of Concepts is underdeveloped (Shea, 2018). Given that 'insight into illness' is positively associated with a patient's prognosis and treatment adherence, developing methods for studying the metacognition of concepts is important. Moreover, given that increasing public knowledge of mental health disorders reduces mental health stigma (Thornicroft et al., 2015), developing methods for communicating mental concepts is also pertinent. Our project addressed these two aims using a novel Patient and Public Involvement in Research (PPI) approach. Two artists, one with lived experience of BP-I, collaborated with two cognitive neuroscientists who conduct research on BP-I. This interdisciplinary team combined evidence from the scientific literature with the subjective lived experience of the artist. Resulting concepts were expressed using creative technologies in an audio-visual installation, thereby demonstrating - and indeed externalizing - the metacognitive awareness of cognitive impairments in BP-I through the creation of physical artistic artefacts to represent mental processes. The installation was then publicly exhibited. In this talk, we discuss how creative methods can be developed further in Arts x Neuroscience collaborations.

POSTER 59: Developing an electrical impedance sensor to predict clot composition and improve stroke patient outcomes in the acute care setting

Cansu Sahin
Post-Doctoral Researcher at University of Galway

Acute ischemic stroke (AIS) is the most common type of stroke. AIS is treated using thrombolysis with tissue plasminogen activator and thrombectomy in which the clot is mechanically removed. Clinicians are relatively blind to clot characteristics which can influence success of thrombolysis and thrombectomy. Development of a medical device using electrical impedance spectrum with machine learning that could identify clot characteristics in the acute care setting could improve stroke patient outcomes. The aim of the study is to advance development of a medical device capable of indicating clot characteristics in the acute care setting to inform the clinical decision making process and improve stroke patient outcomes. 253 thrombi (231 patients) were analysed in Clotbase International Registry. Impedance measurements were taken following clot retrieval by thrombectomy, followed by Martius Scarlet Blue (MSB) stain. Components were quantified via Orbit Software and correlated with impedance predictions and analysed using Kruskal-Wallis. MSB staining identified RBC as the major component in clots (37.6%) followed by platelets/other (30.3%), fibrin (25.5%) and WBC (5.7%). The impedance-based RBC prediction model correlates well with the RBC content determined by histology ($r_m=0.9r_h+7$, $\varrho=0.7$). Clots removed successfully in first-pass effect were richer in RBCs as assessed using histology and impedance prediction ($p<0.01$). Electrical impedance predictions of RBC content in AIS clots are consistent with histological findings. Further work will continue to improve the specificity of the impedance signature, advancing development of a medical device to guide clinical decision making in the stroke acute care setting.

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POSTER 60: Do audio-visual stimuli affect TMS-based measures that are under investigation as ALS biomarkers?

Yasmine Tadjine
Research Assistant at Trinity College Dublin

Transcranial magnetic stimulation (TMS) measures show potential as ALS diagnostic biomarkers[1]. However, TMS-based studies require participants to sit still and do not allow any auditory or visual distractions. Lack of distraction may lead to participants attending to the sound/sensation of TMS pulses, or anticipating/attempting to modulate TMS-induced muscle contractions. Such mental activities can inadvertently affect cortical excitability and TMS measures[2]. Providing a distractor could help to keep mental state consistent, improving statistical power of ALS-related cortical pathophysiology research. 13 right handed controls were recruited. Resting motor threshold (RMT), short intracortical inhibition (SICI), long intracortical inhibition (LICI) and interhemispheric inhibition (IHI) were recorded via threshold tracking-TMS. Each measure was recorded while participant was at rest without sensory input, watched and listened to a documentary, or listened to a documentary. Linear mixed effects modelling was conducted to investigate the effects of distractor stimuli. LICI was greater with auditory-only distraction compared to without. Conversely, during audiovisual distraction, LICI was lower. Significantly less IHI was observed when auditory distraction was present compared to absent. RMT and SICI were not affected. These results indicate that providing participants with distractor stimuli during measurement of RMT and SICI will not affect motor cortical excitability. Such distractors may affect LICI and IHI measurements. Such distractions could make studies more tolerable for participants and help to improve consistency of mental state across and within participants.

References: 1.Vucic, et al., Handbook of clinical neurology, 116, pp.561-575,2013. 2. Cengiz Bet al.. Experimental brain research, 236(2), pp.497-503.

Session 5: Advances in Technology & Computational Neuroscience

SHORT TALK 2: Advancing Brain-Computer Interfaces from bench to bedside for neurorehabilitation using TMS-Neurofeedback

Dr Kathy Ruddy
Principal Investigator at Queen's University Belfast

Studies using BCIs based upon non-invasive, scalp recorded electroencephalography (EEG) have consistently demonstrated utility, both as scientific tools for neuromodulation and for clinical neurorehabilitation purposes. They are particularly appealing in clinical contexts where physical movement is impaired, for instance following stroke. Using a BCI where on-screen avatars are driven by neural activation in motor regions encourages the patient to engage in imagined or attempted movements. By providing tangible visual feedback and rewarding desirable neural features, activity in motor pathways is maintained. This may promote use-dependant plasticity and rewiring for recovery of function. However, clinical adoption of the approach has been limited. This is due mainly to difficulties with implementation in non-research settings, as training to achieve neural control of the BCI requires lengthy sessions over multiple days or weeks (Simon et al., 2021). Neurofeedback of Motor Evoked Potential (MEP) amplitude in response to TMS (TMS-NF) gives direct, real-time muscle-specific feedback, even in situations where the user is unable to generate functional movements. In this talk I will present results demonstrating that priming participants with two days of TMS-NF results in shorter training times and more optimal use of the EEG BCI, making the approach more clinically useful. I will also show results from simultaneously recorded TMS-evoked potentials (TEPs) demonstrating key differences in neural signatures associated with the distinct motor imagery strategies used by participants to control the BCI, learned from the TMS-NF.

Session 6: Behavioural & Cognitive Neuroscience

SHORT TALK 2: The estrogen-immune axis: a key regulator of behavioural inflexibility

Mairéad Sullivan
PhD Student at University College Dublin

Aberrant insulin signalling was recently identified as a key mechanism in Obsessive-Compulsive Disorder (OCD). TALLYHO/JngJ mouse models of Type 2 diabetes are compulsive and anxious, with treatment with the Type 2 diabetes drug metformin generating partial rescue. Here, we aimed to establish the mechanisms behind this insulin-behavioural axis via proteomic analysis of brain and blood. Additionally, data from Genome-Wide Association studies (GWAS) of somatic disorders comorbid with OCD were compared using Ingenuity Pathway Analysis (IPA) (Qiagen). Protein enrichment highlighted dysregulated immunity in TALLYHO/JngJ mice. Based on these findings, pairwise analyses were performed across GWAS studies of inflammatory vs behaviourally inflexible disorders to identify recurring upstream mechanisms. This identified the female sex hormone beta-estradiol. Comparison across aforementioned human GWAS and mouse proteomic analyses indicated that beta-estradiol regulation of Interleukin-1beta, a major proinflammatory cytokine, is a converging mechanism. This was further confirmed as the most enriched mechanism in mass spectrometry of TALLYHO/JngJ mice. Mass spectrometry analysis of brain and blood proteins in TALLYHO/JngJ mice with and without metformin treatment confirms estrogen signalling as a major upstream regulator. We conclude that beta-estradiol-immune dysregulation is a key mechanism underlying behavioural inflexibility in TALLYHO/JngJ mice.

POSTER PRESENTATIONS

Poster 01-08: Advances in Technology & Computational Neuroscience

POSTER 01: An experimental and computational investigation of the damage and remodelling mechanics of concussion

Jamie Concannon
Biomedical Engineering, University of Galway

50-60 million cases of Traumatic brain injury (TBI) are reported each year globally, ~30% of which are sports related. A large meta-analysis of >35,000 patients showed direct correlation in 19/22 studies between mild-TBI and structural damage or neurodegeneration, providing emperical evidence which contradicts the medical definition of TBI: "a nondegenerative insult to the brain from an external mechanical force". This study focuses on the development of an experimental and computational framework to investigate the mechanics underlying brain tissue injury and healing, serving as the first diagnostic indicator of damage and recovery for concussion patients. Finite element based material characterisation reveals that the constitutive behaviour of grey and white matter is nonlinear with tension/compression asymmetry. Currently available materials in commercial software packages which can be used for computationally modelling brain are phenomenological in nature and are not capable of simulating these experimental features. The development of a novel microarchitectural-based user-material law which includes nonlinear axonal behaviour overcomes this challenge and can predict discrete neuronal damage following impact simulations. Following the application of linear forces of 100N and 750N to the frontal skull, simulations also reveal that neglecting CSF fluid in brain models understimates intracranial pressures by ~100%. The anisotropic hyperelastic user-material law allows for individual fibre strain analysis mapped directly from diffusion-tensor MRI data for various loading modes and magnitudes. This computational modelling approach provides a foundation upon which the mechanics of brain tissue damage and healing can be fundamentally investigated, providing advance in terms of diagnostics and treatment of concussion.

POSTER 02: EPIVIEWS: Exploring Patient Impact & Value in Epilepsy Wearables for Seizure Monitoring

Mr. John David Damalerio[1,2], *Dr Ronan Kilbride*[3], *Prof. Colin Doherty*[2,4], *Dr Rob Argent*[1]
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Managing seizures presents a challenge for individuals with epilepsy and their caregivers, given the potential for injury or sudden unexplained death in epilepsy (SUDEP). Wearable devices capable of detecting seizures and alerting caregivers offer promising solutions. This study aims to assess the effectiveness of the Empatica Embrace 2 wearable device for epilepsy seizure detection and the potential value in the management of the condition. The protocol is divided into two phases, and brings together expertise in digital health and clinical epilepsy management, with collaboration from Epilepsy Ireland to assess the device's potential benefits for people with epilepsy. Phase one involves a cross sectional observational study assessing the accuracy of the device by comparing the Embrace 2 with video electroencephalography (EEG), the current gold standard for seizure detection. Participants admitted to the Epilepsy Monitoring Unit (EMU) at Beaumont Hospital will wear Embrace 2 during their stay to evaluate its concurrent validity. Phase two comprises of a prospective mixed-methods longitudinal cohort study of a four-month duration where participants wear Embrace 2 at home, providing insight into everyday performance. Monthly questionnaires and a concluding semi-structured interview will explore participants' experiences and device usability. This study aims to determine the potential value of Empatica Embrace 2 in epilepsy management, enhancing patient quality of life and caregiver support. Recruitment is anticipated to commence in September 2023 and the findings will contribute to a deeper understanding of the role of these devices in enhancing epilepsy care.

POSTER 03: Transfer Learning-based Analysis of EEG-recorded Status Epilepticus has Predictive Value for Subsequent Rates of Spontaneous Seizure in Mice

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Animal models of drug-resistant epilepsy represent an important resource to discover new drug targets and test experimental medicines. A major limitation, however, is the loss of time and resources from generating mice with low or inconsistent rates of spontaneous seizures. Intra-amygdala microinjection of kainic acid in mice is one of the most widely regarded models of drug-resistant epilepsy. Mice develop acute status epilepticus which abates after a few hours and then, within a few days, mice display spontaneous seizures (epilepsy). The frequency of the spontaneous seizures varies between mice, with a minority developing only occasional seizures. The ability to predict soon after status epilepticus which mice will go on to develop a standard frequency of seizures would enable a significant reduction in resources and EEG reviewing time, as well as lead to humane early end-points. In this study, we developed a transfer learning-based method for predicting the emergent spontaneous seizure rates in the intra-amygdala kainic acid model based on the acute EEGs recorded in mice during status epilepticus. The method was trained on data from 12 mice and subsequently tested on data from 17 mice, achieving an impressive accuracy of 76.47% on the test set in classifying the emergent epilepsy as normal or an outlier (low-frequency seizures). This approach holds great promise for researchers, aiding in the analysis of seizure rates within EEGs of the IAKA mouse model and in preclinical drug development and compliance with 3Rs.

POSTER 04: Towards a microfluidic model of ectopic follicle-like structures in Multiple Sclerosis

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CÚRAM SFI Research Centre for Medical Devices, University of Galway

Multiple sclerosis (MS) is a progressive chronic inflammatory disease affecting the CNS. An immunological hallmark of MS is the presence of oligoclonal bands in the cerebrospinal fluid (CSF). They are detected when fragments of IgG antibodies are present in the CNS. Their persistence throughout disease course suggests a survival niche for B-cells within the CNS. The description of highly organised follicle-like structures have been detected in several chronic inflammatory diseases and a large proportion of patients with MS. We aim to do the following: 1) use MRI and post-mortem tissue images to define physical properties of brain regions commonly found to harbour these structures: 2) validate the utility of COMSOL software in modelling CSF flow. Outputs will assist in developing an in vitro microfluidic device that mimics the meningeal surface present in MS. Analysis of already-published PM images indicated that the majority (56%) of follicle-like structures are located in the exterior regions of the brain, specifically the pre-central and cingulate sulci. Characterisation of these sulci suggested a physical ratio of 3:1 (width: depth). Our COMSOL-generated model showed minimal flow into the sulci and a range of shear rates that could impact meningeal cell biology. Initial testing of meningeal cells seeded into prototype devices have shown no detectable changes in cell morphology following application of fluid flow. The work described is the first step in developing a novel testing platform for compounds that could prevent formation of the toxic B cell niche.

POSTER 05: Propagation Loss in Heterogenous Molecular Channels for Epilepsy Detection

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Epilepsy is a persistent neurological disorder, affecting about 50 million people worldwide. In recent years, researchers have focused their attention on neuronal biomarkers that contribute to the pathogenesis of epilepsy. There are several potential biomarkers associated with epilepsy, among them are transfer RNA-derived small RNAs (tsRNAs), which have emerged as a novel type of biomarkers. In this study, we investigate the propagation of tsRNA biomarkers within complex fluidic microenvironments. Specifically, we consider the brain extracellular space and the bioengineered implant i.e., polyethersulfone (PES) hollow fiber tube filled with the collagen gel containing the bioengineered cells (ARPE-19). Thereby, ARPE-19 cells can be used in the detection of tsRNA biomarkers that originate from the extracellular space of the brain. As part of this work, we propose a model and simulation approach for studying the transport of tsRNA biomarkers in microfluidic environments. The aim is to quantify the concentrations of tsRNA biomarkers within each region of the system and potential losses due to its physicochemical properties. The developed framework then will be used to conduct a systematic study of various parameters of brain extracellular space (e.g., tortuosity, viscosity, pressure etc.) and bioengineered devices (e.g., membrane thickness, the fiber length, the fluid velocity, the cellular density, etc.) on tsRNA transport behaviour. Particularly, our primary objective is to optimize the tsRNA biomarker detection capability of the bioengineered implant by systematically assessing these physiochemical factors. It is anticipated that the findings from this study will lead to significant advancements in the detection and treatment of epilepsy.

POSTER 06: Unveiling the Impact of Na^+ Channel Mutations on Brain Function and Learning Processes: From Neurons to AI

Mohammadreza Khodashenas[1], *Daniel Martins*[1], *Sasitharan Balasubramaniam*[2], *Micheal Barros*[3]

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Understanding brain behavior under normal and abnormal conditions is crucial for advancing neuroscience research. This study explores the significance of neuron models and their hyperparameters in simulating neuronal behavior, particularly focusing on gain-of-function and loss-of-function mutations in voltage-gated sodium channels within hippocampal cells, which are associated with neurological disorders like epilepsy. Starting with a CA1 pyramidal cell model based on biological data, a hippocampus network model is constructed. Investigating the effects of Na+ channel mutations on the hippocampus network using the Hodgkin-Huxley (HH) model, the model incorporates excitatory and inhibitory synapses, providing valuable insights into neural activity dynamics. The study investigates the learning process in both normal and abnormal brain conditions using spiking neural networks (SNNs) with leaky integrate-and-fire (LIF) neuron models. Using the MNIST dataset for image processing, the impact of different network architectures and conditions on digit recognition accuracy is evaluated. An autoencoder for image reconstruction is introduced, utilizing the Synaptic neuron model to also mimic biological neurotransmitter release dynamics. This approach enhances the understanding of network information processing. Finally, it has been seen that Na^+ channel conductivity mutations which might be associated to some neurological disorders like epileptic seizures, can influence and/or damage the learning process. By bridging the gap between neuroscience and artificial intelligence, our findings contribute to a deeper understanding of brain function and may inspire advancements in neuromorphic computing and artificial intelligence algorithms.

POSTER 07: Decrypting the thalamic subnuclei and functional composites in adolescents with psychotic experiences

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The thalamus, a dual grey matter formation within the diencephalon is thought to be involved in psychosis. It consists of distinct nuclei with specific functions. To date no study has investigated the volumes of the thalamic nuclei in young adolescents with psychotic Experiences (PE's). This study used T1 imaging with Freesurfer analysis to investigate the differences in thalamic nuclei in 98 young people (53 with PE's) over three time points, from ages 11 to 18. A linear mixed effects (LME) model was used to examine the longitudinal nature of the data. The findings were entirely left sided – specifically a smaller left whole thalamus (p =0.04), left pulvinar (p= 0.008) and left ventral (p =0.005). This study has demonstrated differences in thalamic volume in those who have had a PE compared to controls. The nuclei impacted are known to be involved in psychosis pathology. More research needs to be done on following this cohort up, specifically investigating changes in thalamic nuclei in those who develop a diagnosable psychotic disorder.

POSTER 08: Modeling the microRNA Regulation of TGF-β/SMAD Signaling Pathways for Seizure Control in Temporal Lobe Epilepsy

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Temporal Lobe Epilepsy (TLE) is the most prevalent type of focal epilepsy. Although it typically requires surgery and is drug-resistant, recent developments in sequencing, profiling, and systems biology provide new avenues for investigating potential molecular therapeutic targets. The intracellular signalling pathways (TGF-β and SMAD) implicated in TLE and the microRNAs (miR-21a-5p, miR-142a-5p, and miR-10a-5p) that are often up-regulated after induction of Status Epilepticus (SE) were mathematically modelled in this study using prior systems-based research findings. It has been discovered that there is a changeover between the seizure and anti-seizure cellular states after the injection of antagomirs, which block microRNA expression and its regulation of the intracellular dynamics. As a result, methods for seizure suppression were explored under various antagomir dosages and epileptogenesis situations in order to ascertain the intracellular response. This led to the exploration of proposed strategies of several epileptogenesis experimental designs with different antagomir administrations to determine its effect on the intracellular response, thereby offering approaches for seizure suppression.

Poster 09-34: Behavioural & Cognitive Neuroscience

POSTER 09: The fornix and stria terminalis in adolescents with psychotic experiences

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Hippocampus and amygdala changes are associated with psychosis. However there is little research examining the output tracts of these regions in psychosis. The fornix connects the hippocampus to the basal forebrain anteriorly and hypothalamus posteriorly, while the stria terminalis (ST) connects the amygdala to these same areas. The anterior commissure divides these tracts into anterior (precommisural) and posterior (postcommisural) fibres. This study investigates these two tracts and their pre and postcommissural fibres in young adolescents with psychotic experiences (PEs) and controls across two timepoints (TP), 2 years apart. 51 young adolescents with PEs (37 female) and 43 healthy controls (25 female) had high angular diffusion imaging at TP1 with 39 PEs and 29 controls at TP2. Images were processed with ExploreDTI and using a bespoke method the fornix and ST were separated and precommisural and postcommisural fibres isolated. Analysis of covariance was performed correcting for age, sex and intracranial volume. Right precommisural fornical MD (p=0.035) and RD (p=0.009) were increased, with decreased FA (p=0.045) at TP1, with increases across MD (p=0.004), RD (p=0.005) and AD (p=0.042) at TP2. Only right precommisural fornical MD and RD increases at TP2 survived Bonferroni correction at p=0.0083. No ST differences survived correction for multiple comparisons. Only fornix fibres to the basal forebrain, not fibres to the hypothalamus or ST fibres are impacted in young adolescents wth PEs. Findings were entirely right sided, reflecting similar right sided hippocampal changes found in psychosis. This study suggests right basal forebrain involvement in early psychosis, requiring further investigation.

POSTER 10: Comparison of post genome-wide association study results for autism and sleep-related phenotypes

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Autism is a common neurodevelopmental condition, characterised by social and communication deficits and restrictive and repetitive behaviours. Additionally, up to 83% of people with autism experience sleep disturbances which have been documented to exacerbate core symptomatology. Previous studies observed significant correlations in genetic effects between autism and self-reported tiredness, and autism and self-reported eveningness chronotype. We compared the post-GWAS results for autism and two sleep-related phenotypes: chronotype and insomnia, using the most recent GWAS available from the UK Biobank, PGC and iPSYCH. The aim was to investigate the overlapping genetic variation to elucidate the genes, biological pathways and tissues common to all three phenotypes. The post-GWAS analysis tool FUMA identified significant overlapping genes, and obtained gene-set and tissue enrichment analyses results. MACROD2 and MFHAS1 emerged as significant overlapping genes in autism and chronotype ($P<2x10-6$). Conversely, no overlapping significant genes were observed between autism and insomnia (all P-values>0.05). Gene-set analyses revealed two categories common to all phenotypes: synapse and glial cell related gene-sets ($P<0.03$). Tissue enrichment analyses identified the cerebellum as an area of significance across all phenotypes ($P<0.05$). The present study further implicates the cerebellum in both autism and sleep. Of note, a novel association was recently reported regarding MACROD2 and increased sleep duration during the dark circadian phase in knockout mice. However, a paucity of research exists regarding MACROD2's association with sleep in human subjects - particularly in autism cohorts. This thus demarcates MACROD2 as a locus of interest for further investigation.

POSTER 11: Exploring the Effect of Physiological Short-Chain Fatty Acids Concentrations on Hippocampal Synaptic Plasticity

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Gut microbial metabolites such as short-chain fatty acids (SCFAs), derived from bacterial fermentation of indigestible fibre, have come to light as possible regulators of host behaviour. Alterations to the metabolite profile through methods such as antibiotic supplementation have been seen to increase anxiety and depressive-like behaviour, while the lack of all microbial influence from birth, seen in germ-free mice, produces robust, sex-specific changes, such as a deficit in hippocampal long-term potentiation (LTP) in adult males. This led to our hypothesis that physiologically relevant concentrations of these metabolites could produce changes to synaptic plasticity. Adult C57BL/6 male and female mice were used to investigate the effect of butyrate, a SCFA, on hippocampal synaptic plasticity using electrophysiological field recordings in an ex vivo hippocampal slice model. 3μM butyrate exposure to hippocampal slices increases LTP induction, with a greater effect size seen in slices from female animals. This study shows that physiologically relevant concentrations of butyrate can affect hippocampal plasticity, potentially providing a basis for the gut microbiota's influence on learning and memory behaviour. Possible mechanisms include butyrate's action as a HDAC inhibitor and as an agonist for free fatty acid receptors in the hippocampus. The stronger effect size seen in butyrate-treated slices from female mice is reminiscent of the sex-dependent effects on hippocampal plasticity seen in germ free.

POSTER 12: A bespoke intervention for wellbeing in primary progressive aphasia: Tailored reminiscence interventions for ageing and dementias in community settings (TRIADICS)

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Research has revealed broad benefits of physical activity and cognitive engagement, including improvements in mental well-being (e.g., mood). A growing literature has begun to suggest that the benefits of Reminiscence Therapy can be enhanced by combining it with other, more physically-based interventions such as exercise, meditation or breathwork. This project uses Public and Patient Involvement (PPI) workshops to co-create tailored programming for people living with Semantic Dementia/Primary Progressive Aphasia (PPA). People with PPA have a primary communication impairment of speech and language. PPI is focused on embedding contributors with lived experience into the research process. For this project, people with PPA contributed to the content and design of the intervention. Contributors showed a preference for variety, which will allow us to assess interest and feasibility using a pilot approach. We are implementing and evaluating a four-week programme of a tailored therapeutic intervention in combination with reminiscence sessions to assess benefits to psychological health. This allows us to assess interest and feasibility on the kind of activities that are appropriate for people with PPA. To maximize the persons communication potential it is important to understand how dementia impacts communication, the nature & degree of the communication impairment and how best to support each person's interactions. Measures and activities are tailored to maximise accessibility using a combination of word choice, formatting and inclusion of symbols/emojis. Here we present practical examples of modified materials. An interdisciplinary team will help reveal the participants' communication competence, preferences for activities and potential benefits to wellbeing.

POSTER 13: Early-Life Microbiota Disturbance Impairs Diurnal HPA-axis Signalling and Behaviour

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The microbiota gut–brain axis is pivotal for brain development and maturation of immune system. The initial seeding during birth occurs across neurodevelopmental window and one of the strongest disrupting factors of the normal colonization process is birth by cesarean section (CS). This surgical procedure eliminates the possibility of natural vertical transfer of gut bacteria from mother to infant. Is known that the microbiome regulates different pathway and one of this is the HPA-axis, that plays a role in the body stress response. CS birth bypasses activation of the HPA-axis which would otherwise occur during passage through the birth canal. Also, the glucocorticoids released by the HPA-axis are a strong circadian element. The circadian rhythm is closely tied to the microbiota function with substantial effects on the host in immunity and metabolism. We aim to understand the neurobehavioral consequences associated with C-section coupled with maternal antibiotic administration as a translational approach. In adulthood CS born mice showed an increase in anxiety-like behaviour and a social cognition impairment compared to the vaginal born (VB) control mice. The metabolomics data on the PFC showed that many biochemical pathways involved in amminoacids biosynthesis and metabolism are altered between the CS and VB. Analyzing the corticosterone of post-natal date 9 (PND9) in different time point we saw a disruption of the diurnal rhythmicity of HPA-axis function. Together, these analyses will increase our understanding of the gut-brain axis signalling pathways recruited and identify the role of C-section-related missing microbes in brain health and disease.

POSTER 14: Molecular mechanisms, therapeutic targets, and biomarkers for CDKL5 Deficiency Disorder

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CDKL5 deficiency disorder (CDD) is a severe neurodevelopmental disorder characterized by early-onset epilepsy, intellectual disability, gross motor impairment, and autistic features. It is an ultra-rare disorder, affecting 1 in 40-60,000 individuals however, it is the most common type of childhood epilepsy. Despite major advances in anti-epileptic drugs to control seizures, there is no disease-modifying therapy for CDD yet. We hypothesize that microRNAs dysregulation in the brain underlies the altered networks in CDD driving the hyperexcitable and behaviour impairments. This project will be the first to characterize the role of microRNAs in CDD based on pilot data demonstrating microRNA dysregulation in CDD. A battery of behavioural tests are conducted to investigate cognition, sociability, learning, and memory using protocols including the accelerating rotarod test, open field activity, hindlimb clasping, elevated plus maze and object recognition test. Molecular methods including RNA extraction and small RNA sequencing to explore the microRNA profile of the Cdkl5 exon 6 knock-out mice and matched wild-type controls which are further validated by qPCR using Taqman microRNA assays. We validated the recent Cdkl5 exon 6 model demonstrating behavioral deficits as seen in CDD patients. RNA sequencing revealed significantly dysregulated microRNAs in CDD of which the top 20 were chosen and further validated. These observations are being further explored in different brain regions (hippocampus and cortex) to investigate the link between dysregulated microRNAs and respective behavioral impairments. Using proteomics, we will investigate the relationship between this dysregulation and cellular pathways and/or proteins.

POSTER 15: Neuropsychological Predictors of Decision-Making Capacity Impairment among Brain Cancer Patients (Primary and Metastatic) in the End-of-Life Context: A Study Protocol

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Cancer-related cognitive impairment, including memory deficit, is prevalent among brain cancer patients, both primary and metastatic. Relatedly, high rates of Decision-Making Capacity (DMC) impairment are evident in this cohort, with implications for informed consent and advance care planning in the end-of-life context. However, limited research in this population has explored the associations between neuropsychological deficit and diminished capacity. To model neuropsychological predictors of DMC impairment among brain cancer patients in the end-of-life context. Quantitative, cross-sectional design. Brain cancer patients (primary and metastatic) without mild cognitive impairment/dementia/other neurodegenerative disease and an estimated prognosis of <24 months, aged >18 years and a cohort of age, gender, and education-matched healthy controls will be recruited (total n = 82-90). Patients will be recruited from two hospices in the East of Ireland. DMC will be measured using the Capacity to Consent to Treatment Instrument [1]. The neuropsychological test battery will include measures of verbal fluency, language, memory, attention, and cognitive reserve, including the Repeatable Battery for the Assessment of Neuropsychological Status [2] and the Wechsler Adult Intelligence Scale 4th Edition [3]. Testing will take approximately 75 minutes and can take place over 1-2 sessions. Medical and sociodemographic variables will be abstracted from medical records. Statistical analysis will consist of between-group analyses to contrast neuropsychological and DMC profiles of the clinical and control cohorts and multiple regression analysis to determine which neuropsychological variables predict DMC impairment. Elucidating neuropsychological predictors of DMC impairment may guide DMC assessment and support in this cohort.

POSTER 16: Pain-related behavioural characterisation of the rat hindlimb ischemia-reperfusion model, and investigation into the endocannabinoid system

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Ischemia-reperfusion injury (I/R) can contribute to the formation of chronic wounds and associated pain. The endocannabinoid system (ECS) is involved in pain modulation, and in ischemic preconditioning, an endogenous protective mechanism against I/R. This study characterised pain-related behaviour in the rat hind limb I/R (HLIR) model. Male and female Sprague-Dawley rats (220-350g, n=11-12/group) underwent HLIR or sham procedure on the left hind limb. Mechanical, cold and thermal (heat) hypersensitivity were quantified in the ipsilateral and contralateral hind paws at baseline, up to post-HLIR day 29, via electronic von Frey, acetone drop and Hargreaves' tests, respectively. The affective component of pain was assessed using the place-escape avoidance paradigm (PEAP) on post-HLIR day 23. Levels of endocannabinoids 2-AG and AEA, and N-acylethanolamines PEA and OEA was analysed in discrete brain regions via LC-MS/MS. Persistent cold and mechanical hypersensitivity were observed in male but not female I/R rats vs sham post I/R injury ($p<0.05$). Both male and female HLIR rats had higher percent positive response to ipsilateral paw stimulation in the PEAP vs sham ($p<0.05$). Levels of PEA in the thalamus were higher in female I/R rats vs sham ($p<0.05$). These results indicate sexual dimorphism in the development of persistent pain-related behaviour post I/R in Sprague-Dawley rats. Analysis of discrete brain regions indicates no alterations in levels of AEA, 2-AG or OEA at 30 days post I/R, however subsequent analysis into other potential ECS alterations is warranted.

POSTER 17: Changes in circulating endocannabinoids in a rat model of low back pain

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Chronic low back pain (CLBP) is a major unmet clinical need. The endocannabinoid system is involved in the modulation of nociception, and has been shown to be altered in patients with CLBP. We investigated nociceptive behaviour in a rat model of intervertebral disc injury (IVDI), and associated alterations in levels of endocannabinoids/N-acylethanolamines (ECBs/NAEs) in blood plasma and spinal cord. Male 12-week old Sprague-Dawley rats underwent IVDI or sham surgery (n=10 per group). Mechanical (electronic von Frey-eVF) and heat (Hargreaves-HG) hypersensitivity were assessed at the base-of-the-tail 48/72hrs respectively, and weekly thereafter, until post-surgery day (PSD)20. Following euthanasia on PSD21, tissue levels of ECBs/NAEs were analysed in spinal cord and plasma via LC-MS/MS. Male IVDI rats displayed lower eVF thresholds compared to sham rats from PSD7 onwards. IVDI rats also showed decreased latencies to radiant heat from PSD3 compared to sham counterparts. Both mechanical and thermal hypersensitivity were sustained until day of euthanasia in the IVDI rats. Post-mortem analysis of plasma revealed lower levels of the endocannabinoid 2-AG in IVDI rats compared to shams. Levels of other ECB/NAEs were similar in plasma and in the lumbar and the sacral/coccygeal regions of the spinal cord of IVDI and sham rats. In conclusion, the IVDI model of CLBP is associated with reduced levels of plasma 2-AG, results that may be of relevance to biomarker discovery and/or underlying mechanisms.

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POSTER 18: Shedding light on the mechanisms of Number-Space Mapping using the Pupil-Light Response

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A prominent theory in numerical cognition research postulates that our brains organise numbers spatially from left-to-right (see the SNARC effect). These spatial-numerical associations relate to our abilities to understand and perform mathematics in childhood and adulthood. Further evidence suggests that spatial-numerical associations are not restricted to a horizontal left-right representation, but are in fact subject to individual difference with vertical, sagittal or multiple internal representations. Though this more 'flexible' internal number-space map is associated with higher mathematic performance, it is currently not widely researched using neurophysiological methods. Eye-tracking and more specifically pupillometry, can provide insight into our internal representations of numbers and magnitudes, with pupil dilation or restriction being an indicator of covert spatial attention in paradigms utilising the 'pupil-light response'. In the current ongoing study, we employ an adapted pupil-light response paradigm to examine covert spatial attention in an auditory magnitude comparison task using a split-screen paradigm. The task encompasses 384 trials with variables to investigate covert number-space mapping in both horizontal and vertical directions. Preliminary findings on pupil data from the current sample of 11 undergraduate participants will be presented here. These findings will be discussed in the context of flexibility in number-space mapping and how they will inform a subsequent pupillometry study to uncover the exact mechanism by which our brains map numbers across space.

POSTER 19: Physiological parameters as predictive markers of seizure onset and burden in the mouse intra-amygdala kainic acid model of temporal lobe epilepsy

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There is emerging evidence that spontaneous seizures display cyclic patterns and are therefore predictable in some people with epilepsy. Understanding the factors that influence such patterns and the identification of biomarkers of seizure imminence is a priority. This may include temperature, a known precipitant of seizures in some epilepsies. Intra-amygdala microinjection of kainic acid (IAKA) into mice has become an increasingly common model for studying the mechanisms and treatment of drug-resistant temporal lobe epilepsy. However, various features of the model remain incompletely understood including the relationship, if any, between physiological parameters such as temperature and the epilepsy phenotype. To explore this, we assessed the distribution of spontaneous recurrent seizures (SRS) according to body temperature, the correlation between the duration of SRS and body temperature at the time of seizure, the body temperature shortly before, during and after a SRS, and finally, we overlaid the severity of the epilepsy phenotype against seasonal aspects of temperature variation using local meteorological data. Adult male mice housed in a climate-controlled facility underwent status epilepticus induced by IAKA. A total of 312 hours of EEG containing 1920 SRSs were collected from 41 mice. The peak number of SRSs was detected at a body temperature of 35 – 35.5oC. We found that animal body temperature was higher during the ictal period relative to temperature in the 15 – 30 minutes before or after a SRS. These findings reveal additional features of this model and suggest body temperature as a potential easily accessible biomarker for seizure prediction.

POSTER 20: Contributions of PPL2 dopaminergic neurons to the modulation of olfactory behaviour in *Drosophila melanogaster*

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The role of dopamine as a driver for neural and behavioural plasticity has been well researched across species. Dopaminergic circuits are involved in learning, motivation, arousal and salience-based decision making, for example. In the brain of the fruit fly, Drosophila melanogaster, discrete clusters of dopaminergic neurons innervate the brain area associated with olfactory learning and memory: the mushroom body. These clusters have established roles in encoding the positive or negative valence of a stimulus. However, the role of a specific group of dopaminergic neurons called PPL2 is much less well defined. These neurons are not known to encode stimulus valence, however activation of PPL2 during aversive associative conditioning enhances memory strength and physiological responses to odours. Here we investigated the role of PPL2 in innate olfactory behaviour. Firstly, we addressed how artificial activation of PPL2 neurons affects olfaction at a range of odour concentrations using olfactory Y-mazes. We found that PPL2 activation enhances approach behaviour at low stimulus concentrations, and promotes olfactory aversion at a higher concentrations. Secondly, a connectome-based investigation of PPL2 outputs revealed a specific inhibitory neuron, APL, as one of the main post-synaptic targets. Overall, the data presented here suggests a role for PPL2 in olfaction, regardless of stimulus valence, and provides us with targets to further investigate the PPL2 circuit to shed light onto the dopaminergic modulation of behaviour.

POSTER 21: Targeting Glial β2-adrenoreceptors for the immunomodulation of an inflammatory-driven impairment to attentional and working memory performance in rats

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Disruption of Locus-Coeruleus-Noradrenergic (LC-NA) transmission is associated with multiple psychiatric and neurodegenerative disorders in humans including Alzheimer's Disease. The LC-NA system regulates various cognitive and executive domains that are impaired in Alzheimer's disease like attention and working memory, however the degeneration of the LC-NA system has a two-fold contribution to pathology in that noradrenaline additionally has the propensity to regulate the inflammatory phenotype in the brain and modulate microglial activities facilitating amyloid and tau clearance. The β2-adrenoreceptor subtype, highly expressed on cortical glial cells, mediates the anti-inflammatory action of noradrenaline and presents as a viable disease modifying target in Alzheimer's and related dementia's. For these investigations a delayed non-matching to position (DNMTP) protocol was employed to assess rodents' attention and working memory performance. Pharmacological validation of this assay consisted of observing deficits in working memory following administration of the muscarinic antagonist scopolamine and reversal of these effects with the acetylcholinesterase inhibitor donepezil. Subsequently systemic administration of the bacterial endotoxin and inflammogen, lipopolysaccharide (LPS), induced a sickness like behaviour followed by sustained deficits to working memory in the DNMTP task 24-hrs post-administration, attributed to mnemonic performance alone. Subsequent co-treatment of LPS with the long-acting brain-penetrant β2-adrenoreceptor agonist, formoterol, attenuated the deleterious effects of LPS on working memory performance in male rats.

POSTER 22: Distinct profiles of multisensory processing between professional goalkeepers and outfield football players

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In association football (soccer), the position of goalkeeper is the most specialised position in the sport and has the primary objective of stopping the opposing team from scoring. While previous studies have highlighted differences in physiological and match performance profiles between goalkeepers and outfield players, surprisingly little research has focused on whether goalkeepers differ in terms of their perceptual-cognitive abilities. Given that goalkeepers use multiple sensory cues and are often required to make rapid decisions based on incomplete multisensory information to fulfil their role (Franks & Harvey, 1997), we hypothesised that professional goalkeepers would display enhanced multisensory temporal processing relative to their outfield counterparts. To test this hypothesis, we measured the temporal binding windows of professional goalkeepers, professional outfield players and a control group with no professional football experience using the sound-induced flash illusion (Shams et al., 2000). Our results revealed a marked difference in multisensory processing between the three groups. Specifically, we find that the goalkeepers displayed a narrower temporal binding window relative to both outfielders and control participants indicating more precise audiovisual timing estimation. However, this enhanced multisensory temporal processing was accompanied by a general reduction in crossmodal interactions relative to the other two groups that could be attributed to an a priori tendency to segregate sensory signals. We propose that these differences stem from the idiosyncratic nature of the goalkeeping position that puts a premium on the ability of goalkeepers to make quick decisions, often based on partial or incomplete sensory information.

POSTER 23: Atrophy of the insula as a biomarker for Prodromal Dementia with Lewy Bodies

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Dementia with Lewy Bodies (DLB) is the second leading cause of dementia yet remains largely under-diagnosed. Correct diagnosis is challenging due to overlapping symptoms with other neurodegenerative disorders. Sensitive and specific biomarkers are required to detect DLB in the early stages, so that appropriate treatments can be prescribed before significant brain damage occurs. Atrophy of the insula presents one potential biomarker for early DLB and could be used to aid early and accurate diagnosis. To determine the efficacy of using visual assessment of insula atrophy as a biomarker for early-stage DLB, in distinguishing it from early-stage Alzheimer's Disease (AD). Methods: 3 raters visually assessed 163 T1 MRI images for atrophy of the insula and hippocampus using visual rating scales. 6 patient groups were compared; advanced DLB and AD, early-stage DLB and AD, mixed DLB+AD and healthy elderly controls. The raters were blinded to patients' diagnoses and each other's ratings. Visual results were compared to those attained from Freesurfer volumetric analysis. Visual analysis revealed notable differences in insula volume between dementia cohorts and controls. No appreciable difference in insula volume was found between the two early-stage groups. Freesurfer volumetric analysis showed significantly reduced hippocampal volume in both AD and early-stage AD, but not early-stage DLB. Volume of the insula differs visibly between dementia patients and healthy controls. Subtle changes in insula volume, as found in early-stage DLB and AD, are difficult to detect visually and may require more than simple visual analysis to be of diagnostic use.

POSTER 24: Recognition of Positively Valenced Emotional Faces Relates to Altered Microstructural Organization of Several White Matter Tracts in Euthymic Bipolar Disorder

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Social cognitive deficits are reported in euthymic bipolar disorder, including mood congruent deficits. Diffusion MR techniques suggest the potential role of the uncinate fasciculus underpinning this deficit in bipolar disorder (BD). We examine whether social cognition impairment is related to microstructural organization of white matter in euthymic BD. Fractional anisotropy (FA) maps were derived for participants with euthymic-BD (DSM-V) and controls (diffusion MRI) who underwent a test of social cognition. Maps were registered to an atlas (FMRIB58) and skeletonized (TBSS) prior to permutation-based analysis. We investigated a main effect, and interaction with diagnosis, for the relationship between social cognitive performance (positive, neutral, negative, total) and the microstructural organization of white matter (FA, TFCE, $p<0.05$). Recognition of facial expression valence was poorer in BD (n=36, mean age±SD,43±12) relative to controls (n=46,40±14) driven by performance on negative expressions. Accuracy on positive (not negative or total) was directly related to FA in BD relative to HC groups in external/internal capsules, left superior-longitudinal (SLF), right inferior-frontal-occipital (IFOF) and inferior-longitudinal-fasciculi (ILF), fornix and the corpus callosum. Overall performance was negatively related to left fornix, SLF, ILF and IFOF. Accuracy in the recognition of emotionally-positive facial expressions in BD, during euthymia, was directly related to microstructural organization of the ILF, IFOF, fornix, UF and splenium. These findings extend our understanding of white matter involvement, especially temporal-limbic and posterior-commissural pathways, in altered emotional processing and underscore the importance of assessing valence of emotional and mood state congruence for the development of appropriate interventions in BD.

POSTER 25: Acting in concert - soluble Tau and Aß in patient brain-derived extracts rapidly and persistently disrupt synaptic plasticity *in vivo*

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Amyloid ß (Aß) and tau, the two central proteins involved in causing Alzheimer's disease (AD), are proposed to trigger synaptic dysfunction long before apparent synaptic loss occurs in vulnerable brain circuits. Previously, we discovered that aqueous extracts of certain AD brains acutely inhibited long-term potentiation (LTP) and facilitated long-term depression (LTD) of synaptic transmission in an Aß-dependent manner. Whereas soluble Aß aggregates from AD brains are well-established potent synaptotoxins less is known about the synaptotoxicity of soluble tau in the brains of patients with AD or other tauopathies like Pick's disease (PiD). Recently, we reported that acute inhibition of LTP by certain brain aqueous extracts required the presence of tau or both Aß and tau (Ondrejcak et al. 2018 J Neurosci 38(50):10595 and In Press). Here, we further explore how soluble Aß and tau in extracts of patient brains contribute to persistent disruption of synaptic plasticity in the hippocampal CA1 area of urethane-anaesthetized male rats. Acutely after i.c.v. injection, soluble tau species in extracts of PiD brains facilitated a rapid-onset synaptic depression by weak low-frequency stimulation (LFS, 300 pulses at 1Hz). We also found that persistent LTP disruption caused by single i.c.v. injection of aqueous extracts from AD or PiD brains was abrogated by immuno-neutralization using the anti-tau antibodies, Tau5 and HT7, when administered 2-4 weeks later. These findings support a critical role for diffusible tau in causing rapid onset, persistent synaptic plasticity deficits and in promoting Aß-mediated synaptic dysfunction.

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POSTER 26: The interaction of Reminiscence Therapy plus Tai'Chi or Breathwork interventions on cognitive performance and well-being of older adults living in the community settings

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The human lifespan has expanded drastically in the last few centuries, due to improvements in sanitation, medicine, and nutrition, but with this increase in longevity comes higher rates of cognitive pathology such as mild cognitive impairment (MCI) and dementia; the latter is estimated to reach more than 75 million people by 2030. In the absence of a cure for dementia, recent research has sought to preserve and protect brain health in cognitively healthy older adults. Studies have revealed broad benefits of physical activity and cognitive engagement, including improvements in mental well-being (e.g., mood, life satisfaction) and cognitive performance (e.g., memory). Separately, research also provides evidence that actively engaging in guided use of one's memory, for example through simple reminiscence, leads to improvements in well-being. Building on previous research conducted by our lab, we investigated the effects of Reminiscence Therapy (RT), combined with selected activities, on cognition and well-being in healthy older adults aged 65+. A Patient and Public Involvement (PPI) approach was utilised to ensure relevance of the intervention and informed contribution from those with lived experience. Eighteen older adults completed a 6-week intervention whereby they engaged with RT and one of two chosen activities (Tai'Chi or Breathwork). Changes in pre- and post-intervention measures of cognition and well-being will be discussed in the context of potential benefits and future studies. Tai'Chi or Breathwork, combined with RT, may represent an accessible, easily implemented and non-invasive therapy for older adults living in the community settings.

POSTER 27: Maternal high-fat diet-induced microbial changes are associated with altered foetal brain metabolome and adolescent behaviour

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Maternal overweight and obesity perinatally has been linked to changes in neurodevelopment, plasticity and affective disorders in the offspring, with implications for microbial input from maternal intestines. Here, we investigate how maternal microbial signals imprint foetal brain metabolomics and adolescent behaviour. Adult female C57/Bl6 mice were fed either a control diet (CD: 10% fat) or a high-fat diet (HFD: 60% fat) from 8 weeks prior to mating throughout lactation. Whole brain metabolomic analysis in embryos and maternal caecal microbiota composition were assessed at embryonic day 18 (E18). Locomotor activity and anxiety-like behaviour were assessed in the adolescent offspring. HFD induced weight gain (p=0.0098 HFDvsCD) and altered caecal microbial composition (p=0.0022 HFDvsCD) in dams at E18. Maternal HFD led to upregulation of microbial genes linked to quinolinic acid synthesis (p=0.005 HFDvsCD), a neuroplasticity mediator linked to glutamate metabolism. Metabolomic analysis of embryo brains detected molecules linked to glutamate-glutamine cycle mediated by diet, such as alanine (p=0.0011 HFDvsCD), glutamate (p-=0.0029 HFDvsCD) and glutathione disulphide (p=0.0001 HFDvsCD). Pathway enrichment analysis of the differentially abundant metabolites revealed 35 times higher glutamine and glutamate metabolism in the foetal brains than expected (p= 0.00115 HFDvsCD). Female adolescent offspring from HFD-fed dams led to increased locomotor activity (total distance travelled p=0.004 HFDvsCD in open field) and anxiety-like behaviour (p=0.017 HFDvsLFD number of transitions in closed arms of the elevated plus maze). Our results suggest that maternal microbiota-mediated behavioural imprinting in the offspring is sex-specific, and might be linked to altered brain metabolites during critical developmental windows perinatally.

POSTER 28: Characterisation of Anxiety- and Depression-Related Behaviour and the Endocannabinoid System in the Rat Hindlimb Ischemia-Reperfusion Model of Chronic Wounds

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Ischemia-reperfusion injury can be an aetiology underlying the formation of chronic wounds, which are associated with a high incidence of comorbid anxiety and depression. The endocannabinoid system (ECS) may have a role in ischemia-reperfusion injury and is involved in the modulation of mood and anxiety. This study characterised anxiety- and depression-related behaviour in a rat model of hindlimb ischemia-reperfusion (HLIR) injury and investigated alterations in the ECS in discrete brain regions. Male and female Sprague-Dawley rats (220-350g, n=11-12/group) underwent HLIR injury or sham procedure on the left hind limb. Anxiety-related behaviour was assessed using elevated plus maze, light-dark box, and open field tests between post-HLIR days 16 and 26. Sucrose preference and splash tests assessed depression-related behaviour between post-HLIR days 17 and 20. Quantification of endocannabinoids (2-AG and AEA) and N-acylethanolamines (PEA and OEA) in brain tissue was carried out by LC-MS/MS. There was no effect of HLIR injury on anxiety- or depression-related behaviour. Female HLIR animals reared for longer than male HLIR animals in the open field test. Lower levels of 2-AG were found in the amygdala of female HLIR animals compared to female shams, with no differences in AEA, PEA or OEA levels. No differences existed in levels of analysed endocannabinoids or N-acylethanolamines in the hippocampus or striatum. These results indicate sex differences in locomotor activity and the ECS in discrete brain regions following HLIR injury. Further work is required to determine the implications of reduced 2-AG levels in the amygdala of female HLIR rats.

POSTER 29: PreCog: Exploring the Impact and Expression of Pre-treatment Cancer Related Cognitive Impairment in Patients to Support Postoperative Cognitive Function: Study Protocol & Preliminary findings

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Approximately 10-30% of cancer patients can experience cancer related cognitive impairment (CRCI) impacting their cognitive function pre-treatment or surgery. Little is currently known about the prevalence or development of this issue. This study aims to explore CRCI within this rare cancer cohort as they engage with a prehabilitation programme who are scheduled for surgical treatment. Fifty patients with peritoneal malignancy scheduled for CRS-HIPEC are recruited from the national centre for peritoneal malignancy at the Mater Hospital, Dublin. Patients are randomised to care as usual or intervention. Intervention patients receive individualised exercise and nutrition structured programmes pre- and post-surgery (pre-surgery: in the time window available >2 weeks and post-surgery for 6 weeks). Patients are assessed at five timepoints from baseline to 6-month follow-up. Outcomes include, health related quality of life (Euro-Qol EQ5D, FACT-G), subjective cognitive function (FACT-Cog), qualitative experience via semi-structured interviews and self-efficacy (GSE, CRSE). During the 6-month follow-up assessment, patients will take part in an objective test of cognitive function (MoCA). Pre-Operative Themes explored included: Experiences of Exercise and Nutrition, Perceptions of Surgery, Cognitive Health and Health Behaviour Change. The first 10 patient preoperative interviews have been analysed. Relevant themes include: 1. Thinking about cognition 2.Intervention Experiences 3. Autonomy 4. Emotional Conflict. Implications: Recruitment is ongoing as of June 2023. This study will potentially increase our understanding of this under-researched area of CRCI, whilst also providing valuable evidence for the benefits of a bimodal prehabilitation program within a rare cancer cohort.

POSTER 30: Alterations in the oral microbiome in individuals with schizophrenia

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Oral dysbiosis has been associated with the pathophysiology of numerous systemic diseases with underlying inflammatory components, including psychiatric disorders, with growing evidence linking the oral microbiome and schizophrenia. The aim of this study was to conduct 16S rRNA sequencing to characterise the composition and examine functional differences in the oral microbiome in individuals with schizophrenia compared to controls. Microbial DNA was extracted in duplicate from saliva samples from adults with schizophrenia (n=21) and matched healthy controls (n=25). Microbiome analysis was conducted using 16S rRNA sequencing on an Illumina MiSeq. The paired-end reads were trimmed using the DADA2 package in R (v4.2.2) and the online software package EZBioCloud was used to carry out secondary analysis, including alpha diversity, beta diversity and taxonomic and functional profiling. Subtle but significant differences in alpha and beta diversity of the salivary microbiome were observed, with clear separation of schizophrenia and healthy control cohorts into distinct clusters. Several bacterial taxa were also found to be differentially abundant in the schizophrenia cohort. In this preliminary study we have shown that the composition of the oral microbiome is associated with schizophrenia. Further studies are now warranted, particularly investigations into whether such shifts play any role in the underlying aetiology of schizophrenia.

POSTER 31: Suppression of mutant HTT acts on neurotransmission and protein clearance pathways to ameliorate symptoms in the r6/1 mouse model of Huntington's Disease

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Huntington's disease (HD) is a neurodegenerative disorder caused by a mutation in the HTT gene. This results in a devastating proteinopathy, characterised by severe motor, cognitive and behavioural symptoms. Lowering of mutant-HTT is a promising therapeutic approach, however efficacy in the clinic remains elusive. We aimed to test the effect of HTT-lowering in the R6/1 mouse model of HD, investigate whether earlier treatment was more effective, and to explore associated proteomic signatures. R6/1 mice were treated with antisense oligonucleotide (ASO) or vehicle via intracranial stereotaxic injection. Mice were subject to a battery of behavioural tests to explore disease phenotype and its potential rescue. Subsequent downstream proteomic analysis was performed via LC-MS/MS. Latency on the rotarod was increased in ASO-treated R6/1 mice ($p=0.0487$) and earlier treatment further improved motor coordination ($p=0.0184$). We show improved spatial memory on the Barnes maze, where the use of spatial strategy was increased in R6/1 mice treated early ($p=0.0113$) and late ($p=0.0183$). When reversal learning was tested, only mice treated earlier with ASO continued to use spatial strategy ($p=0.001$). We show rescue of recognition memory in novel object tests in mice treated early ($p=0.0015$) and late ($p<0.0001$). Differential protein expression results indicate that changes in dopaminergic, mitochondrial and synaptic structural proteins are responsible for observed behavioural improvements. Pathway enrichment analyses suggests protein trafficking/degradation and synaptic neurotransmission play key roles in pathogenesis. HTT suppression ameliorates neurodegenerative phenotype and earlier treatment is more effective. Proteomic analyses provides insight into pathways that could be targeted with combination therapy.

POSTER 32: Herbicides & The Microbiota-Gut-Brain Axis - Glyphosate Induces Behavioural Changes at Doses Relevant to Human Health

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The gut microbiota plays a vital role in maintaining the physical and mental well-being of the host. It is influenced by various factors, including xenobiotics such as pesticides. Glyphosate, a widely used herbicide, is believed to be harmless to humans because it targets the shikimate pathway, which is absent in animal cells. However, this belief is now being questioned as studies suggest that glyphosate may negatively affect the pathway in microorganisms residing in the gut, such as gut bacteria, which could have an impact on the host. Previous research has focused on either high dose exposure for toxicological effects or commercially available glyphosate-based herbicides. Indeed, the impact of glyphosate exposure at doses relevant to human health indicators are lacking e.g., Acceptable Daily Intake (ADI). In this study, adult C57BL/6 male mice were chronically exposed to glyphosate (0, 0.5 [ADI in Europe]), 5, 50 mg/kg/day) via drinking water. In week 5, behavioural analysis was initiated with a focus on anxiety, stress-coping, cognition, and sociability. Strikingly, glyphosate exposure increased anxiety in the open field test and diminished social novelty preference in the three chamber test in animals exposed to glyphosate in a dose independent manner. Future analysis will focus on understanding the potential mechanisms underlying these behavioural impairments. For this, we aim to analyse compositional and functional changes in the gut microbiome from pesticide exposure. Additionally, changes in the gut and brain will be explored with a focus on immune system, neuroplasticity and physiology.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 33: Inoculation of human traumatic brain injury (TBI) tissue homogenates induces cognitive deficits and widespread tau pathology in wild-type mice

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Traumatic brain injury (TBI) afflicts 55 million people worldwide. It represents a huge burden for the health system, and a leading cause of injury-related death and disability, with devastating impact on individuals and society. TBI is a complex disease characterised by dynamic pathophysiological adaptive and maladaptive processes that may predispose to chronic neurodegeneration and increase risk of dementia later in life including Alzheimer's disease (AD). However, the mechanisms driving the transition from the acute biomechanical impact to late neurodegeneration still need to be fully addressed. The development of progressive proteinopathies is a shared feature of dementia and TBI. Tau pathology has sparked our interest being a hallmark of AD and pathognomonic feature of chronic traumatic encephalopathy. In this study we document the presence of tau pathology in human brain contusion samples surgically removed after severe TBI in patients. We provide evidence that human TBI-induced tau (tauTBI) has self-templating properties and spreads throughout the brain causing a widespread tau pathology, associated with synaptic dysfunction and cognitive impairment. Moreover, we show that tauTBI can be horizontally transmitted to naïve mice by intracerebral inoculation, causing memory deficits. Thus, human tauTBI holds prion-like properties, suggesting a mechanism by which an acute biomechanical impact may predispose to neurodegeneration in patients. Finally, we exploit the C. elegans model to demonstrate that the hexapeptide Aβ1-6A2V(D), acting against amyloid β and tau, could represent an innovative pharmacological approach to counteract pathological aggregates formation and mitigate the progression of dementia and post-traumatic neurodegenerative processes.

POSTER 34: Multimedia methods for metacognition of concepts: A PPI pilot study demonstrating applications of creative technologies to understanding Bipolar I Disorder

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Bipolar I Disorder (BP-I) is a psychiatric disorder characterized by shifts in mood between periods of mania and depression. Mood episodes negatively affect psychosocial functioning and are associated with cognitive impairments in both social and non-social domains. One such impairment observed in BP-I is in metacognition - the capacity to assess the reliability of one's own mental representations and processes. However, how people select and use abstract concepts for understanding and decision-making is unclear because the literature specifically on Metacognition of Concepts is underdeveloped (Shea, 2018). Given that 'insight into illness' is positively associated with a patient's prognosis and treatment adherence, developing methods for studying the metacognition of concepts is important. Moreover, given that increasing public knowledge of mental health disorders reduces mental health stigma (Thornicroft et al., 2015), developing methods for communicating mental concepts is also pertinent. Our project addressed these two aims using a novel Patient and Public Involvement in Research (PPI) approach. Two artists, one with lived experience of BP-I, collaborated with two cognitive neuroscientists who conduct research on BP-I. This interdisciplinary team combined evidence from the scientific literature with the subjective lived experience of the artist. Resulting concepts were expressed using creative technologies in an audio-visual installation, thereby demonstrating - and indeed externalizing - the metacognitive awareness of cognitive impairments in BP-I through the creation of physical artistic artefacts to represent mental processes. The installation was then publicly exhibited. In this talk, we discuss how creative methods can be developed further in Arts x Neuroscience collaborations.

Poster 35-60: Clinical & Translational Neuroscience

POSTER 35: Circulating microRNA profiles distinguish epilepsy from seizure mimics in a hospital emergency department setting

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Emergency departments represent challenging settings where epilepsy and non-epilepsy patients may present with a seizure or a seizure mimic. Simple and rapid tests to distinguish these groups would enable prompt decision-making. This study was designed to explore whether differences in circulating small noncoding RNAs called microRNAs can distinguish between seizure and seizure mimics. This study focused on obtaining a cohort from a real-world setting. Patients presenting to an acute hospital with a history of seizure or collapse were invited to participate. An early and late serum sample was collected; the timing of these varied as patients presented to the hospital at different intervals. Patients were categorised into five clinical groups, epileptic seizure, syncope, psychogenic non-epileptic seizure, alcohol withdrawal seizure and first seizure. A discovery phase analysing small RNA via sequencing was conducted on 20 seizure samples versus 20 seizure mimics. Preliminary results of the discovery phase show a down-regulation of a large number of miRNAs in seizure vs seizure mimics. A large proportion of these downregulated miRNAs are from a miRNA cluster on chromosome 14 that includes miRNA134, a brain-enriched miRNA shown to be a potential therapeutic target for seizure control. The central hypothesis to be tested is that blood samples contain unique molecular patterns that change after a seizure. The present study indicates blood analysis of microRNAs could assist with clinical decision-making in an emergency department setting at the earliest stage of the patient journey (i.e. upon first presentation of a seizure).

POSTER 36: Functional connectome-based prediction of individual clinical and cognitive scores in midlife population with risk of dementia

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It is well acknowledged that Alzheimer's Disease (AD) neuropathology start decades before clinical manifestations, but the brain mechanism of sporadic AD in midlife remains unclear. Resting-state functional connectivity (FC) is increasingly used to understand early brain changes in Alzheimer's disease (AD) (Sperling, 2011; van den Heuvel & Sporns, 2019). We asked whether risk for late-life dementia impacts functional connectivity in cognitively healthy middle-aged individuals. Functional Magnetic Resonance Imaging and detailed neuropsychological assessments were obtained for 585 (207/378 female/male) cognitively healthy individuals, aged 40-59 years (mean = 50.9), from the PREVENT-Dementia study. Dementia risk was calculated with the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) score. A novel connectome-based predictive method called NBS-Predict was used to investigate the association between FC and CAIDE score and its role in cognition. FC significantly predicted CAIDE scores across the whole cohort ($r = 0.207$, $p < 0.001$,). FC within and between the cingulo-opercular network (CON) and sensorimotor network (SMN), as well as between CON and fronto-parietal network (FPN), and between SMN with default mode network (DMN), and FPN contributed the most (Figure 1). Furthermore, we found that, in the high dementia risk group (CAIDE > 6) only, FC, mainly in DMN-SMN and DMN-CON (Figure 2), significantly predicted multisensory processing cognitive score ($r=0.114$, $p<0.05$). Our results show that FC can be used to detect early brain changes associated with risk of future dementia in cognitively healthy individuals. This method has implications of the early detection of dementia in preclinical populations.

POSTER 37: Using Hexb^{tdTomato} mice to track microglial responses to spinal cord injury

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Spinal cord injury (SCI) is a complex and debilitating condition, resulting in motor, sensory and autonomic deficits. Microglia – the resident immune cells of the nervous system – are primary drivers of the secondary neuroinflammatory response associated with SCI, and can exert either beneficial or detrimental effects, depending on their activation state. Further insight into the modulation of microglial activation states is required prior to clinical translation. However, discriminating between resident microglia and blood-borne macrophages remains a challenge, particularly in a trauma setting. We aim to construct a detailed spatiotemporal map of microglial responses to further understand their activation states (with/without immunomodulation) after SCI, using novel genetic tools. We are utilising Hexb-tdTomato mice where the selective expression of a reporter fluorophore (tdTomato) allows us to assess individual microglial responses in a clinically relevant rodent model; contusion SCI. Through fluorescence microscopy, we are tracking microglial behaviour and phenotype, both within and around the lesion microenvironment, at key timepoints post-injury. Preliminary data suggest an increase in microglial number and circularity within the lesion microenvironment. We will further assess their responsiveness to interleukin (IL)-13; a cytokine which we have previously demonstrated improves both functional and histopathological recovery after SCI. This project aims to further our understanding of how microglia respond to pro- (SCI) and anti-inflammatory (IL-13) stimuli in an in vivo trauma environment. These data will ultimately unveil details of spinal pathology and microglial mechanisms not yet described, forming the basis for future immune-based therapeutic interventions that exceed previous approaches.

POSTER 38: Investigating the potential of a neurotrophins enriched collagen hydrogel for cell derived brain repair in Parkinson's disease: an early comparison between cyclosporine immunosuppressed Sprague Dawley rats and athymic nude rats

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Previous studies in our group have shown how to enhance the survival and differentiation of iPSC derived dopaminergic progenitors (iPSC-DAPs) by encapsulating them in a neurotrophins enriched collagen hydrogel prior to transplantation in the Parkinsonian rat brain. However, the beneficial effect of the collagen hydrogel was only observed in athymic nude rats but not in cyclosporine immunosuppressed Sprague Dawley rats. Therefore this study had two aims: determine the mechanism underlying the beneficial effect of the enriched collagen hydrogel and understand the differences between athymic nude rats and cyclosporine immunosuppressed Sprague Dawley rats which prevented the beneficial effect to manifest in the latter. These were assessed with two studies: one in each strain. Rats received unilateral 6-hydroxydopamine lesion followed by unilateral intra-striatal transplantation of iPSC-DAPs either alone, with neurotrophins or encapsulated in a collagen hydrogel with or without neurotrophins. Rats were euthanized at 1, 4 and 7 days post-transplantation. In both strains of rats, the hydrogel was able to polymerize in situ and to retain the neurotrophins which led to an early beneficial effect on the survival of the iPSC-DAPs. Although the Sprague Dawley rats were cyclosporine immunosuppressed, residual T-cells were found at the transplantation site. These findings suggest that the beneficial effect of the hydrogel might be related to its ability to retain the neurotrophins in the vicinity of the transplant. However, the hydrogel might not show its beneficial effect in the cyclosporine immunosuppressed Sprague Dawley rats because of the residual T-cells population.

POSTER 39: The KCNQ1 channel controls behavioural flexibility and regulates mitochondrial respiration

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Obsessive-Compulsive Disorder GWAS analyses and transcriptomic studies in compulsive TALLYHO/JngJ mice have identified the voltage-gated potassium channel KCNQ1 as a candidate gene underlying compulsive behaviour. Here, we characterised the impact of KCNQ1 knockout in C57/BL6 mice. We first conducted a battery of behavioural tasks in mice with a constitutive KCNQ1 knockout against wildtype controls. Mass spectrometry proteomic analysis was conducted in blood and brain to identify altered signalling mechanisms. Electrophysiological analysis of the hippocampal field postsynaptic potentials (fEPSP) following challenge (hypoxia and oxygen/glucose deprivation) and long-term potentiation (LTP) was deployed to investigate synaptic plasticity. KCNQ1 knockout mice showed significantly increased compulsive circling behaviour, head tics and repeated object checking compared to controls, in addition to reduced spontaneous alternation in the Y-maze, a reflection of behavioural flexibility. KCNQ1 knockout mice also showed significantly impaired spatial learning and memory in the Barnes maze. Interestingly, KCNQ1 knockout mice spend significantly more time in the centre of an open field apparatus and on the open arms of the elevated plus maze, indicating reduced anxiety or environmental sensitivity/awareness. Mass spectrometry analysis and protein enrichment pathway analyses of the anterior cingulate cortex, dorsal striatum and cerebellum shows a consistent proteomic signature of mitochondrial dysfunction and disrupted oxidative phosphorylation. Following hypoxia, fEPSP in KCNQ1 knockout hippocampal slices were slower to recover than wildtype, with overall reduced LTP. In summary, KCNQ1 is a strong regulator of compulsive behavioural patterns, potentially via regulation of mitochondrial bioenergetics. Additionally, KCNQ1 mediates neuronal resistance to hypoxic stress and appropriate LTP.

POSTER 40: MicroRNA-335-5p suppresses voltage-gated sodium channel expression and may be a target for seizure control

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Sodium channel blockers are among the most effective anti-seizure medicines (ASMs) but there remains an urgent need for new therapies for drug-resistant epilepsy (DRE). MicroRNAs (miRNA) are small non-coding RNAs which negatively regulate gene expression. Several miRNAs control neuronal excitability and, when targeted, can protect against seizures in preclinical models. Here we show that genome-wide miRNA screening of hippocampal tissue from a rat epilepsy model, mice treated with the anti-seizure medicine cannabidiol, and plasma from patients with treatment-resistant epilepsy, converge on a single target - miR-335-5p. Pathway analysis on predicted and validated miR-335-5p targets identified multiple voltage-gated sodium channels (VGSCs). In vivo studies in adult C57/BL6 mice used intracerebroventricular injection of antisense oligonucleotides against miR-335-5p which resulted in upregulation of various VGSCs in the mouse brain and an increased action potential rising phase and greater excitability of hippocampal pyramidal neurons in brain slice recordings, consistent with VGSCs as functional targets of miR-335-5p. Blocking miR-335-5p also increased voltage-gated sodium in human induced pluripotent stem cell-derived neurons. Inhibition of miR-335-5p increased susceptibility to tonic-clonic seizures in the pentylenetetrazol seizure model, whereas AAV9-mediated overexpression of miR-335-5p reduced seizure severity and improved survival. These studies suggest modulation of miR-335-5p may be a means to regulate VGSCs and affect neuronal excitability and seizures. Changes to miR-335-5p may reflect compensatory mechanisms to control excitability and could provide new biomarker or therapeutic strategies for different types of treatment-resistant epilepsy.

POSTER 41: Myosin-9 Protein is More Highly Expressed in Acute Ischemic Stroke Clots of Cardioembolic Origin

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Myosin-9 is a contractile protein involved in clot contraction by pushing platelets and fibrin toward the periphery of the clot leading to the formation of a fibrinolysis-resistant clot. Acute ischemic stroke (AIS) clots from cardioembolic (CE) origin are stiffer and harder to extract due to their fibrin/platelet-rich composition. We investigated the possibility of etiological differences in myosin-9 expression and whether it affects the revascularization outcome in AIS patients classified according to modified 'Thrombolysis in Cerebral Infarction' m(TICI) scale. Clots collected per-pass from 50 cases from each stroke etiology, CE, large artery atherosclerosis (LAA) and cryptogenic as part of the RESTORE registry of AIS clots. Sections were immunohistochemically stained for myosin-9 expression. Quantification of the positive staining was performed on Orbit (www.orbit.bio). Data was not normal and was analysed by Kruskal-Wallis and Mann-Whitney tests. Data expressed as median[IQR]. CE clots have a significantly higher myosin-9 expression (20[30-12]) compared to LAA (16[22.5-10]) and cryptogenic clots (17[21.3-9.4])($p<0.05$). Myosin-9 expression was significantly higher in clots from cases with poor recanalization outcome (mTICI ≤2a) compared to cases with good recanalization outcome (mTICI ≥2b) ($p<0.05$). Myosin-9 correlates negatively with RBC composition but correlates positively with fibrin/platelets and WBC composition. These findings show that myosin-9 is most abundant in CE clots and in cases with poor revascularization outcomes. Myosin-9 positively correlates with fibrin/platelets and WBCs and may be necessary in characteristics consequent to etiology. Improved understanding of the clots causing AIS could lead to rapid advancement in the development of novel therapeutic approaches.

POSTER 42: Investigating the impact of lifetime traumatic brain injury and Alzheimer's risk factors on brain health in middle age

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Approximately half of the global population will experience one or more traumatic brain injury (TBI) during their lifetime (Maas et al., 2016). TBI is a significant risk factor for dementia, leading to cognitive impairments, subjective memory complaints, and abnormalities in brain structure (Zijlmans et al., 2022). The aim of this study is to investigate the long-term cognitive and brain structural effects of lifetime TBI in a cohort of cognitively healthy middle-aged individuals from the PREVENT-Dementia study. This study explores the interaction between TBI and risk factors for late-life Alzheimer's disease (AD) using three different risk stratification approaches: APOE4 genotype, family history of dementia (FHD), and the Cardiovascular Risk Factor Aging and Dementia (CAIDE) score. 91 (41 Females) participants from Dublin study site completed clinical, cognitive and imaging testing. Hierarchical regression model analysis was conducted on the cognitive data, total gray matter volume (TGMV) and risk factors. A significant interaction was found between TBI and APOE4 in short-term memory binding [β (SE) = -0.208 (.060), $p<0.001$]. In TGMV, TBI significantly interacted with APOE4 [β (SE) = -0.004 (.002), $p<0.041$] and this seemed to only be the case for female carriers of APOE4 [β (SE) = -4301.5 (1830.3), $p = .008$]. To investigate preventative strategies for dementia, it is necessary to identify at risk subjects' years before the onset of clinical symptoms. Understanding the neurodegenerative profile in middle-aged individuals at risk of future dementia is of great importance for planning interventional studies and clinical trials.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 43: Mid-region tau fragments secreted from induced pluripotent stem cell-derived neurons carrying trisomy of chromosome 21 inhibit long-term potentiation *in vivo*

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We previously found that secretomes of induced pluripotent stem cell (iPSC)-derived human Trisomy 21 (Ts21) but not control neurons blocked hippocampal long-term potentiation (LTP) in the CA1 area of live rats under urethane anaesthesia and immunodepletion with the mid-region anti-tau antibody tau5 prevented the inhibition of LTP (Hu et al., Cell Reports, 2018). Here, we report that , in contrast, immunodepletion with the C-terminal antibody tau46 did not reduce LTP inhibition. To investigate synaptotoxicity of tau fragments in more details we concentrated Ts21 secretomes and separated proteins using size-exclusion chromatography (SEC). Notably, tau5 immunodepletion prevented LTP inhibition by concentrated Ts21 secretomes as well. SEC revealed that Ts21 secretomes contain mainly truncated tau species. Compared to other SEC fractions, we found that SEC fraction 15 (and 16) which is enriched with a relatively small mid-region tau fragments (4-17 kDa), was particularly effective at inhibiting LTP. As expected, in contrast to tau immunodepletion with tau5, immunodepletion with tau46 had very little effect on the concentration of the tau fragments in fraction 15. Consistent with this observation, tau5 but not tau46 completely eliminated LTP inhibition by fraction 15. Our results support further investigation of extracellular forms of tau in secretomes of iPSC-derived neurons modelling various neurogenerative conditions.

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POSTER 44: C-reactive protein expression in acute ischemic stroke blood clots

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Acute ischemic stroke (AIS) is a common cerebrovascular disease. C-reactive protein (CRP) is a prototypic marker of inflammation. To determine whether CRP can become a potential biomarker indicating stroke etiology, we examined CRP expression in AIS clots from cardioembolism (CE), large artery atherosclerosis (LAA) and cryptogenic subtypes. We collected blood clot samples from AIS patients of different etiologies, including CE (n=27), LAA (n=26) and cryptogenic (n=27). Assessment of clot composition was carried out using Martius Scarlet Blue. Immunohistochemistry of AIS clots were used to investigate CRP expression. Colocalization studies were used to investigate if there was any colocalization between CRP and platelets or fibrin. Data was analysed by Chi-square. Overall, 24% of clot samples expressed CRP. Nine of 27 CE, 7 of 27 cryptogenic and 3 of 26 LAA clots expressed CRP. The proportion of CRP expressed in CE was higher than that in LAA samples ($X2(1,n=53)=3.592, P=0.058$). CRP expression in cryptogenic and CE samples was similar. Clots expressing CRP had more fibrin than clots not expressing CRP ($P=0.002$). Immunofluorescence showed the colocalization of CRP and fibrin. There was no colocalization between CRP and platelets. AIS clots of CE origin expressed CRP more commonly than clots of LAA suggesting CE related stroke may be more strongly linked to inflammation. CRP in clots colocalized with fibrin suggesting a relationship between CRP and fibrin. Future work will increase sample size and explore the link between stroke etiology, inflammatory state, and clot pathogenesis.

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POSTER 45: Polymeric nanoparticles as drug delivery tools for brain degenerative disorders; in vitro assessment and release properties

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Drug therapies for neurodegenerative disease are limited in their efficacy and tolerability, largely due to poor penetration across the BBB and off-target peripheral effects. Polymeric nanoparticles (NPs) are advantageous for brain drug delivery due to their safety profiles, controlled drug-release properties and potential to reduce doses required and associated side effects. The aim of this work was to investigate the biocompatibility of NPs synthesised using the FDA-approved poly(lactic co-glycolic acid) (PLGA) polymer with CNS cells. NPs were synthesised using a PLGA-polyethylene glycol (PEG) block copolymer. PLGA-PEG NPs were applied to primary rat cortical neurons or mixed glia. Immunocytochemistry was performed for the MAP2 (neurons), IBA1 (microglia) or GFAP (astrocytes) proteins, cells were imaged under fluorescent microscopy and neuronal complexity or glial morphology were analysed. PCR was performed to quantify the expression of pro-inflammatory molecules including interleukin 1 and tumour necrosis factor by glial cells. Conditioned media from mixed glia exposed to NPs was transferred to neurons and their complexity was assessed. Neuronal complexity was not altered following direct exposure to PLGA NPs or the transfer of conditioned media from mixed glia. Direct exposure to PLGA NPs did not cause a change in glial morphology or the expression of pro-inflammatory markers. These investigations show that PLGA NPs are compatible with primary CNS cells in vitro and do not cause glial activation. Future studies will assess the drug release capabilities of these particles prior to selection of appropriate candidates for in vivo screening and testing in preclinical models of neurodegenerative disease.

POSTER 46: Unearthing the shortcomings in assessing cannabis use and dependence in research: a comprehensive review

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Despite the longstanding history of recreational cannabis use and its prevalence in adolescents, there is no standardised method for quantifying and classifying participants' cannabis use in research. Methods: This comprehensive analysis evaluates the approaches used to quantify cannabis use and dependence in neuroimaging research comparing cannabis users to non-using controls. Cohort, case control, and randomised control studies published from 1980 were included. 4,227 relevant abstracts were screened. A nested analysis was conducted on a final 187 studies. Data on the measures of frequency, quantity, duration, and dependence obtained from participants was extracted. 29% of papers measured both frequency and quantity of use, while 57% measured frequency alone and 9% measured quantity alone. The most prevalent method of assessing frequency was counting the number of smoking events, while the most common method of measuring quantity was totalling the number of joints smoked within given periods. 58% of papers used biological measurements such as urinary THC levels. 74% of studies employed an established cannabis use battery or questionnaire, however only 42% of studies used a questionnaire which assesses level of dependence. Current approaches rely heavily on self-reported measures, which invariably produce discrepancies. Such shortcomings are examined in this review, and the ramifications of disregarding precise THC exposure, along with simplistic frequency measures that do not consider quantity or the interval between smoking events. The importance of developing more robust interview and classification methods amongst the evolving landscape of cannabis research is emphasised.

POSTER 47: Sequential exposure to AAV-α-synuclein and FN075 as an approach to modelling Parkinson's disease in the rat

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There are many issues impeding the development of neuroprotective treatments for Parkinson's disease (PD), but consistently identified is the lack of clinically-relevant animal models. Viral vector overexpression of α-synuclein is widely considered the most relevant model, however this has been limited by high variability and inconsistency. One potential method of optimizing this model is pairing it with a secondary insult such as FN075, a synthetic molecule demonstrated to accelerate α-synucleinopathy. Thus, we investigate if sequential exposure of AAV-α-synuclein and FN075 into the rat brain can replicate the features of PD. 40 female Sprague-Dawley rats received a dual unilateral injection of AAV-WT-α-synuclein or AAV-GFP into the substantia nigra (SN). Followed 4 weeks later by unilateral injection of FN075 or vehicle control into four sites in the striatum. Animals underwent behavioural testing (corridor, stepping, and whiskers) every 4 weeks until sacrificed at 20 weeks. Immunohistochemistry post-mortem analysis was carried out to assess dopaminergic degeneration in the SN. In the behavioural assessments AAV-α-synuclein, administered either alone or sequentially with FN075, did not induce any impairment in contralateral motor function in the Corridor, Stepping, or Whisker test. However there was a trend for decreased paw placements in the whiskers test in the combined group. Preliminary post-mortem analysis showed no significant difference between groups for dopaminergic degeneration. Although this experiment did not replicate the degeneration and motor defects observed in PD further investigation is warranted as more representational models will be necessary in the testing of novel compounds and treatments for PD.

POSTER 48: Evaluation of Brain Natriuretic Peptide (BNP) and NT-proBNP as potential Biomarkers for Stroke Aetiology in Acute Ischemic Clots

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The importance of biomarkers for acute ischemic stroke (AIS) that can effectively differentiate between various aetiology subtypes is of critical importance. Brain Natriuretic Peptide (BNP) and NT-proBNP have demonstrated some potential in diagnosing the cardioembolic (CE) aetiology. To assess their viability as biomarkers for stroke aetiology, we examined their expression levels in AIS clots from both CE and large artery atherosclerosis (LAA) subtypes. 80 thrombi from 80 AIS patients, 40 of which were of CE and 40 of LAA aetiology, were analysed. Immunohistochemistry for BNP and for NT-BNP was performed and quantified using Orbit Image Analysis. Immunofluorescence was performed to investigate co-localization between NT-proBNP and T-lymphocytes, neutrophils and macrophages. Chi-square or Kruskal-Wallis test were used for statistical analysis. Spearmann's Rho was used for correlation analysis. A statistically significant positive correlation between BNP and NT-proBNP expression (Spearmann's Rho= 0.668 P<0.0001*) was observed. There was no statistically significant difference in BNP expression between LAA and CE clots (0.66 [0.13-3.54]% vs 0.53 [0.14-3.07]%, P=0.923). Similarly, there was no statistically significant difference in NT-proBNP expression between LAA and CE thrombi (0.29 [0.11-0.58]% vs 0.18 [0.05-0.51]%, P=0.119). BNP was distributed throughout the thrombus and most clearly evident within platelet-rich regions. In contrast, NT-proBNP co-localized with neutrophils, macrophages and with T-lymphocytes. Our findings do not provide any evidence that brain natriuretic peptides can serve as specific biomarkers for cardioembolic stroke aetiology. However, the presence of NT-proBNP expression in AIS clots by neutrophils, macrophages, and T-lymphocytes indicates its association with thromboinflammation.

POSTER 49: Differential cortisol responses to physical and psychological stressors in psychosis: a meta-analysis

Sahar Riaz, Vitallia Sooknarine, Linda Kelly, An Hsu, Michael O'Connor, Emma O'Hora, Amhad Almulla, Mary Cannon, Darren Roddy
Royal College of Surgeons Ireland

Cortisol, secreted by the hypothalamic pituitary adrenal axis (HPAA), increases in response to stress. Physical and psychological stressors may differently influence how amygdala modulates HPAA and cortisol secretion. Psychosis, a condition with problems with reality testing, is associated with stress and HPAA perturbations. This is the first meta-analysis to explore the effects of stressors on cortisol secretion in psychosis. Using Covidence, the terms cortisol OR [HPA OR hypothalamic pituitary adrenal OR awakening response] AND [psychosis OR mania OR schizophrenia OR psychotic depression OR schizoaffective] were used to identify papers. Studies with sufficient post-stressor or pre-post stressor difference cortisol data were included for a metanalysis using Stata 17. 1675 abstracts were screened. 188 underwent text review. Post-stressor and pre-post stressor difference cortisol data was extracted from 47 and 28 studies respectively. Patients with psychosis showed higher post physical ($d = 0.388$, $p = < 0.001$) and dexamethasone ($d = 0.756$, $p < 0.001$) cortisol compared to controls. Patients with psychosis demonstrated lower cortisol pre-post differences from psychological stressors, compared to controls ($d = -0.344$, $p = 0.01$). Meta-Regression demonstrated that age and severity of psychosis were correlated with post-stressor effect size estimates with female sex positively correlated with effect size for pre-post cortisol difference. Patients with psychosis demonstrate a differential cortisol response to physical/dexamethasone stress and psychological stress. Patients have higher cortisol after physical/dexamethasone stressors, whereas psychological stressors produce flatter cortisol increases compared to controls. This hints at a divergence in the neural processing pathways influencing the HPA axis in psychosis.

POSTER 50: Neural Mechanisms underlying self-regulation of corticospinal excitability; a TEP pilot study

Narin Suleyman, Kathy Ruddy
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Neurofeedback based on responses to Transcranial Magnetic Stimulation (TMS-NF) can be used to train individuals to upregulate or downregulate the amplitudes of their Motor Evoked Potentials (MEPs). This is typically achieved using different mental strategies to increase or decrease corticospinal excitability of motor projections to the target muscles. The distinct trained brain states for upregulating and downregulating motor excitability are associated with different profiles of neural oscillations and presynaptic GABAB disinhibition (Ruddy et al., 2018, eLife). In the current pilot experiment we investigated differences in TMS-evoked potentials (TEPs) recorded over motor cortex while using TMS-NF to self-regulate brain state, in order to further probe the underlying mechanisms. We recorded TEPs while 5 healthy participants used TMS-NF to both upregulate (UP) and down-regulate (DOWN) the amplitude of their MEPs, using a computer game based upon operant conditioning to reward large (or small) MEPs providing real-time feedback following each TMS pulse. Background muscle activity was monitored, and elevations above 7microvolts in the target muscle or surrounding muscles caused the trial to halt until sufficient relaxation was achieved. TEPs recorded during UP, DOWN, and REST trials demonstrated different patterns of evoked positivity and negativity, particularly around the N45. DOWN trials where MEP amplitudes were inhibited compared to baseline produced a very minimal N200 component, compared with UP trials or baseline REST trials. As TMS-NF may be a potential future approach for promoting functional recovery in stroke survivors, understanding the neural mechanisms underlying self-regulation of corticospinal excitability is an important prerequisite for clinical adoption.

POSTER 51: Transcranial Magnetic Stimulation with Neurofeedback (TMS-NF) for upper limb stroke rehabilitation

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Upper limb weakness is a frequent consequence of stroke, affecting 80% of stroke survivors. Existing upper limb rehabilitation post-stroke regularly requires the patient to generate movement in their stroke affected limb. However, this is often not possible for many individuals in the early period following a stroke, making existing approaches limited in their efficacy during a period of enhanced plasticity for relearning motor function. Transcranial Magnetic Stimulation with Neurofeedback (TMS-NF) shows promise in filling this gap as it can be used by the patient before they have regained any functional ability in their stroke affected limb. Despite being unable to move their paretic limb, many stroke patients exhibit Motor Evoked Potentials (MEPs) when stimulated over the damaged motor areas of the brain using Transcranial Magnetic Stimulation (TMS), showing that pathways from the brain to their stroke affected limb are still intact. TMS-NF may be used by stroke patients to engage these pathways by performing appropriate mental imagery to re-activate the damaged motor pathways. Here we present feasibility data showing that sub-actue stroke patients can learn to make MEP amplitudes larger using TMS-NF. This data has informed a larger randomized controlled trial which is ongoing to test whether this intervention ultimately impacts upon recovery of upper limb motor function.

POSTER 52: A Neurolinguistic task and composite biomarkers to assess cognitive abilities in Fragile X Premutation Carriers

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Fragile X Premutation Carriers (FXPCs) carry a premutation of the FMR1 gene (Fragile X Messenger Ribonucleoprotein 1). While a full mutation (>200 CGG nucleotide repeat expansion) leads to the neurodevelopmental disorder Fragile X Syndrome (FXS), the premutation (55-200 CGG repeat expansion) can lead to various conditions, including a disorder Fragile X Tremor-Ataxia Syndrome (FXTAS). FXTAS is a Parkinsonian disorder which, like Parkinson Disease's (PD), shows a range of tremor and ataxia symptoms but unlike PD there are no tremors when the patient is at rest. Typically naming objects or actions is an automatic process. In an ageing population completing this task can be challenging and impairment or delay to this process can be a hallmark of cognitive decline. This process is being investigated as an early marker of cognitive decline generally, but we are now developing this measure to identify individuals at risk of developing FXTAS. Here we are using a trio of linguistics tasks in conjunction with plasma biomarkers to develop a composite biomarker for FXTAS in FXPCs. Results of data collected so far show a general impairment in FXPCs compared to controls, particularly in retrieving objects compared to actions. This is in contrast to results from PD patients, who are generally more affected in retrieving action words, potentially because of motor system impairments. This finding might be fundamental for differential diagnosis of FXTAS and PD at its early stages, and for the development of appropriate biomarkers for drug discovery efforts in FXTAS.

POSTER 53: Tuberous Sclerosis Complex (TSC). Lived Experience (Republic of Ireland)

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To explore the lived experience of individuals with a diagnosis of Tuberous Sclerosis Complex (TSC) and their carers/families in the Republic of Ireland. 30 interviews were conducted. Adults with TSC (n=11) Family/carers of adults with TSC (n= 7) , Parents of children with TSC (n=12) Semi structured interviews were organised to suit participants, with the majority conducted in individuals' homes. Interviews were audio recorded, transcribed and thematically analysed. Experiences differ and are associated with symptom variability and where/how healthcare is delivered. Epilepsy and Tuberous Sclerosis Associated Neuropsychiatric Disorders (TAND) are identified as key challenges, as are poor access to respite and services for individuals with special needs. From the interviews, it is clear that managing TSC and the unknown trajectory of the disease can be difficult for patients and families. Lack of coordinated care causes communication complexities, difficulties in accessing care and is perceived as stressful. Diagnosis is frequently experienced as traumatic. Although the care and commitment of healthcare professionals is appreciated, low awareness and lack of knowledge about TSC amongst healthcare professionals are identified as concerns. There is variation in the lived experience of individuals/families affected by TSC. The management of epilepsy and TAND are identified as significant issues. Coordinated care is desired and may alleviate many reported concerns. Education of healthcare professionals about TSC is seen as important. Increased support for patients and families might assist them in coping with the impacts of this disease.

POSTER 54: Biomimetic Scaffolds for Spinal Cord Applications Exhibit Stiffness-Dependent Immunomodulatory and Neurotrophic Characteristics

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After spinal cord injury, inflammation at the site of injury and changes in the surrounding tissue produce an inhibitive environment that prevents regeneration. Through the development of implantable biomaterial conduits or "scaffolds" which mimic the mechanical and structural properties of the native tissue, it was hypothesized that materials could be developed whose innate properties and composition control important aspects of cell behaviour. To address this challenge, taking cues from the structure and composition of the cord, a comparative analysis of the pro-regenerative signalling effects of a wide variety of native cord matrix components was performed in multiple spinal cord cell models; including SH-SY5Y pre-neuronal cells, primary human astrocytes and primary adult rat dorsal root ganglia (DRGs). A novel mix of collagen-IV and fibronectin (Coll-IV/FN) was found to optimally enhance neuronal, astrocyte and DRG growth, neurite/axonal extension and induce morphological features typical of resting astrocytes. When incorporated into macroporous hyaluronic acid scaffolds of varying mechanical stiffness (0.8-3KPa), Coll-IV/Fn matrix-enhanced scaffolds promoted a range of growth-promoting behaviours in seeded cells in a stiffness-dependent manner. Softer scaffolds which exhibited mechanical properties similar to the stiffness of native tissue were shown to mediate astrocyte polarization and significantly increased IL-10 production. Furthermore seeded neurons and DRGs exhibited longitudinal alignment of neurites through the aligned pore structure and significantly increased axonal extension. These results indicate that the interaction of stiffness and the biomaterial surface plays an essential role in mediating repair-critical cellular responses and provide a flexible platform for the treatment of spinal cord injury.

POSTER 55: Rett Syndrome in Ireland: A demographic study

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Rett syndrome (RTT) is a rare neuropsychiatric condition associated to mutations in the gene coding for the methyl-CpG-binding protein 2 (MECP2). It is primarily observed in girls and affects individuals globally. The understanding of the neurobiology of RTT and patient management has been improved by studies that describe the demographic and clinical presentation of patients with RTT. However, in Ireland, there is a scarcity of data regarding patients with RTT, which impedes the ability to fully characterize the Irish RTT population. Together with the Rett Syndrome Association of Ireland (RSAI), we prepared a questionnaire to determine the characteristics of RTT patients in Ireland. Twenty five families have participated in the study to date, providing information about demographics, genetics, familial history, clinical features, and regression. The main finding of this study is the limited number of genetic tests conducted to support the clinical diagnosis of RTT. The results shows that Irish patients with RTT have comparable presentation with respect to patients in other countries, however, they had a better response to anti-epileptic drugs and fewer skeletal deformities were reported. Nonetheless, seizures, involuntary movements and regression were more frequently observed in Irish patients. Despite the limited sample size, this study is the first to characterise the RTT population in Ireland and highlights the importance of genetic testing for patients with RTT in order to sharpen the characterization of the phenotype and increase the visibility of Irish patients in the international RTT community.

POSTER 56: Effect of antibiotics on anxiety-associated neuronal activity in rat medial prefrontal cortex and amygdala

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Anxiety disorders cause substantial impairment of daily functions, with global prevalence estimations approximating 7.2% and accounting for up to 3.3% of the global burden of disease. Among the brain regions implicated in anxiety, two key areas are the medial prefrontal cortex (mPFC) and amygdala, which have both been shown to be involved in the regulation of anxiety-like behaviours. Additionally, studies have shown that alterations in the gut-microbiome can impact mood and neuronal activity. In this study, we investigated if the depletion of the gut-microbiome through a 4-week course of a cocktail of oral antibiotics could influence neuronal activity in regions implicated in anxiety in Sprague-Dawley rats. To measure neuronal activity, we implanted multi-site silicon electrodes in prefrontal cortex and paired tungsten electrodes in the amygdala of antibiotic-treated and control rats. Electrophysiological data was recorded during activity in behavioural paradigms and in their homecage environment. Behavioural analysis results showed no observable differences between the treatment groups, but the neural analysis data evidenced anxiety-associated coupling between amygdala and mPFC. Additionally, we found that the regularity of firing was less variable in antibiotic-treated rats when in the more exposed area of the open field test. These results provide multiple insights. Firstly, the behavioural data suggests that the influence of alterations to the gut-microbiome on anxiety-related behaviours due to antibiotics may be susceptible to multiple factors such as experimental set-up. Secondly, they suggest that the relative anxiogenic nature of an animal's environment may be encoded by the regularity of neuronal firing in the mPFC.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 57: Does Moderate or High Intensity Exercise Influence Multisensory Integration in a Cohort of University Students: An Exploratory Study

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Exercise can affect cognitive abilities short- or long-term, with varied task performance outcomes based on modality and intensity. We evaluated moderate and high intensity exercise effects on the Sound-Induced Flash Illusion (SIFI) task, assessing multisensory integration of audio and visual input. The SIFI task's viability in pitch side assessment of sports-related concussion (SRC) depends on its resilience to exercise. 192 participants (88 Males, 104 Females) undertook two exercise protocols on separate days; a high-intensity, interval anaerobic protocol and a moderate-intensity, steady-state protocol. Subjects were assessed pre- and post-exercise on the SIFI neurocognitive test, blood lactate, and heart rate (HR). The effect of exercise on SIFI performance was analysed for statistical stability via test–retest reliability to assess the internal consistency of each SIFI condition. A significant difference in lactate ($p = 0.00$, effect size = -1.89) and HR ($p = 0.051$, effect size = -0.14) was observed between post-moderate and post-high intensity exercise, proving that each exercise protocol induced the desired physiological changes. Both reliability and internal consistency statistics were deemed 'excellent' for both moderate (ICC2k= 0.909; 95% CI [0.85-0.94]; $\alpha = 0.951$) and high intensity exercise (ICC2k= 0.907; 95% CI [0.84-0.94]; $\alpha = 0.955$) respectively and proven statistically significant ($p<0.000$ in each case). These results show that neither moderate nor high intensity exercise affected SIFI performance across the cohort. These data suggest the SIFI remains immune to exercise's impact on perceptual performance, making it a suitable tool to assess SRC and brain health in athletes.

Key Words: Exercise; Cognition, Concussion; Perception; Brain Health.

POSTER 58: Optimization and characterization of a PLGA microparticle-embedded GelMA hydrogel as a therapeutic delivery system for potential spinal cord injury repair

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Spinal cord injury (SCI) is a devastating condition with limited regeneration, and no curative therapy is currently available. We have previously demonstrated that cell-based delivery of the immunomodulatory cytokine interleukin(IL)-13, drives alternative immune cell activation and improves both functional and histopathological recovery after SCI in mice. However, from a translational perspective there are many caveats associated with cell-based delivery approaches, such as poor cell graft survival and localization. Therefore, we have developed an injectable biomaterial-based delivery system consisting of poly(lactic-co-glycolic acid) (PLGA) microparticles embedded in a photocrosslinkable gelatin methacrylate (GelMA) hydrogel for localized and sustained delivery of IL-13 in preclinical SCI. Recombinant IL-13 was successfully encapsulated in PLGA microparticles using the double emulsion synthesis method. The release of IL-13 from GelMA hydrogel, PLGA microparticles, or a combination of PLGA-in-GelMA was measured over 6 weeks in vitro. IL-13 bioactivity was assessed in vitro by demonstrating that released IL-13 increased Arginase-1 expression and decreased LPS-induced expression of TNF-α and iNOS in BV2 microglia. Finally, ongoing work focuses on investigating the therapeutic efficacy of this hydrogel system in vivo using a mouse contusion SCI model. Thus far, we have shown that the hydrogel is well tolerated in vivo and that encapsulated microparticles are distributed throughout the lesion site following hydrogel injection, demonstrating the potential for localised therapeutic delivery. Taken together, these results suggest the utility of our biomaterial-based delivery system for controlled therapeutic release which may have significant potential for SCI repair.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 59: Developing an electrical impedance sensor to predict clot composition and improve stroke patient outcomes in the acute care setting

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Acute ischemic stroke (AIS) is the most common type of stroke. AIS is treated using thrombolysis with tissue plasminogen activator and thrombectomy in which the clot is mechanically removed. Clinicians are relatively blind to clot characteristics which can influence success of thrombolysis and thrombectomy. Development of a medical device using electrical impedance spectrum with machine learning that could identify clot characteristics in the acute care setting could improve stroke patient outcomes. The aim of the study is to advance development of a medical device capable of indicating clot characteristics in the acute care setting to inform the clinical decision making process and improve stroke patient outcomes. 253 thrombi (231 patients) were analysed in Clotbase International Registry. Impedance measurements were taken following clot retrieval by thrombectomy, followed by Martius Scarlet Blue (MSB) stain. Components were quantified via Orbit Software and correlated with impedance predictions and analysed using Kruskal-Wallis. MSB staining identified RBC as the major component in clots (37.6%) followed by platelets/other (30.3%), fibrin (25.5%) and WBC (5.7%). The impedance-based RBC prediction model correlates well with the RBC content determined by histology ($rm=0.9rh+7$, $\varrho=0.7$). Clots removed successfully in first-pass effect were richer in RBCs as assessed using histology and impedance prediction ($p<0.01$). Electrical impedance predictions of RBC content in AIS clots are consistent with histological findings. Further work will continue to improve the specificity of the impedance signature, advancing development of a medical device to guide clinical decision making in the stroke acute care setting.

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POSTER 60: Do audio-visual stimuli affect TMS-based measures that are under investigation as ALS biomarkers?

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Transcranial magnetic stimulation (TMS) measures show potential as ALS diagnostic biomarkers[1]. However, TMS-based studies require participants to sit still and do not allow any auditory or visual distractions. Lack of distraction may lead to participants attending to the sound/sensation of TMS pulses, or anticipating/attempting to modulate TMS-induced muscle contractions. Such mental activities can inadvertently affect cortical excitability and TMS measures[2]. Providing a distractor could help to keep mental state consistent, improving statistical power of ALS-related cortical pathophysiology research. 13 right handed controls were recruited. Resting motor threshold (RMT), short intracortical inhibition (SICI), long intracortical inhibition (LICI) and interhemispheric inhibition (IHI) were recorded via threshold tracking-TMS. Each measure was recorded while participant was at rest without sensory input, watched and listened to a documentary, or listened to a documentary. Linear mixed effects modelling was conducted to investigate the effects of distractor stimuli. LICI was greater with auditory-only distraction compared to without. Conversely, during audiovisual distraction, LICI was lower. Significantly less IHI was observed when auditory distraction was present compared to absent. RMT and SICI were not affected. These results indicate that providing participants with distractor stimuli during measurement of RMT and SICI will not affect motor cortical excitability. Such distractors may affect LICI and IHI measurements. Such distractions could make studies more tolerable for participants and help to improve consistency of mental state across and within participants.

References: 1.Vucic, et al., Handbook of clinical neurology, 116, pp.561-575,2013. 2. Cengiz Bet al.. Experimental brain research, 236(2), pp.497-503.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

Poster 61-93: Molecular & Cellular Neuroscience

POSTER 61: Forced polarisation of microglia by IL-13 is modified by microenvironmental context

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Traumatic spinal cord injury (SCI) is a severe clinical challenge, often leading to long-term sensory, motor, and autonomic dysfunction. The SCI cascade involves a primary physical damage phase and a secondary phase characterized by inflammatory signalling driven by microglia and other infiltrating immune cells. Immunomodulatory therapies may help promote healing and restrict secondary damage. We have previously demonstrated that interleukin (IL)-13 delivery improves functional and histopathological recovery after SCI in murine models, primarily by polarising macrophages towards an alternatively activated pro-reparative M2-like phenotype and reducing axonal contacts. Although microglia respond robustly to IL-13 in vitro, polarisation of microglia in vivo is more difficult. To better understand what conditions may restrict microglial responses to IL-13 in vivo, we sought to examine the effect of cellular context or microenvironment on IL-13 efficacy in forcing microglia polarisation in vitro. Transcriptional changes (RT-qPCR) and cytokine release (ELISA) were examined in BV2 microglia following IL-13 treatment. IL-13 leads to increased expression of the anti-inflammatory marker arginase-1 while lowering expression and secretion of the pro-inflammatory markers IL-1beta, iNOS, and TNFalpha, signifying effective polarisation of microglia. Concomitant administration of lipopolysaccharide (LPS) with IL-13 reduces IL-13 polarisation efficacy in BV2 cells, suggesting that IL-13 efficacy is reduced in inflammatory contexts. Other microenvironmental conditions, such as extracellular matrix proteins were also examined, revealing key constraints that act to limit IL-13 efficacy in forcing microglial polarisation. These data will inform future studies into the microglial pathways that may be targeted to improve IL-13 efficacy *in vivo*.

POSTER 62: Targeting dysregulated long non-coding RNA expression as a new therapeutic strategy in epilepsy

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Temporal lobe epilepsy (TLE) is a chronic brain disorder characterized by spontaneous recurrent seizures. It commonly develops after a precipitating brain insult, which is driven by large-scale changes in epigenetic-mediated regulation of gene expression. In contrast to other epigenetic mechanisms, the functional involvement of long non-coding RNAs (lncRNAs) in epilepsy pathogenesis remains largely unexplored, although they are increasingly recognized as key modulators of RNA processing. Here, we perform the first comprehensive profiling study of lncRNAs in epilepsy development and assess their utility as novel drug targets. To study lncRNA dysregulation in TLE, kainic acid-induced post-Status Epilepticus mouse models were used. Genome-wide transcriptomic sequencing performed on hippocampal brain tissue collected at key timepoints during epilepsy development revealed significant changes in numerous lncRNAs strongly influenced by the time after the initial insult. Several of them are known for their importance during embryonic development, in plasticity and cell death, which indicates lncRNA-mediated effects on major epileptogenic disease mechanisms. We then applied stringent bioinformatic filtering to predict those dysregulated lncRNAs with the highest pro-epileptogenic potential and selected the five most promising lncRNA candidates based on various characteristics including the expression level, expression change and inter-species conservation. Antisense oligonucleotides are now used to investigate the disease-modifying effects of targeted lncRNA inhibition and identify the underlying mechanisms of action. To conclude, extensive dysregulation of lncRNA expression is a likely contributor to TLE development and progression, which renders lncRNAs promising targets for the development of novel preventive and/or therapeutic treatment approaches.

POSTER 63: Effects of short-term aerobic exercise on systemic LPS-induced inflammation and microglial activation in young adult male and female mice

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Regular aerobic exercise has been shown to protect brain health, with recent evidence suggesting its role in modulating inflammatory mediators and microglia states and functions in the central nervous system. The effects of exercise may partly be attributed to direct/indirect actions of exercise-derived factors, such as lactate. Circulating lactate concentrations increase post-exercise, and peripheral lactate can cross the blood-brain barrier via monocarboxylate transporters (MCT), where it can act as a fuel/signalling molecule. Here, we investigated the impact of 7 consecutive days of low-to-moderate-intensity treadmill running on microglial activation in 3-month-old C57BL/6J mice who were subsequently subjected to systemic inflammation via lipopolysaccharide (LPS) injection. Additionally, we explored any modulatory effects of lactate by administering a daily dose of an inhibitor of the MCT 1 and 2 or its vehicle before exercise sessions. Spatial memory of the mice was assessed using the novel object location task. Preliminary findings indicate that one week of aerobic exercise did not significantly modulate the response to the immune challenge induced by LPS, nor did it lead to a notable improvement in spatial memory. However, sex-specific effects were observed, with exercising female mice treated with the MCT inhibitor showing improvement in cognitive performance during the test, with males exhibiting the opposite effects; while cytokine expression also differed between sexes. These results suggest that male and female mice may respond differently to both LPS challenge and exercise, emphasising the need for further investigation into the underlying molecular mechanisms associated with the observed effects and the potential translational impact of these data.

POSTER 64: RNA binding protein Rbfox1 has an evolutionary conserved role in regulating normal nociception and pain processing

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Nociceptive escape responses to noxious thermal and mechanical stimuli are widely conserved across metazoan species, including the fruit fly. Drosophila larvae and adults possess peripheral somatosensory neurons, which resemble vertebrate nociceptors both structurally and functionally. Studies in larval and adult models demonstrated that the peripheral nociceptors exhibit chronic sensitization following epithelial and nerve injury. About 70% of disease genes are conserved in flies and therefore encourage use of Drosophila genetics for identification of molecular mechanisms important for chronic pain. Here, we discuss evidence that RNA binding protein Rbfox1 has an evolutionary conserved role in regulating normal nociception and sensitisation of the nociceptive system. Significant number of target genes which are regulated by Rbfox1 are also associated with chronic pain and abnormal nociception. Additionally, there is a considerable genetic and functional evidence for Rbfox1 involvement in a number of musculoskeletal conditions and therefore warrants further inquiry into its contribution to pain mechanisms. We have developed video assisted behavioural assays that allow automated and unbiased quantification of stereotypic escape behaviours in Drosophila. Using this assays in combination with traditional sensory testing analyses in genetically modified mice we provide robust evidence that Rbfox1 has an evolutionary conserved role in regulating normal behavioural response to noxious stimulus. Additionally, we employed translational reporter tools to demonstrate that Rbfox1 activity adapts to noxious stimulation and is upregulated following sensitisation in fly nociceptors. We propose that Rbfox1 is a critical contributor to the adaptation of the nociceptive circuit in the process of pain resolution following injury.

POSTER 65: Epileptogenesis remaps the diurnal gene expression in the mice hippocampus

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Epileptogenesis is the process in which a healthy brain becomes susceptible to the generation of spontaneous recurrent seizures and epilepsy development. Despite the circadian system being a relevant candidate to exert a maladaptive activity during epileptogenesis, the key mechanism that drives epileptogenesis is unclear. Here, we profile the diurnal oscillatory molecular pattern in the mice hippocampus during epileptogenesis. Male adult C57Bl6 mice (n=5/group/time-point) underwent intra-amygdala kainic-acid-induced (i.a.KA) status epilepticus (SE) or vehicle (i.a.PBS) injection. From 24h after SE, mice were euthanised and the ipsilateral-hippocampi were collected at 6 different Zeitgeber-Times (ZT; every 4h over 24h, starting at 8am) for RNAsequencing or qPCR. Differential expression and oscillatory analysis were performed using DESeq2, t-test or JTK_CYCLEs, respectively. The RNAsequencing (adjusted p-value<0.001) showed a time-of-the-day separation when comparing the 6 ZT under light with dark exposure. The number of significantly differentiated protein-coding genes in epileptogenesis during the light phase was 4,620 (3,549 up- and 1071 down-regulated), while in the dark phase, 3,127 genes were differently expressed (2,786 up- and 341 down-regulated). Top 4 genes were accordingly validated by qPCR across all time points ($p<0.05$) (upregulated: GFAP, C4b, Serpina3n; downregulated: Glul). Oscillatory analyses showed that 1468 genes, which presented diurnal rhythms in i.a.PBS, lost their rhythmicity in epileptogenesis. Epileptogenesis rendered 140 new rhythms, while only 21 genes kept cycling in both groups. This pioneer study profiled the diurnal gene expression during epileptogenesis in mice hippocampus. Future studies are necessary to further understand how it can impact epileptogenesis and epilepsy development.

POSTER 66: The maternal gut microbiota influences neural and vascular cortical development in prenatal mice

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Growing evidence has revealed that the perinatal gut microbiota has a role in the aetiology of neurodevelopmental and neuropsychiatric disorders. In particular, the maternal gut microbiota has been shown to modulate offspring neurodevelopment in the sterile uterine environment, with consequences on later brain functioning and behaviour. However, the mechanisms underlying the regulation of prenatal brain development by the maternal microbiota remain poorly understood. We hypothesise that signals from the maternal gestational gut microbiota influence prenatal neurodevelopment by modulating neuro-glia-vascular interactions. The coordinated development of the neural and vascular systems is critical for the developing brain, which relies on common developmental cues. In addition, neurovascular interactions are required for the correct development of brain barriers (blood-brain barrier and blood-cerebrospinal fluid barrier), which serve as essential interfaces between the developing brain and the periphery, acting as gateways for microbiota-brain communication. Our preliminary data suggest that disruption of the maternal microbiota with a broad-spectrum antibiotic cocktail has consequences on the proliferation, differentiation, and structural integrity of neural progenitor cells. Furthermore, we observed deficits in brain vascular and neurovascular development. Unravelling these processes and their associated mechanisms will provide a new lens in our understanding of the role of the gut microbiome in neurodevelopmental disorders.

POSTER 67: Defining selective neuronal vulnerabilities in human/rat tissue and hNPCs-derived cortical neurons *in vitro* model

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Chronic neuronal degeneration is the prime substrate of cognitive abnormalities in progressive multiple sclerosis (PMS). In MS lesions, cortical demyelination is sustained by deficient remyelination mechanisms, and its extent may be determined by meningeal inflammation, further correlating with neuronal damage and loss. Moreover, pathological changes are widespread across the upper cortical layers, with heightened vulnerability of Cux2-, RORβ-, PV-expressing pyramidal neurons (PNs) and SST-expressing interneurons (INs). Thus, labelling and tracking cortical neuronal subtypes may provide invaluable data for the development of improved models of PMS-like pathology. We therefore aimed to establish in vitro rat and human models of excitotoxicity, with particular focus on cortical neurons from layers II/III and V. To facilitate the monitoring of different cortical cell populations, a panel of antibodies against 14 cortical neuron markers was tested and validated in rat and human (non-MS) paraffin-embedded tissue, using colorimetric staining. In parallel, human stem cell-derived cortical neurons were obtained via small molecule-induced differentiation. The cortical cultures were characterized by their neuronal heterogeneity at 24 days in vitro after the neuronal progenitor (NPC) stage. Immunocytochemistry allowed the evaluation of the relative expression of PNs and INs, accounting for approximately 20% and 55% of the cell population, respectively. Full validation of cortical markers revealed the expression of mixed cortical neurons, including the upper layer cortical subpopulation Cux2. To test neuronal vulnerability to excitotoxicity, NPC-derived monocultures were treated with 1 mM glutamate for 24h and axonal damage was screened using the antibodies validated in human paraffin tissue.

POSTER 68: Differential effects of TLR3 activation on social behaviour and prefrontal cortical inflammatory gene expression in the valproic acid model of autism: a role for the endocannabinoid system?

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Autism is associated with immune alterations and neuroinflammation. Increasing endocannabinoid tone attenuates autism-related behavioural changes in rodent models and modulates TLR-induced neuro-immune responses. This study examined TLR3 activation, in the presence or absence of a FAAH inhibitor, on behaviour, neuroinflammatory gene expression and endocannabinoid levels, in a preclinical rodent model of autism. Female Sprague-Dawley rats prenatally exposed to saline or VPA received 1) polyI:C (3mg/kg i.p.) or saline vehicle and were euthanised 4h later OR 2) FAAH inhibitor PF3845 (10mg/kg i.p.) or vehicle, prior to polyI:C, and underwent nociceptive and social behaviour testing 24h later before euthanasia. The PFC from both cohorts was assessed for endocannabinoid and N-acylethanolamines levels using LC-MS/MS and inflammatory gene expression using RT-qPCR. PFC inflammatory gene expression was increased in saline-exposed rats at 4h & 24h post polyI:C. In VPA-exposed rats, polyI:C-induced increases in IL-1β and CCL2 expression were blunted at 4h, while inflammatory gene expression returned to baseline levels at 24h. PFC 2-AG levels were reduced in saline-exposed poly I:C-treated and VPA-exposed vehicle-treated rats, when compared to saline-exposed vehicle-treated counterparts. PF3845 increased N-acylethanolamine levels in saline- and VPA-exposed rats, an effect associated with blunted poly I:C-induced inflammatory gene expression in saline-exposed rats only. Nociceptive responding did not differ between the groups, however, polyI:C reduced social novelty preference of VPA-, but not saline,-exposed rats, an effect unaltered by PF3845. VPA-exposed female rats display differential behavioural and neuroimmune responses to a viral immune challenge, which were unaltered by FAAH inhibition.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 69: Pro-inflammatory signaling along the P2X7R/NOX2 inflammatory axis in microglia

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Microglia play both protective and damaging roles in secondary injury following traumatic brain injury (TBI). The P2X7 receptor (P2X7R) is a ligand gated ion channel, predominantly expressed on microglia, which is activated by high concentrations of its endogenous ligand, ATP. Under injury conditions where ATP levels increase (mM range) due to neuronal cell death, ATP acts as a potent DAMP. ATP-dependent microglial activation promotes release of cytotoxic proinflammatory mediators, including IL-1β and TNFα. Furthermore, P2X7R activation enhances NOX2 activity, leading to extracellular reactive oxygen species (ROS) production that can act downstream promoting NLRP3 inflammasome assembly, IL1β and IL18 release. The goal of this project was to investigate proinflammatory signaling along the P2X7R/NOX2 inflammatory axis in microglia. Immortalized microglial (IMGs) cells were activated by lipopolysaccharide in combination with BzATP, an ATP homologue specific to P2X7R, and were treated with increasing concentrations of inhibitors, A438079 (P2X7R), JNJ47965567 (P2X7R), or GSK2795039 (NOX2). We found that stimulating P2X7R induces proinflammatory microglial activation, as shown by increased nitric oxide (NO), ROS, TNFα, and IL1β. P2X7 inhibitors attenuated NOX2 activation, iNOS expression and NLRP3 inflammasome activity, resulting in a significant reduction in proinflammatory mediators (ROS, NO, TNFα, IL1β and GSDMD). Similarly, selective inhibition of NOX2 using GSK2795039 reduced P2X7R induced proinflammatory activation of microglia suggesting cooperativity between these signaling pathways. Thus, P2X7R/NOX2 inflammatory axis may be an important mechanism of microglial activation that may be therapeutically targeted in TBI.

POSTER 70: A Novel Therapy for the Treatment of TLR Mediated Neuroinflammation

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Alzheimer's disease is a neurodegenerative disease characterised by the accumulation of amyloid β(Aβ) plaques and tau tangles in the brain. Current disease-modifying therapies which target these aspects alone show limited clinical efficacy. Aβ aggregation is promoted by interaction with free metals including Cu2+, which also determines its capacity for oxidative damage and excitotoxic neuronal death. Aβ is also the primary inflammatory stimulus in the AD brain and has been shown to be mediated through activation of toll-like receptor(TLR)2, leading to uncontrolled microglial activation and neuronal dysfunction. Our collaborators developed a novel suite of coumarin-derived Schiff base compounds with the ability to regulate oxidative capacity in cancerous cells and chelate free Cu2+. Therefore we investigated their potential as novel multifunctional neurotherapeutic agents. Coumarin-derivative L4 was selected for investigation based on its previously-determined solubility and cellular tolerability. In BV2 cells, microglial activation was induced by TLR2 agonist lipoteichoic acid(LTA) in the presence and absence of L4. Two-way ANOVA revealed a significant, concentration-dependent attenuation in TNFα and IL-6 release from LTA-stimulated cells. Moreover, L4 significantly reduced the LTA-induced expression of iNOS and nitrite. Further analysis in THP-1 monocytes indicates that L4 likely mediates these effects via inhibition of NF-κB. To explore its neuroprotective effects, cell viability and reactive oxygen species(ROS) were evaluated in tBHP-stimulated N2a neuroblastoma cells. L4 significantly reduced ROS production, and mitigated neuronal death in response to oxidative stress. Taken together, our findings support the further investigation of coumarin-derivative L4 as a strategy to target multiple facets of AD pathology.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 71: Interaction of high-fat diet and brain trauma alters adipose tissue macrophages and brain microglia associated with exacerbated cognitive dysfunction

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Obesity leads to heightened microglial activation and worsening of traumatic brain injury (TBI)-induced neurological dysfunction. However, the mechanisms underlying the interplay between obesity and TBI are unknown. Adult male mice were fed a high-fat diet (HFD) for 12 weeks prior to exposure to controlled cortical impact (CCI) or Sham surgery. Cohort 1: Mice were euthanised at 28 days post-injury (dpi). Visceral adipose tissue (VAT), brain tissue, and blood samples were processed for RNA/protein analysis. Cohort 2: Following CCI/Sham surgery, mice underwent cognitive neurobehavioral tasks and were euthanised at 90 dpi. Isolated microglial cells and VAT were analysed using a Nanostring Neuroinflammation panel. Statistical analysis was performed using a two-way ANOVA with Tukey post hoc tests. Cohort 1- HFD induced significant increases in body weight (g), metabolic markers, and VAT weight (g/g BW); effects of which were independent of TBI. HFD resulted in significant increases in VAT expression of TNF-a, NLRP3, NOX-2, p22phox, and IL-10. TBI significantly exacerbated HFD-dependent increases in IL-1β and NLRP3. TBI resulted in significant increases in hippocampal expression of IL-1β, NOX-2, and p22phox; HFD exacerbated TBI-induced increases in p22phox. Cohort 2 - Combined TBI and HFD resulted in additive dysfunction in cognitive behavioural tests. Analysis of isolated microglial cells and VAT in combined HFD and TBI showed amplification of central and peripheral microglia/macrophage responses. Diet-induced obesity and TBI can independently prime and support the development of altered states in brain microglia and VAT macrophages, that may, in part, underlie exacerbation of cognitive deficits.

POSTER 72: Alzheimer's disease Aβ and tau cause an age-dependent facilitation of LTD in live rats: role of TNFα and the integrated stress response

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Synaptic weakening by the pathogenic proteins amyloid β (Aβ) and tau likely plays a key role in the insidious evolution of Alzheimer's disease (AD). We hypothesized that diffusible tau in AD brain, like Aβ, would promote synaptic weakening and that this potentially deleterious effect of both proteins would be accentuated in the ageing brain. Field excitatory postsynaptic potentials were recorded from the stratum radiatum in the CA1 area of the hippocampus of urethane-anesthetized young adult and middle-aged (9-16-month-old) rats. Synaptic weakening was assessed by applying relatively weak low-frequency electrical conditioning stimulation of the Schaffer collateral-commissural pathway to trigger peri-threshold long-term depression (LTD). Aβ and tau were administered intracerebroventricularly. We discovered that: (i) Tau in certain AD brain aqueous extracts and trisomy of chromosome 21 secretomes, or recombinant tau oligomers facilitated LTD in an age-dependent manner. (ii) Synthetic Aβ oligomers or synaptotoxic Aβ-containing AD brain extracts facilitated LTD in an age-dependent manner. (iii) The TNFα inhibitor etanercept prevented the facilitation of LTD by synaptotoxic tau and Aβ in middle-aged animals. (iv) Systemic administration of ISRIB, a small molecule inhibitor of the integrated stress response, prevented the facilitation of LTD by tau and Aβ in middle-aged animals. Overall, these findings reveal a shared age-dependent TNFα/integrated stress response-mediated synaptic weakening by both AD diffusible tau and Aβ. Pharmacologically targeting these shared mechanisms of tau and Aβ synaptotoxicity provides an attractive strategy to treat early AD.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 73: Characterisation of a human induced pluripotent stem cell-derived cerebral organoid model of cocaine-mediated neurodevelopmental perturbation

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Cocaine addiction is a worldwide problem affecting millions with particular concern regarding its implications for exposure during foetal development. Prenatal exposure to cocaine throughout development produces persisting deficits in higher cognitive functions such as attention, executive function, and language. While in vivo animal studies have been instrumental in understanding the dangers of cocaine to the developing foetus, such models may be limited in their translation to the human. To address this limitation, human induced pluripotent stem cells (HiPSCs) have been used to generate cerebral organoids, offering a novel model for investigating cocaine exposure and its effects on developing neural networks, cell types and gene expression patterns. This study details the use of the Lancaster organoid model to develop cerebral organoids from HiPSCs and to characterise their response to cocaine exposure. Through assessing messenger RNA and protein levels, we confirmed the presence of machinery involved in cocaine-induced signalling, encompassing transporters (SERT, VGLUT, DAT1) and receptors (5HT1A, D1). Additionally, ELISAs were employed to evaluate the levels of the key neurotransmitters dopamine and serotonin. Subsequently, we explored the effects of cocaine on each component of the established machinery within the cerebral organoids. This study emphasizes the significance of hiPSC-derived cerebral organoids as a valuable in vitro model, offering insights into brain development processes related to exposure to drugs of abuse. Furthermore, these findings offer insights to the mechanisms underlying cocaine-mediated changes in neurodevelopment.

POSTER 74: mHTT Aggregates and Neuroinflammation in the Huntington's Disease Midcingulate Cortex

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Huntington's disease (HD) is a neurodegenerative disorder that can result in motor, mood and cognitive symptoms. HD mood symptomotology correlates with neuronal death in the cingulate cortex. Neuroinflammation, involving reactive glial cells and inflammatory mediators in the brain parenchyma, may influence HD pathophysiology. Accumulation of mutant huntington (mHTT) aggregates has also been linked to neuroinflammation and neuronal loss. Importantly, the degree to which these neuroinflammatory changes are detrimental to neurons and contribute to HD pathology progression is not well understood. Using fluorescent immunohistochemistry, we labeled HD and control post-mortem human midcingulate cortex tissue with HLA DP/DQ/DR, an inflammatory marker, and Iba-1, labeling microglia. We qualitatively and quantitatively assessed activation and morphology changes, indicating neuroinflammation, and mHTT levels - linking neuroinflammation and mHTT burden. We found increased activated microglial morphologies across all HD cases (53.82%), and increased ramified microglia in control cases (67.41%). HD cases showed decreased number of ramified and ameboid microglia. Activated microglia were localised close to neurons containing mHTT aggregates in HD cases, which positively correlated with mHTT burden. Total microglia number did not increase in HD cases. Total microglia number remaining constant between HD and control cases suggests ramified microglia change to activated states in HD, increasing neuroinflammation. This data indicates an association between mHTT burden and neuroinflammation in HD.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 75: Long-lasting Microglial Activation after Neonatal Hypoxia Correlates with Neurological Outcomes in a Mouse Model, which are Altered Following Acute Treatment with MCC950

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Hypoxic-Ischaemic Encephalopathy (HIE), the most common form of neonatal encephalopathy, is strongly associated with neonatal seizures, infant mortality, and high risk of long-term neurological deficits in surviving neonates. Many studies have implicated neuroinflammation, particularly microglia, in both the adverse neurological outcomes and neuroprotective strategies. Microglia carry out maintenance of neurons and neural circuitry; however, once activated, they mediate the neuroinflammatory response. Studies of severe HIE in rodents have shown increased numbers of hippocampal microglia post-hypoxia at both acute and chronic timepoints relative to same-age controls. Using a moderate murine model of HIE, we aim to identify microglia activation after hypoxia in neonates. Manual cell counting and anatomical analysis of imaged Iba1+ cells for functional phenotypes was carried out, alongside neonatal reflex and behaviour tests to identify correlations with behaviour deficits post-hypoxia. Increased numbers of Iba1+ cells and phagocytic microglia were found at 72hrs and 6 weeks post-hypoxia relative to same-age controls. We then evaluated whether targeting microglia could improve neurological outcomes by pharmaceutically targeting the NLRP3 protein, a key component of the inflammasome, using MCC950. MCC950 is a selective inhibitor of the NLRP3 inflammasome, which is mostly expressed in microglia within the brain, forming an important element of the IL-1β signalling cascade., Our data suggest MCC950 is an anti-inflammatory therapeutic option for mice treated immediately post-hypoxia. Overall, the results of this study show that the acute neuroinflammatory activation post-hypoxia persists long after the original insult, supporting the hypothesis that treatments targeting neuroinflammation hold promise for attenuating post-HIE neurological sequelae.

POSTER 76: CPEB4 - CLOCK crosstalk during temporal lobe epilepsy

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Messenger RNA (mRNA) polyadenylation is a key regulatory mechanism governing protein expression by enhancing mRNA stability and translation. Previous studies have shown large-scale changes in mRNA polyadenylation in the hippocampus of mice during epilepsy development. The cytoplasmic polyadenylation element-binding protein CPEB4 was found to drive epilepsy-induced poly(A) tail changes and mice lacking CPEB4 develop a more severe seizure and epilepsy phenotype. The mechanisms controlling CPEB4 function and the downstream pathways that influence the recurrence of spontaneous seizures in epilepsy remain poorly understood. Status epilepticus was induced in wild-type and CPEB4-deficient male mice via an intra-amygdala microinjection of kainic acid. CLOCK binding to the CPEB4 promoter was analyzed via Chromatin immunoprecipitation assay and melatonin levels via High-Performance Liquid Chromatography in plasma. Here we show increased binding of CLOCK to recognition sites in the CPEB4 promoter region during status epilepticus in mice. In turn, CLOCK expression was increased in the hippocampus in mice post-status epilepticus and during epilepsy, and in resected hippocampus and cortex of patients with drug-resistant temporal lobe epilepsy. Further, CPEB4 is required for CLOCK expression after status epilepticus, with lower levels in CPEB4-deficient compared to wild-type mice. Last, CPEB4-deficient mice showed altered circadian function, including altered melatonin blood levels and altered clustering of spontaneous seizures during the day. Our results reveal a new positive transcriptional-translational feedback loop (TTFL) involving CPEB4 and CLOCK, which may contribute to the regulation of the sleep-wake cycle during epilepsy.

POSTER 77: Maternal Microbiome-Mediated Effects on Brain Barriers: Insights from Caesarean-Section Offspring in Early Life

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Increasing evidence links the maternal microbiome to offspring development and behaviour. In particular, the vertical transmission of vaginal and faecal microbes from the mother to the infant at birth is critical for immune system priming and establishment of the microbiota gut-brain axis. Caesarean-section, a life-saving procedure performed to deliver offspring through the abdominal wall, hinders this vertical transmission and has been linked with increased disease risks and altered neurodevelopmental trajectories. However, the mechanisms through which the microbiome modulates neurodevelopment of the neonate are not fully understood. Here, we hypothesise that caesarean-section and associated absence of maternal microbiota exposures at birth impact the integrity of the brain barriers, thereby leading to alterations in brain function. Interestingly, the blood-brain barrier (BBB) and the blood cerebrospinal fluid barrier (BCSFB) present functional and structural deficits in germ-free mice, which lack entirely a microbiota. We compared the immune status, structure and permeability of the BCSFB and BBB in mice born vaginally or by caesarean-section in the early perinatal period. Our results suggest that caesarean section, possibly due to the lack of maternal microbiota transfer, leads to deficits in brain barriers in early life. Understanding the complex relationships between birth mode, microbiota seeding, and neurodevelopment will guide potential interventions to combat caesarean-section-induced deficits.

POSTER 78: Isolation rearing as a model of neuropsychiatric illness: Transcriptomic profiling identifies a core immune signalling-associated dysregulation that precedes behavioural disruption

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Treatment and diagnosis of neuropsychiatric illnesses, such as schizophrenia, are complicated by the fact that each patient experiences a different combination of symptoms along with considerable differences in response to therapeutics. This creates a unique unmet need for novel treatment options beyond current strategies. This study aimed to identify potential targets for future therapeutic exploitation using an established model of neuropsychiatric disease. We have correlated the emergence of behavioural, neurochemical and synapse ultrastructure deficits to transcriptional dysregulation in both the medial prefrontal cortex and dentate gyrus of the hippocampus of Wistar rats reared in isolation. A temporal map of sequential dysregulation across key life stages in both brain regions has been established, allowing a unique insight into the potential molecular cascade underlying disease emergence. The temporally altered genes were from a wide range of functional domains including transcriptional regulation, synaptic structure and function and, strikingly, immune-related signalling. Our in vitro characterisation of members of this latter gene cluster suggests that altered expression of such immune-related genes may contribute to aberrant synaptic pruning, thought to be a key deficit underpinning the symptoms of schizophrenia. This study provides a molecular framework to understand the developmental emergence of transcriptional and synaptic deficits that may in part define psychiatric illness. Further dissection of immune-related gene expression alterations, identified to be common to both brain regions, may reveal key insights into neuronal circuitry dysregulation and subsequent emergence of neurocognitive and psychotic symptoms of schizophrenia.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 79: Investigating the role of neuro-glial lipid homeostasis in inherited motor neuron disease

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Hereditary spastic paraplegias (HSPs) are an inherited group of motor neuron diseases, which are characterised by length-dependent axonopathy of long motor neurons. HSP's symptoms present as lower-limb weakness or spasticity which progresses with age and leads to eventual crutch or wheelchair use. There are currently no treatments or cures available, putting increased emphasis on current research. HSPs are highly genetically heterogeneous, with over 80 causative genetic loci associated with the disorder, and the underlying disease pathology not understood. Disrupted lipid homeostasis is increasingly recognised as a characteristic feature of HSP: mutations in several genes encoding enzymes which regulate lipid metabolism cause HSP and disrupted lipid content have been detected in animal models and patient samples associated with these mutations. Interestingly, recent work carried out in our lab and elsewhere has also detected lipid disruption in models of HSP which are not known to directly function in lipid homeostasis. This work aims to further our understanding of the mechanisms underpinning lipid disruption in HSP and how it contributes to disease pathogenesis. We use the fruit fly, Drosophila melanogaster, to model disease-causing mutations in HSP genes which enable us to examine lipid droplet (LD) accumulation within neurons and glia within affected motor neuron axon bundles. Here we show that LDs accumulate within axonal glia in some, but not all, Drosophila models of HSP. Importantly, this glial LD accumulation appears to contribute to neurodegeneration in these models as pharmacological restoration of lipid homeostasis partially rescues progressive locomotor deficits in HSP models.

POSTER 80: An automated imaging screen for gene modifiers of HSP-associated neurodegeneration

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Hereditary Spastic Paraplegias (HSPs) are a heterogeneous group of mono-genetic inherited neurological disorders, whose primary manifestation is the disruption of the pyramidal system, observed as progressive impaired gait and leg spasticity in patients. Despite the large list of genes linked to this group, which exceeds 80 loci, the number of functions in which the gene products segregate is relatively limited, among which endoplasmic reticulum (ER) morphogenesis appears central. ER-shaping proteins are mutated in most common HSP subtypes, highlighting the importance of correct ER organization for long motor neuron survival. However, a major bottleneck in the study of ER morphology is the current lack of quantitative methods, with most studies reporting instead on qualitative changes. Here we outline a novel methodological approach for quantitative image-based analysis of ER distribution within 2D cell cultures. This analysis reveals significant quantitative changes in tubular ER (TER) organisation caused by loss of the HSP-causing ER-shaping protein ARL6IP1. In addition, this quantified ER phenotype served as a readout in a cellular screen to identify molecular modifiers of disease. This screen constitutes the first attempt to examine ER distribution in cells in a high-content manner and to detect genes which impact ER organisation.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 81: Examination of In Vitro Beta-Amyloid Oligomerization

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Alzheimer's disease (AD) is a progressive neurodegenerative disease, characterised by β-amyloid plaques and neurofibrillary tangles. The amyloid hypothesis postulates that β-amyloid is the pathological trigger leading to AD. The administration of aggregated β-amyloid oligomers has been widely used as an AD model; however all commercially available β-amyloid preparations differ, and thus aggregation of a β-amyloid preparation prior to administration requires careful planning. This project aims to develop a procedure for aggregation of toxic β-amyloid oligomers by investigating both their presence and toxicity. β-amyloid1-42 was aged for 48 or 120 hours to assess aggregation. Western blotting was completed under three conditions (SDS-PAGE and prior boiling of sample, Native-PAGE and prior boiling and Native-PAGE without prior boiling) with two different concentrations of β-amyloid. The ReadyProbes Cell Viability Kit was used to determine SH-SY5Y cell viability following 21-hour treatment with β-amyloid aggregated for 48 hours. Cells were counted using ImageJ and analysis was completed using GraphPad Prism. Images obtained from western blot performed under the three predefined conditions verified that low molecular weight (8kDa) and high molecular weight (15kDa) oligomers are present after both 48 and 120 hour β-Amyloid aggregation. Longer incubation time did not increase the amount of toxic aggregates. Analysis showed that treatment of SH-SY5Y cells with β-Amyloid aggregated for 48 hours increases cell death, highlighting the toxicity of the β-amyloid oligomers formed. 48 hours and 37°C are ideal conditions for formation of toxic high and low-molecular weight β-amyloid oligomers. These conditions will be used for future experiments to ensure standardization.

POSTER 82: Lentiviral Vectors in combination with Biomaterial Scaffolds for Spinal Cord Injury Regeneration

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Spinal cord injury (SCI) causes chronic pathological processes that persist for months to years preventing neural regeneration and recovery. The varying nature and prolonged timespan of these processes calls for combinatory strategies to promote repair. Lentiviral vectors (LVs) provide sustained therapeutic effects more efficiently than repeated biomolecule/drug administration due to integration of therapeutic genes into the DNA of host cell genome. LV delivery via biomaterials after SCI can target additional pathological processes, increase LV persistence through controlled release, improve LV localization, stability, transduction efficiency and reduce immune clearance producing superior therapeutic effects. In this study LVs were combined with Hyaluronic acid (HA) and Oligo(poly(ethylene glycol) fumarate) (OPF) hydrogels. HA is ubiquitous in neural tissue and can help regulate angiogenesis and inflammation after injury. OPF hydrogels have been shown to improve regenerative markers in SCI models. LVs encoding GFP were loaded into hydrogels prior to/post crosslinking. Hydrogels were incubated in cell culture media at 37°C and LV release/function was evaluated through GFP expression in cells cultured in hydrogel incubation media. Few functional LVs were released from gels at any timepoint investigated (up to 120hrs) despite evidence for some functional LVs remaining in HA gels at 48hrs. To determine whether interaction with HA or OPF biomaterial affects LV functionality, LVs were incubated in solutions containing HA or ground OPF gels. LV functionality was initially increased but decreased faster in HA solutions. Incubation with OPF decreased LV functionality. In conclusion, careful consideration must be given to biomaterial selection when approaching this treatment modality.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 83: MicroRNAs Rhythmicity During Epileptogenesis in Mice

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MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression and are largely influenced by the circadian rhythms. The role of miRNAs rhythmicity in epileptogenesis, a process in which a previously healthy brain becomes prone to the development of epilepsy, remains unclear. Here, we investigated the rhythmicity of relevant miRNAs during epileptogenesis in mice. We performed differential gene expression analysis from RNA sequencing data of 3 different epilepsy models: pilocarpine, intra-amygdala kainic-acid and perforate-pathway-stimulation to select the most relevant miRNAs at 24h, 48h and 72h after status epilepticus. Next, we used male adult C57Bl6 mice (n=5/group/time-point) injected with intra-amygdala kainic-acid or vehicle (PBS) to evaluated whether the selected miRNAs presented diurnal rhythmicity in expression during epileptogenesis. Ipsilateral hippocampus were collected at 6 different Zeitgeber Times (ZT; every 4h starting at 8 am; from 24 after status epilepticus) for TaqMan MicroRNA assay. Gene miRNAs expression were analysed by t-test or two-way-ANOVA and rhythmicity by JTK_CYCLEs. We found that miR-146a-5p, miR-106b-5p, miR-128-1-5p, miR-376a-5p, miR-92a-1-5p, miR-127-3p, miR-335-5p, and miR-155-5p were dysregulated in at least 2 out of the 3 epilepsy models. MicroRNA assay showed that miR-155-5p (ZT8,ZT12,ZT20), miR-335-5p (ZT0,ZT16) and miR-92a-1-5p (ZT0,ZT4,ZT8) were up-regulated ($p<0.05$), while miR-127-3p (ZT20) was downregulated ($p<0.05$) in ipsilateral-hippocampus during epileptogenesis. Oscillatory analyses showed that miR-146a ($p=0.04$) and miR-335 ($p=0.0002$) acquired rhythmicity in epileptogenesis.

POSTER 84: Microglial immunometabolic changes in LPS-induced NOX activation are mediated by pentose phosphate pathway

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NADPH-oxidases (NOX) are a family of superoxide-producing enzymes that promote the pro-inflammatory activation of microglia, including the secretion of interleukin-1beta (IL-1b) and tissue necrosis factor-alpha (TNF-a). The sustained activation of microglial NOX is associated with chronic neurodegeneration following traumatic brain injury (TBI). NOX activity is limited by NADPH availability, produced from glucose at the pentose phosphate pathway (PPP). Sustained NOX activation could contribute to microglial immunometabolic changes that support inflammatory-mediated neurodegeneration following TBI, yet the relationship between NOX and microglial metabolism remains unknown. Our goal was to investigate the role of NOX and PPP in the immunometabolic response to lipopolysaccharide (LPS) in immortalized microglia (IMG) cells. IMGs were stimulated with LPS for 24 hours, and co-incubated for 24h with an inhibitor of PPP, 6-aminonicotinamide (6AN). IMGs were assayed for NOX activity by lucigenin-enhanced chemiluminescence, mitochondrial membrane potential by tetramethylrhodamine fluorescence, and IL-1b and TNF-a by ELISA. A dose-response of LPS (50, 100, and 200 ng/ml) demonstrated that LPS 100 ng/mL alone promotes increases NOX activity, TNF-a, and IL-1b production, and a concomitant decrease in mitochondrial membrane potential, when compared to controls. Further, inhibition of PPP by 6AN (0.1, 10, 50, and 200 uM) resulted in a dose-dependent attenuation of LPS-induced NOX activation, mitochondrial membrane potential dysfunction, and pro-inflammatory cytokine release. Finally, we showed that IMGs cotreated with LPS+6AN and supplemented with exogenous NADPH (100µM) partially restored the LPS-NOX-induced pro-inflammatory phenotype in IMGs. This indicates that PPP mediates microglial NOX-driven pro-inflammatory responses, which may support inflammatory-mediated neurodegeneration after TBI.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 85: Characterisation of Arginase-2 in Triple Negative Breast Cancer Brain Metastasis

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Breast cancer brain metastasis (BCBM) is a clinical problem. Approximately 30% of triple negative breast cancer (TNBC) patients develop brain metastasis, resulting in a median survival of six months. As treatment options are limited, there is an urgent need for specific prognostic biomarkers and improved therapeutic strategies. Comparing patient-matched primary tumors and their metastasis to various organs, we observed that Arginase-2 (ARG2) is associated with worse distant metastasis-free survival and that ARG2 is significantly upregulated in brain metastasis. ARG2 is one of two arginase enzymes involved in metabolism of L-arginine to urea, an important step in cell proliferation. We have reported that ARG2 is critical in sustaining an anti-inflammatory status in macrophage cells. In this project we aim to examine if ARG2 is a potential therapeutic target to prevent BCBM. We characterised ARG2 expression in TNBC. High ARG2 expression was found in two TNBC lines, MDA-MB-231 and MDA-MB-436, and two TNBC brain metastasis patient derived xenograft models. We next tested inhibition of ARG2 by treatment with pan arginase inhibitor Nω-Hydroxy-nor-L-arginine acetate (Nor-NOHA) or selective siRNA knock down of ARG2. Arginase activity assays demonstrated that siRNA treatment suppressed arginase activity, without significantly changing tumor cell proliferation. Organotypical brain slice cultures have been established to assess the role of ARG2 in tumor cell proliferation. Future work will focus on the effect of ARG2 siRNA on the tumor micro-environment specifically examining polarisation of tumor associated macrophages TAMs and tumor immune surveillance.

POSTER 86: Temporal analysis of IL-17 and IFNγ producing innate and adaptive immune cells following experimental TBI in mice

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Traumatic brain injury (TBI) is the leading cause of death and disability in young adults, resulting in severe cognitive and physical disabilities in survivors. Interleukin-17 (IL-17) is a pro-inflammatory cytokine that can be produced by immune cells such as CD4+, γδ T cells, and innate lymphoid cells. Production of IL-17 contributes to secondary injury during ischemic stroke, but whether it plays a pathogenic role in TBI remains unknown. This study aims to measure IL-17 and interferon-γ (IFNγ) production following TBI and identify its major cellular origins. Adult C57BL/6J male mice underwent moderate-level controlled cortical impact or sham surgery. Mice were euthanized, and brains were harvested at 1, 3, 10, and 28 days post-injury (DPI). Mononuclear cells were obtained by percoll density gradient, stained to identify different infiltrating immune cells in the brain (Neutrophils, Monocytes, Dendritic cells, T-cell subsets (CD4+, CD8+, TCRγδ+, NK) as well as intracellular cytokine production (IL-17 and IFN-γ)). Acutely after TBI, neutrophils, dendritic cells, and monocytes infiltrate into the brain at 1 and 3 DPI. Production of IL-17 starts at 3 DPI and peaks at 10 DPI and is majorly derived from γδ T cells. T-cell infiltration peaks at 10 DPI and persist until 28 DPI. IFN-γ is primarily produced by CD4+, CD8+ T, and NK cells. In summary, this time course analysis of moderate-severe TBI revealed that IL-17 is mainly produced by γδ T cells while IFN-γis produced by CD4+, CD8+, and NK T-cells.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 87: Alterations in glutamate receptor and transporter expression in the hippocampus of an *in vivo* alzheimers disease mouse model

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Alzheimer's Disease (AD) is the leading type of dementia worldwide, and with an increasing burden due to an aging population combined with a lack of any foreseeable cure, it warrants a large driving force of research. Glutamate is the main excitatory neurotransmitter in the brain and plays an essential role in the function and health of neurons and neuronal excitability. Previous studies have shown alterations in expression of glutamatergic signalling components in AD. This study aimed to characterise changes in specific glutamate receptors and transporters 30 days post hippocampal beta-amyloid (Aβ1-42) stereotactic injection of a mouse model of AD using immunohistochemistry and confocal microscopy. We report significant decreases in density of glutamate receptor subunits GluA1, GluN2A and the vesicular glutamate transporter VGluT1 in the CA1 region of the hippocampus in the AD mice compared to controls, notably in the stratum oriens and stratum radiatum. These changes are in line with findings observed in the human AD hippocampus. Glutamate receptor subunits GluA2, GluN1 and transporter VGluT2 showed no changes in expression. These findings indicate that the expression of the glutamatergic receptors and transporters show brain region and layer specific changes in AD, suggesting complex activation mechanisms and expression changes during neuropathology.

POSTER 88: Characterising the role of Arginase-2 in Breast Cancer Brain Metastasis

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Breast cancer brain metastasis (BCBM) has emerged as a challenging clinical issue with poor diagnosis and survival. Arginase enzymes, arginase-1 (ARG1) and arginase-2 (ARG2), contribute to cell growth by completing the final step of the urea cycle. We have reported ARG2 is also critical in sustaining an anti-inflammatory status in macrophage. ARG2 is significantly elevated during the metastasis of many malignant tumors including glioblastoma, gastric, breast, colorectal, liver, and lung. By comparing patient-matched primary tumors and their metastasis, we found ARG2 was significantly upregulated in brain metastasis. Additionally, inhibition of arginase has been proven to suppress melanoma lung metastasis providing a rationale to pursue arginase as a potential anti-metastatic target. We characterized arginases in BC cell lines, including HER2+ and triple negative breast cancer (TNBC). ARG2 expression was high in TNBC lines with low levels detected in HER2+. ARG1 expression was comparable between lines. ARG2 was also elevated in PDX TNBC brain metastasis models by IHC. Delving further into the role of ARG2, we employed nor-NOHA, a pan-arginase inhibitor to block the biological activity of arginase or performed selective knockdown of ARG2 by siRNA. Treatment with siARG2 significantly inhibited arginase activity in TNBC with no significant change in HER2+ lines. This may be due to compensation by ARG1 in HER2+ cells. Organotypical brain slice cultures have been established to assess the role of ARG2 in tumor cell proliferation in co-culture experiments. Future work will focus on the effect of siARG2 on the tumor micro-environment and tumor associated macrophage (TAM) polarization.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 89: Patient-derived cellular models as tools to elucidate the pathophysiology of Hao-Fountain syndrome

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Synaptic plasticity (SP) plays a key role in the human ability to adapt to environmental input, along with learning and memory processes. Altered SP significantly contributes to neurological and psychiatric disorders, including Autism Spectrum Disorders (ASD). Furthermore, mutations in essential proteins facilitating SP have also been identified in human patients with intellectual disabilities. Recently, loss of function mutations in ubiquitin-specific protease 7 (USP7, also called herpes virus-associated ubiquitin-specific protease, HAUSP), have been identified as a disorder-causing variant, linked explicitly to Hao-Fountain syndrome, a neurodevelopmental disorder manifesting intellectual disability, ASD, and seizures. Located at chromosome 16p13.2, USP7 encodes a deubiquitinating proteolytic enzyme that cleaves multiple ubiquitin chain linkages. Previously, USP7 was shown to regulate the ubiquitination of proteins, including the MDM2-p53 pathway, which is vital for DNA repair, transcription, and cancer. However, the precise mechanisms of how USP7 mutation causes the clinical phenotype of Hao-Fountain syndrome on a cellular level are missing so far. In this collaborative project, using patient-derived human induced pluripotent stem cells in combination with omics approaches (proteomic and transcriptomic analysis) and targeted biochemical analyses (qrt-pcr and western blot analysis), we aim to understand the functions of USP7 in neuronal development and SP by recapitulating neurodevelopmental processes using in vitro model systems including 2D models from iPS cells to differentiated mature neurons along with 3D models systems such as cerebral organoids. Our studies have revealed several ASD and ID-linked protein dysregulations and, thereby, cellular pathways that will be validated and explored as future drug targets.

POSTER 90: NOX2-mediated regulation of microglial NLRP3 inflammasome in traumatic brain injury

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NADPH oxidase 2 (NOX2) is an enzyme complex responsible for reactive oxygen species (ROS) production in microglia. NOX2/ROS is a priming signal for NLRP3 inflammasome activation. GSK2795039 is a novel small molecule drug that inhibits NOX2. Here, we characterised GSK2795039 in models of microglial activation in vitro and translated findings to an experimental traumatic brain injury (TBI) model in mice. Immortalised Microglial (IMG) or primary microglia from p1 Wistar rats were pre-treated with GSK2795039(1-40μM), or MCC950(NLRP3 inhibitor; 0.5μM) and stimulated with lipopolysaccharide(LPS; 100ng/ml) and ATP(1mM)/Nigerecin(10μM) to induce NOX2/ROS and NLRP3 inflammasome activation. ROS production and cell viability were measured in cells. The conditioned media was analysed for IL-1β, IL-18 and TNF-α by ELISA, nitric oxide, and lactate dehydrogenase to measure pyroptosis. Protein expression of NLRP3, Caspase-1 and ASC were measured in cell lysates and supernatants by Western immunoblot. In LPS/ATP and LPS/Nigerecin models in IMG and primary microglia, GSK2795039 attenuated ROS, IL-1β, IL-18 release, and NLRP3 and cleaved-caspase-1 protein expression, which may be due to reduced NOX2/ROS signalling. Using a controlled cortical impact in adult male C57Bl/6J mice, flow cytometry studies demonstrated moderate-level TBI resulted in rapid infiltration of inflammatory monocytes with increased NOX2/ROS/Caspase-1/IL-1β+ expression and proliferation of resident microglia compared to control mice. Follow-up studies are assessing the therapeutic potential of post-injury GSK2795039 administered on TBI neuroimmunological, neurobehavioral and neuropathological outcomes. In conclusion, GSK2795039 may be a promising drug for mitigating NOX2-mediated neuroinflammation in microglia.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 91: Loss of Opa1 results in mitochondrial disruption and neurodegeneration in novel *in vivo* models of optic atrophy in zebrafish and fruit flies

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Optic atrophy (OA) is the most common form of inherited optic neuropathy, characterised by progressive and irreversible degeneration of retinal ganglion cells (RGCs), resulting in sight loss. Approximately 70% of OA patients carry mutations in the mitochondrial fusion protein OPA1. However, it is unclear why OPA1 mutations lead to RGC death and subsequent vision loss. Fruit fly and zebrafish models of OA were developed using CRISPR/Cas9 gene editing to create tissue-specific or whole animal knockouts (KO) of endogenous Opa1. qPCR validated Opa1 disruption in both models. In flies, survival and axonal mitochondrial morphology was monitored compared to control animals. In zebrafish larvae, visual behaviour was measured using optokinetic response (OKR) assays and a seahorse extracellular flux analyser measured metabolic changes. Mass spectrometry was used for proteomics analysis in zebrafish. Neuron-specific Opa1 KO flies demonstrate a significantly reduced median life expectancy. Axonal mitochondria in these Opa1 KOs are significantly smaller and more rounded, consistent with a fusion defect. Zebrafish Opa1 mutants display a significant loss of visual acuity compared to control siblings. Seahorse analysis demonstrates metabolic disruption in Opa1 KO larvae, including a reduction in both basal and maximal respiration. Proteomics analysis indicated differential expression of proteins involved in oxidative phosphorylation and stress response. I have generated novel models of OA by targeted loss of Opa1 in both zebrafish and fruit flies. Disrupted mitochondrial flux (organisation and function) and neurodegeneration (survival and visual function) are evident in both systems, indicating that highly conserved functions of Opa1 likely contribute to disease pathogenesis.

POSTER 92: Investigating mechanisms of demyelination and its consequences for axons

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The loss of myelin from axons, known as demyelination, is a hallmark feature of diseases such as Multiple Sclerosis and occurs throughout ageing. While the long-term consequences of myelin loss are known to be detrimental, little is understood about mechanisms driving the process of demyelination itself. Using two demyelination models, we have observed that myelin swelling, or vacuolation, precedes overt myelin loss, and is a common feature of myelin damage. While vacuolation always accompanied myelin loss, it did not always lead to demyelination and could even be reversed, suggesting there is a threshold of damage below which individual sheaths can recover. Furthermore, we found that increasing neuronal activity exacerbated myelin vacuolation, which could be slowed by suppressing action potential firing in zebrafish, suggesting that the normal physiological role of oligodendrocytes in ion buffering cannot be met in situations where the cell is damaged. Finally, we saw by live imaging that myelin vacuolation affects axonal structure, indicating that damage to axons occurs even before they have been demyelinated. Together these data suggest that demyelination itself may be a regulatable, cell biological process that can be manipulated, with immediate consequences for axonal structure.

NEUROSCIENCE IRELAND CONFERENCE 2023 RCSI, Dublin 29-30 AUG '23

POSTER 93: Microglial-specific knockdown of Bmal1 leads to behavioural changes, an increased susceptibility to seizures and an altered inflammatory profile in mice

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Neuroinflammation is a feature of epilepsy and contributes to seizure development. The inflammatory response is mediated by microglia, which are regulated by the circadian rhythms; the 24-hour variations in physiological function orchestrated by autoregulatory genes, including Bmal1. The disruption of circadian rhythms is associated with increased microglial activation. Here we explored the microglial-specific Bmal1 deletion impact on behaviour and seizure susceptibility in mice. Forty young adult Bmal1-Cx3CR1Cre-ER mice were injected with either tamoxifen (40mg/kg; IP/daily/10 days) to induce microglial-specific Bmal1 knock-down (Bmal1-KD) or vehicle. Two weeks after recombination, mice underwent behavioural tests. A subset of this cohort was implanted with electrodes for electroencephalographic (EEG) recordings and underwent the injection of a low dose of kainic-acid (KA;IP;15mg/kg) to test seizure susceptibility. Pro-inflammatory gene expression was assessed by qPCR in hippocampi and cortices from naïve and KA-treated mice. Bmal1-KD mice were significantly more active ($p<0.05$) than controls. No difference was observed in cognition. Bmal1-KDs had an increased susceptibility to develop acute seizures ($p<0.0001$) and significantly increased seizure severity measured by the total EEG power ($p<0.0002$) after KA administration. TNF-α was significantly reduced at baseline in Bmal1-KD mice and was significantly upregulated in Bmal1-KDs compared with controls following KA ($p<0.01$). Microglial-specific depletion of Bmal1 led to disrupted behaviour and higher propensity to develop seizures. Bmal1 reduction led to alterations in cytokine expression at baseline and following KA. Further studies will elucidate how Bmal1 disruption affects epileptogenesis.

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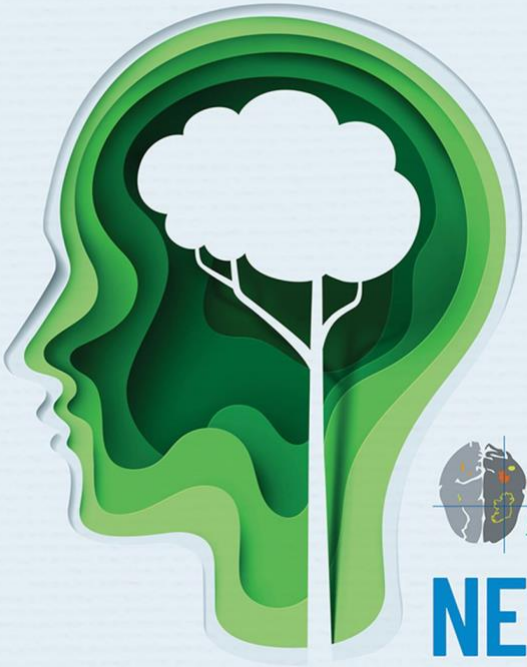

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