

NEUROSCIENCE
Ireland



9th Neuroscience Ireland Conference



1st-2nd September 2015

**School of Nursing and Human Science (SNHS),
Dublin City University (DCU),
Glasnevin Campus, Dublin, Ireland**

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Welcome
to the
Neuroscience Ireland Conference at DCU on
‘Frontiers in Neuroscience: Diseases and Treatments’

The Local Organising Committee would like to welcome you to DCU and Dublin for this biennial conference. This has been organised by the International Centre for Neurotherapeutics in conjunction with the School of Nursing and Human Sciences, under the auspices of Neuroscience Ireland (NI). It brings together scientists working on diverse aspects of Neuroscience, and researchers from other related fields. Thus, the conference should serve as a multi-disciplinary forum for knowledge and expertise sharing and collaboration. In the spirit of NI, the conference provides a platform for scientists at all career stages to present their work in various formats. The theme of this meeting is *‘Frontiers in Neuroscience’* and the main sessions focus on major topics within this thematic area, especially *‘Diseases and Treatments’*. The scientific programme includes distinguished international and Irish speakers, as well as presentations from Post-docs and Ph.D. students. A Nobel Laureate lecture by Prof. Thomas Südhof is an added major attraction, arranged by the President of DCU and sponsored by Magnet Networks.

We thank SFI and our trade exhibitors/sponsors for the generous support that has made the conference possible. Gratitude is extended to those who devoted much time and effort to fund raising, and organising this conference to make it a success. It is hoped that you find the scientific presentations inspiring and enjoy the social activities.

Local Organising Committee:

Prof. Oliver Dolly (Chair), Dr. Stella Vlachou (Co-ordinator), Prof. Alan Harvey, Sharon Whyte, Dr. Michael Keane, Marc Nugent, Patrick Boylan, Dr. Gary Lawrence, Dr. Ahmed Al-Sabi, Prof. Teresa Burke, Dr. Jiafu Wang and Dr. Loraine Boran.

The organisers wish to express their special thanks to the major sponsors of this event



Conference Information

Location: this year's Conference takes place in the School of Nursing and Human Sciences (SNHS) at DCU, Glasnevin Campus.. Please see map and floor plan on the following pages—SNHS is indicated by H on the map.

Nobel Laureate Lecture: takes place in the Mahony Hall, The Helix, DCU—indicated by Z on the map.

Registration and name badges: the registration desk will be located in the Foyer of the SNHS Building. Delegates are asked to wear their badges throughout the meeting.

Posters: poster sessions will take place in the SNHS Building.

Lunch and tea/coffee breaks: tea, coffee, snacks and lunch will be served in SNHS Building.

Services: there are a number of ATMs available on the Glasnevin Campus—see map. There is also a Bank of Ireland located in the building indicated by CA.

Internet access: free wifi access is available for conference attendees. Wifi code will be provided in your conference bag.

Car parking: there is a multi-storey car park on the campus—indicated by F on the map.

Taxis: the number for VIP Taxis is (+353 1) 478 3333.

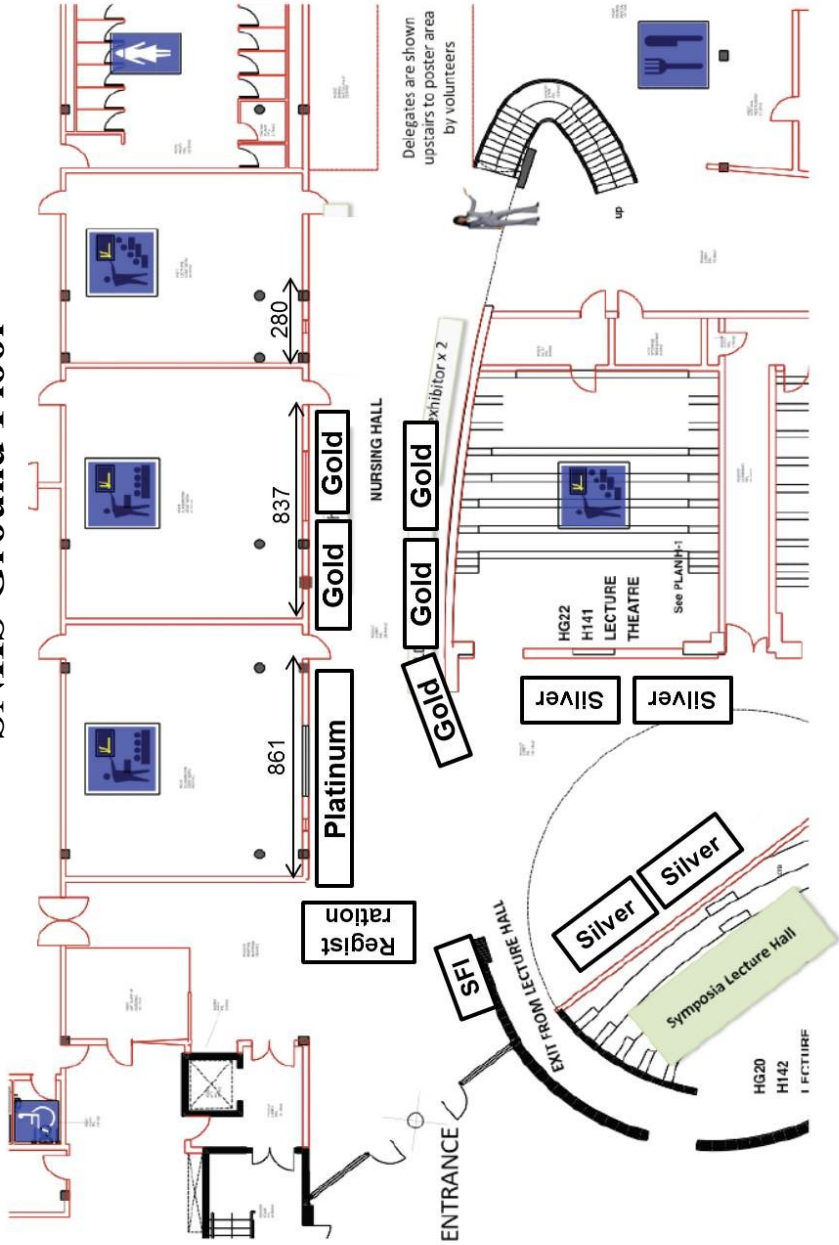
Conference banquet: the Conference Banquet will take place in the evening of the 1st of September at The Clontarf Castle Hotel. Transport has been arranged with a bus leaving the SNHS Building at 18.45h to the venue and from the venue at 23.15h, with stops in the city centre and The Croke Park Hotel, Drumcondra.

General help and information: student volunteers will be available throughout the Conference at the registration desk and will be happy to answer any queries you may have.

DCU Glasnevin Campus

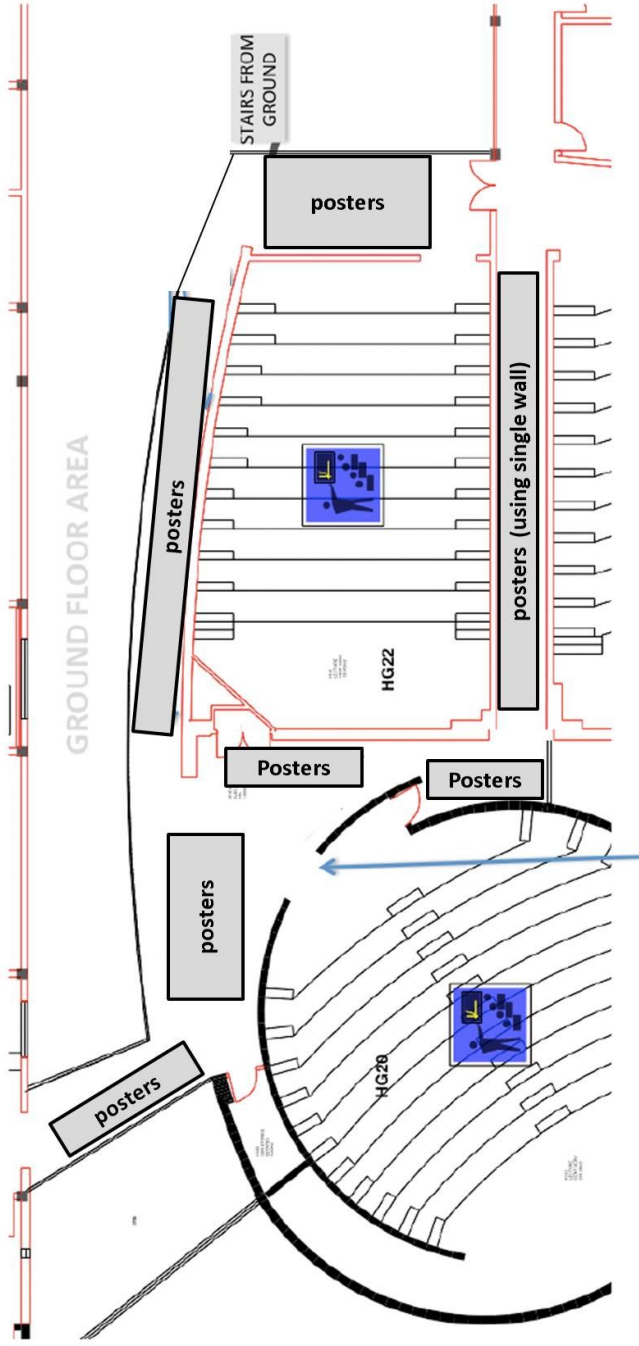


SNHS Ground Floor



FIRST FLOOR

(Ground floor can be seen from walkway where posters are displayed)



Symposia Lecture Hall – entrance to back of theatre




Neuroscience Ireland 2015 Conference Programme

Frontiers in Neuroscience: Diseases and Treatments


School of Nursing and Human Sciences (SNHS), DCU, Glasnevin Campus

Day 1 : Tuesday, 1st September, 2015

08.30 – 09.00	Registration, SNHS; Tea and coffee, sponsored by Pall Life Sciences  Life Sciences
09.00 – 09.10	Welcome address and opening of the Conference Prof. Alan Harvey, Vice-President for Research and Innovation, DCU

Lecture Session 1 : PAIN : Analgesics – HG23

Chairs/Discussants: Prof. David Finn and Dr. Jianghui Meng

09.10 – 9.45	S1.1: Prof. John Wood FRS, Head of the Molecular Nociception Group, Wolfson Institute for Biomedical Research, University College London <i>Sodium channels and pain pathways – new routes to analgesia?</i>
9.45 – 10.20	S1.2: Dr. Hagen Wende, Institute of Pharmacology, Heidelberg University <i>Generation of hESC/iPSC-derived peripheral neurons: a new approach to study sensory mechanisms</i>
10.20 – 10.40	 Life Sciences Tea/coffee, sponsored by Pall Life Sciences and poster viewing, SNHS
10.40 – 11.10	S1.3: Prof. J. Oliver Dolly, Director, International Centre for Neurotherapeutics (ICNT), DCU <i>EnSNAREing the transduction of chronic pain with botulinum neurotoxins</i>
11.10 – 11.40	S1.4: Dr. Connail McCrory, Medical Director of Pain Medicine, St James's Hospital and Senior Lecturer at the School of Medicine, TCD <i>The role of CSF neuropeptides in chronic pain perception in man</i>

Nobel Laureate Lecture – Mahony Hall, The Helix, DCU

12.00 – 13.00	Prof. Thomas Südhof, Avram Goldstein Prof. Molecular and Cellular Physiology, Howard Hughes Medical Institute, Stanford University School of Medicine
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Mechanism of neurotransmitter release

Chair/Discussant: Prof. Brian MacCraith, DCU President

Sponsored by Magnet Networks

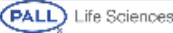


13.00 – 14.30	Lunch and poster viewing, SNHS Building – presenters in attendance
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Day 1 : Tuesday, 1st September, 2015 (continued)

Lecture Session 2 : ENDOCYTOSIS and VESICLE TRAFFICKING – HG23

Chairs/Discussants: Prof. Mary McCaffrey and Dr. Gary Lawrence

14.30 – 15.05	<p>S1.5: Prof. Volker Haucke, Molecular Pharmacology, Leibniz Institut für Molekulare Pharmakologie, Berlin</p> <p><i>Where the tortoise and the hare meet - clathrin and adaptors in synaptic vesicle cycling</i></p>
15.05 – 15.40	<p>S1.6: Prof. Harvey McMahon FRS, MRC Laboratory of Molecular Biology, Cambridge Biomedical Campus</p> <p><i>A fast endophilin-dependent, clathrin-independent endocytic mechanism</i></p>
15.40 – 16.00	<p> Tea/coffee, sponsored by Pall Life Sciences and poster viewing, SNHS</p>
16.00 – 16.30	<p>S1.7: Dr. Jiafu Wang, Faculty of Science and Health Research Lecturer, DCU</p> <p><i>Multiple pathways of acceptor-mediated endocytosis are exploited by botulinum neurotoxins to enter neurons</i></p>

Lecture Session 3 : Postgraduate Presentations – HG23

Chair/Discussant: Prof. John Kelly

16.30 – 16.45	<p>P3.03: Edel Hennessy, Trinity College Institute of Neuroscience, School of Biochemistry & Immunology, Trinity College Dublin</p> <p><i>Astrocytes are primed by chronic neurodegeneration to produce exaggerated chemokine and cell infiltration responses to acute stimulation with the cytokines IL-18 and TNF-α</i></p>
16.45 – 17.00	<p>P2.05: Steven G. Fagan, Trinity College Institute of Neuroscience, Department of Physiology, Trinity College Dublin</p> <p><i>The involvement of panx-1 in amyloid-induced neurodegeneration and the protective effect of the endocannabinoid system</i></p>
17.00 – 17.15	<p>P5.04: Ruth M. Concannon, Pharmacology & Therapeutics and NCBES Galway Neuroscience Centre, National University of Ireland Galway</p> <p><i>Pharmacological targeting of the cannabinoid type-2 (CB₂) receptor protects the nigrostriatal pathway against inflammation-driven neurodegeneration in the LPS rat model of Parkinson's disease</i></p>
17.15 – 17.30	<p>P4.02: Joan Lenihan, School of Biochemistry and Cell Biology, University College Cork</p> <p><i>Characterisation of LNX family E3 ubiquitin ligases</i></p>
17.30 – 18.30	Poster viewing, SNHS

Conference Banquet – Clontarf Castle Hotel

19.30 – 22.30	Conference Banquet: After dinner address by Prof. Mark Ferguson, Director General of SFI and Chief Scientific Advisor to the Government of Ireland
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Day 2 : Wednesday, 2nd September, 2015 – All Sessions HG23

08.30 – 09.00



Life Sciences

Tea/coffee, sponsored by Pall Life Sciences SNHS

Lecture Session 4 : NEUROPSYCHOPHARMACOLOGY OF DRUGS OF ABUSE, REWARD AND ADDICTION: Targets, Mechanisms and Treatments

Chairs/Discussants: Prof. Keith Murphy and Dr. Stella Vlachou

09.00 – 09.35

S2.1: Prof. Gaetano Di Chiara, Pharmacology and Pharmacotherapy, Faculty of Pharmacy, University of Cagliari, Italy
Dopamine, reward and addiction: new evidence on a classic theme

09.35 – 10.10

S2.2: Prof. Elena Chartoff, Psychiatry, Harvard Medical School, USA
Sex differences in kappa opioid receptor function and their impact on addiction

10.10 – 10.40

S2.3: Dr. Stella Vlachou, Lecturer in Psychology, SNHS, DCU
Potential therapeutic treatments for nicotine dependence: Focusing on reward, impulsivity and attentional performance

10.40 – 11.10

S2.4: Prof. John Cryan, Anatomy and Neuroscience, University College Cork
Glutamate, Stress and the Adolescent Brain: Impact on the Rewarding Effects of Cocaine

11.10 – 11.30



Life Sciences

Tea/coffee, sponsored by Pall Life Sciences and poster viewing, SNHS

Lecture Session 5 : Topical Neuroscience Research – open slots

Chair/Discussant: Dr. Paul Young

11.30 – 11.45

P5.08: Dr. John Kealy, Maynooth University
Real-time changes in oxygen and local field potential in the brains of freely-moving rats following NMDA receptor antagonism

11.45 – 12.00

P1.10: Dr. Cara M. Hueston, University College Cork
Lentiviral overexpression of interleukin-18 in the hippocampus induces neurogenesis-associated cognitive deficits in adult male rats

12.00 – 12.15

P7.06: Dr. Andrew J. Lindsay, University College Cork
Rab coupling protein (Rab11-FIP1C), Rab14 and endosomal recycling in neuritogenesis

12.15 – 13.00

Lunch and poster viewing, SNHS – presenters in attendance

Lecture Session 6 : NEURONAL EXCITABILITY AND INFLAMMATION: Multiple Sclerosis and Epilepsy

Chair/Discussant: Dr. Una Fitzgerald

13.00 – 13.35

S2.5: Prof. Manuel Friese, Institute of Neuroimmunology and Multiple Sclerosis, Centre for Molecular Neurobiology, Hamburg
Ion channels as neuroprotective targets in multiple sclerosis

13.35 – 14.05

S2.6: Dr. Patrick Walsh, School of Medicine, TCD
The soluble IL-2 receptor in MS; more than a biomarker?

14.05 – 14.35

S2.7: Dr. Ahmed Al-Sabi, SFI funded researcher, ICNT
Neuronal Kv1.1 channels as promising targets for a novel selective blocker to normalise impaired conduction in demyelinated axons mimicking that in multiple sclerosis

14.35 – 15.05

S2.8: Prof. David Henshall, Molecular Physiology and Neuroscience, Physiology & Medical Physics, RCSI
MicroRNA as treatment targets for epilepsy

15.05 – 15.25




Life Sciences

Tea/coffee, sponsored by Sophion and poster viewing, SNHS

Lecture Session 7 : NEUROSCIENCE and THE LAW

Chair/Discussant: Prof. Teresa Burke

15.25 – 16.00	S2.9: Prof. Francis Shen, Associate Professor of Law; McKnight Land-Grant Professor, University of Minnesota; Exe. Dir. of Education and Outreach, MacArthur Foundation Research Network on Law and Neuroscience <i>Law and Neuroscience 2.0</i>
16.00 – 16.35	S2.10: Dr. Lisa Claydon, Lecturer in Law, Open University and Council Member of the European Association of Law and Neuroscience; Dr. Paul Catley, Head of The Open University Law School and Council Member of European Association of Neuroscience and Law <i>The use of neuroscientific evidence by those accused of criminal offences in England and Wales 2005-12</i>
16.35 – 17.05	S2.11: Dr. Simone Carton, Principal Clinical Psychologist, National Rehabilitation Hospital, Dublin <i>Neuropsychological assessment of mental capacity and decision-making with vulnerable adults</i>
17.05 – 17.35	S2.12: Dr. Lorraine Boran, Lecturer in Psychology, SNHS, DCU <i>The ethical and legal implications of the neuroscience of self-regulation in understanding criminal culpability, prediction and rehabilitation of criminal behaviour</i>
17.35 – 17.55	 Life Sciences Tea/coffee, sponsored by Pall Life Sciences and poster viewing, SNHS

Session 8 : Tom Connor Distinguished Investigator Award Lecture, Prize Giving, Reflections and Conference Close

17.55 – 18.25	Tom Connor Distinguished Investigator Award Lecture: introduced by Dr. Stella Vlachou. Presentation by: Prof. Paul J. Kenny, Experimental Therapeutics Institute, New York <i>New insights into the mechanisms of nicotine addiction</i>
18.25 – 18.35	Prize giving: presented by Prof. Oliver Dolly: Voted best poster – Post-doctoral Voted best poster – Postgraduate Passport to Prizes
18.35 – 18.45	Reflections from the Conference: Dr. Kevin Mitchell, Dept. of Genetics, TCD
18.45	Neuroscience Ireland AGM followed by closing of the meeting by Prof. David Henshall, President, Neuroscience Ireland

Day 1

Speaker Abstracts

S1.1 Sodium channels and pain pathways – new routes to analgesia?

John N. Wood FRS

Molecular Nociception Group, University College London

Loss of function mutations in the *SCN9A* gene encoding voltage-gated sodium channel $\text{Na}_v1.7$ cause congenital insensitivity to pain in humans and mice. Surprisingly, many potent selective antagonists of $\text{Na}_v1.7$ are weak analgesics. We investigated whether $\text{Na}_v1.7$, as well as contributing to electrical signalling, may have additional functions. We found that $\text{Na}_v1.7$ deletion has profound effects on gene expression, leading to an upregulation of enkephalin precursor *Penk* mRNA and met-enkephalin protein in sensory neurons. In contrast, sodium channel $\text{Nav}1.8$ null mutant sensory neurons show no upregulated *Penk* mRNA expression. Application of the opioid antagonist naloxone potentiates noxious peripheral input into the spinal cord, and dramatically reduces analgesia in both male and female $\text{Na}_v1.7$ null mutant mice, as well as in human $\text{Na}_v1.7$ null mutants. These data suggest that $\text{Na}_v1.7$ channel blockers alone may not replicate the analgesic phenotype of null mutant humans and mice, but may be potentiated with exogenous opioids.

S1.2: Generation of hESC/iPSC-derived peripheral neurons: a new approach to study sensory mechanisms.

Katrin Schrenk-Siemens, **Hagen Wende**, Vincenzo Prato, Kun Song, Charlotte Rostock, Alexander Loewer, Jochen Utikal, Gary R Lewin, Stefan G Lechner & Jan Siemens

Institute of Pharmacology, Heidelberg University

Mechanotransduction, the conversion of mechanical force into electrochemical signals, is the basis for several sensory phenomena such as hearing, balance and touch sensation. *In vivo*, touch receptors, also referred to as low-threshold mechanoreceptors (LTMRs), are intermingled with sensory neurons finely tuned to detect a variety of other (non-mechanical) thermal and chemical stimuli. The heterogeneity of sensory ganglia and very low abundance of LTMRs have hampered their isolation and characterization. Moreover, human LTMRs are not accessible at all for functional examination.

In order to examine human touch receptor function, we recapitulated sensory neuron development *in vitro* and established a multi-step differentiation protocol to generate LTMRs via the intermediate production of hES-cell-derived neural crest cells, the sensory neuron progenitors. The generated neurons feature morphological hallmarks of prototypic sensory neurons, such as a pseudounipolar architecture, and they express a highly distinct set of LTMR specific genes. Interestingly, other sensory subtypes such nociceptors appear not to be present in the cultures. Most importantly the derived sensory neurons convert mechanical stimuli into electrical signals, their most salient characteristic *in vivo*. The differentiation procedure is not only effective in hES cells but also facilitates the conversion of human iPSC cells into LTMRs.

Two molecules that recently have been implicated in sensing mechanical force in different cellular contexts are the large transmembrane proteins Piezo1 and 2. Strikingly, we find that mechanosensitivity is lost in hESC-derived LTMRs following CRISPR/Cas9-mediated *PIEZO2* gene deletion.

This is the first time, to our knowledge, that highly specialized, functional human touch receptors have been generated *in vitro*.

S1.3: EnSNAREing the transduction of chronic pain with botulinum neurotoxins

J. Oliver Dolly, Jianghui Meng, Laura Casals-Diaz, Omprakash Edupuganti, Tomas Zurawski, Charles Metais, John Nealon, Gary Lawrence and Jiafu Wang

International Centre for Neurotherapeutics, Faculty of Science and Health, Lonsdale Building, Dublin City University, Dublin 9.

Pain-inducing stimuli detected by sensory neuron endings cause peripheral sensitisation via activation of transducers [e.g. transient receptor potential (TRP) vanilloid 1 and A1 proteins], their up-regulation and translocation to the plasmalemma. Opening of the channels triggers SNARE-mediated exocytosis of excitatory transmitters, and pain-mediating peptides from large dense core vesicles (LDCVs). Confocal fluorescence microscopy showed that botulinum neurotoxin type A (BoNT/A) — a Clostridial protein whose protease inactivates SNAP-25 — not only inhibits evoked release of CGRP but, also, decreases the TNF α -elevated co-trafficking of TRPV1 and TRPA1. The latter occurs in LDCVs and requires SNAP-25, syntaxin 1 and VAMP1 as well as Munc 18-1. TNF α -induced relocation of either channel increased agonist-elicited Ca²⁺ influx, and this was restored by pre-treatment with BoNT/A. Clearly, the neurotoxin has a dual compounded effect, inhibiting transmitter neuro-exocytosis as well as the augmented appearance of transducers that underpin peripheral hyper-sensitisation/pain. To obtain an effective analgesic, therapeutically-advantageous characteristics of types E and A were harnessed in a chimera. After expression in *E. coli*, this purified, composite protein displayed the pertinent properties, including inhibition of CGRP release from sensory neurons evoked by TRPV1 activation. Most importantly, in a rat model of neuropathic chronic pain, a local injection gave a profound and prolonged amelioration of both mechanical and cold hyper-sensitivity compared to that of daily administered pregabalin. These *in vivo* findings, in conjunction with the successful use of BoNT/A complex for treating many motor and hyper-secretory disorders as well as chronic migraine, heighten the prospect of future long-acting, efficacious and non-addictive analgesics.

S1.4: The role of CSF neuropeptides in chronic pain perception in man

Connail McCrory

Trinity College, Dublin and St. James Hospital, Dublin

Chronic pain remains an enormous problem for patients affecting approximately 13% of the Irish population with significant morbidity in terms of disability, absence from work and social disintegration. Preclinical research has improved our understanding of the pathophysiology of chronicity and the factors, which affect the conversion of acute protective pain to chronic destructive pain. Significant strides have been made in our knowledge regarding neural plasticity and central sensitization with a growing consensus regarding the central role played by glial cell activation and neuropeptide biosynthesis in response to given stimuli. This preclinical knowledge is starting to be applied to the clinical scenario leading to improvements in our knowledge of the factors maintaining chronic pain in vivo in man and potentially enhancing our ability to develop techniques to neuromodulate these central neuropeptide activation processes. This will facilitate optimization of current interventional techniques and the development of new techniques. This presentation will delineate our current knowledge regarding the pathophysiology of chronic pain in vivo in man and describe the evidence for the mechanisms of action of some of the therapeutic techniques used clinically by pain physicians.

S1.5: Where the tortoise and the hare meet - clathrin and adaptors in synaptic vesicle cycling

Volker Haucke

Leibniz Institute for Molecular Pharmacology

The function of the nervous system depends on the exocytotic release of neurotransmitter from synaptic vesicles (SVs). To sustain neurotransmission SV membranes need to be retrieved and SVs have to be reformed locally within presynaptic nerve terminals. In spite of more than forty years of research the mechanisms underlying presynaptic membrane retrieval and SV recycling remain controversial. In my talk I will present latest data regarding the molecular mechanisms of presynaptic membrane retrieval and SV reformation and the role of endocytic proteins in these processes.

S1.6: A fast endophilin-dependent, clathrin-independent endocytic mechanism

Harvey T McMahan

MRC Laboratory of Molecular Biology, Cambridge

Cell and organelle shape are adapted to function. We focus on the dynamic regulation of membrane shape, which can occur by the interplay between the transient and regulated insertion of membrane bending motifs and the detection and stabilisation of membrane shape. This approach has allowed us not only to describe the biophysics of membrane shape changes but also to take a fresh look at membrane dynamics in physiological processes like exocytosis and endocytosis. In doing so we have noted that proteins with amphipathic helices or hydrophobic membrane-inserting loops are likely to effect or respond to curvature and that the membrane interaction surfaces of proteins can sense shape (like proteins of the BAR Superfamily). This molecular view has allowed us to ascribe novel cell-biological functions to proteins (e.g. the mechanistic affect of synaptotagmin in membrane fusion) and to give a more insightful view of how these processes work. I will present our recent work on a novel pathway of endocytosis that we are in the midst of characterising. It is a ubiquitous pathway operating especially in synapses but also in all cell types we have tested. It is clathrin-independent and dynamin dependent and operates at a much faster timescale than clathrin vesicle formation. We believe that a molecular understanding of this pathway will lead to fresh insights into fast membrane trafficking responses, like synaptic vesicle retrieval. For further details of our approaches see: <http://www.endocytosis.org/>

S1.7: Multiple pathways of acceptor-mediated endocytosis are exploited by botulinum neurotoxins to enter neurons

Jiafu Wang, Jianghui Meng, Tom Zurawski, Gary Lawrence, Minhong Tang, Kim Orange and J. Oliver Dolly

International Centre for Neurotherapeutics, Faculty of Science and Health, Lonsdale Building, Dublin City University, Dublin 9.

Botulinum neurotoxin type A (BoNT/A) is the most potent toxin due to its inhibition of acetylcholine release and subsequent flaccid paralysis. However, a wide variety of neurogenic hyper-activity disorders are successfully treated by locally injecting a minute amount of BoNT/A complex. This highly specific neurotoxin exploits synaptic vesicles (SVs) to enter neurons by binding to SV2 protein and gangliosides, via a C-terminal binding sub-domain (H_{CC}). Herein, we show that dynamin, clathrin, amphiphysin and adaptor protein complex-2 are required for depolarization-evoked uptake of BoNT/A or a chimera of BoNT/E and /A into small clear synaptic vesicles (SCSVs) of rodent cerebellar granule neurons (CGNs), and large dense core vesicles (LDCVs) enriched trigeminal ganglionic neurons (TGNs). Notably, distinct isoforms of dynamin and amphiphysin are required for neurotoxin entry into these different neuron types. CGNs predominantly use dynamin 1 for fast recycling of SCSVs whereas LDCV-releasing TGNs employ amphiphysin 1, dynamins 2 and 3 but not 1 for a less rapid mode of stimulated endocytosis. Interestingly, resting uptake of BoNTs into CGNs and TGNs does not require the above-mentioned classical, endocytosis mediators. Ongoing site-directed mutagenesis is pinpointing a domain that facilitates BoNTs cytosolic entry following binding to the neuronal ecto-acceptors. A dileucine in the C-terminal of the BoNT/A protease domain underlies its long-lasting therapeutic action. Hence, BoNT/A has proven to be an excellent research probe for endo-/exocytosis, in addition to its astonishing therapeutic effectiveness.

Day 2

Speaker Abstracts

S2.1: Dopamine, reward and addiction: new evidence on a classic theme

Gaetano Di Chiara

Department of Biomedical Sciences, University of Cagliari, Cagliari , Italy

Microdialysis and voltammetry studies in rats show that shell dopamine (DA) is preferentially activated by drugs of abuse after passive, acute as well as i.v self-administration (SA). Palatable food and sucrose pellet feeding in naive rats also increase dialysate DA in the NAc shell and core but this response undergoes single-trial habituation only in the shell. Drugs of abuse do not induce single-trial habituation of shell DA. These observations, coupled to the evidence for a role of DA in incentive learning, provided the basis for a DA-dependent incentive learning theory of drug addiction. This theory in turn, has been much strengthened by recent optogenetic studies on a sufficient role of DA for reward and incentive learning. However we recently found that habituation of shell DA to sucrose is lost after a two weeks of contingent and non contingent sucrose feeding. Responding under extinction also activates shell DA. Thus, after training, sucrose conditioned stimuli (CSs) replace UCS taste stimuli in controlling responding for sucrose as well activation of shell DA. Thus, the property of stimulating DA transmission in the NAc shell in a non-habituating fashion, typical of drugs of abuse, is homologous to that of incentive sucrose CSs. However, while the shell DA stimulant property of sucrose CSs undergoes extinction if not reinforced, in the case of drugs of abuse that property is unconditioned (US) and therefore resistant to extinction. This might provide the basis for a new incentive learning hypothesis of drug addiction.

S2.2: Sex differences in kappa opioid receptor function and their impact on addiction

Elena Chartoff

Department of Psychiatry, Harvard Medical School, McLean Hospital

There are pronounced sex differences in the behavioral, biological and social sequelae that lead to addiction, particularly those related to stress. For example, females are more sensitive to the aversive effects of drugs of abuse and stress-induced relapse. Increasing evidence shows that the neuropeptide dynorphin, an endogenous ligand at KORs, is necessary for stress-induced aversive states and is upregulated in the brain after chronic exposure to drugs of abuse. In males, KOR agonists produce signs of anxiety, fear, and depression in laboratory animals and humans, findings that have led to the hypothesis that drug withdrawal-induced dynorphin release is instrumental in negative reinforcement processes that drive addiction. Only recently is evidence available that there are profound sex differences in the effects of KOR activation on affective state. Using intracranial self-stimulation (ICSS), we found that female rats are less sensitive than males to the depressive-like effects of the KOR agonist U-50,488, regardless of estrous cycle stage. This suggests that sex differences in KOR-mediated depressive-like states are not due to circulating gonadal hormones. Furthermore, KOR activation produces sex-dependent alterations in neuronal activation in brain regions comprising the extended amygdala and hypothalamic pituitary adrenal (HPA) axis. Using quantitative real-time RT-PCR on tissue from these brain regions, we have found baseline sex differences in the expression of stress-related genes including those encoding dynorphin, KORs, and corticotropin releasing factor (CRF). Taken together our data suggest that neural circuits necessary for mediating stress responses differ between males and females at a molecular level and may underlie sex differences in addictive behavior. These findings underscore the importance of understanding KOR function in both sexes such that pharmacotherapeutics targeting addictive disorders can be rationally designed.

Support: NIH Grant DA033526

S2.3: Potential therapeutic treatments for nicotine dependence: focusing on reward, impulsivity and attentional performance

Styliani Vlachou

School of Nursing and Human Sciences, Faculty of Science and Health, DCU, Dublin 9, Ireland

Tobacco smoking is partly attributed to the addictive properties of nicotine and constitutes a worldwide drug abuse problem with serious health effects. γ -aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and is implicated in the modulation of brain reward and cognitive processes. Acute or chronic administration of γ -aminobutyric acid B (GABAB) receptor agonists and/or positive allosteric modulators (PAMs) decreases self-administration of various drugs of abuse and inhibits cue-induced reinstatement of drug-seeking behavior. Impulsivity, a tendency to pursue rewarding stimuli without consideration for potential harmful/negative consequences, is strongly associated with habitual tobacco smoking. High impulsivity levels may be a risk factor for nicotine dependence, leading to its initiation and maintenance. Further, little is known about the effects of GABAB receptor PAMs in cognitive processes (e.g., attentional performance) and impulsivity/compulsivity. A number of studies conducted as part of my post-doctoral training (Supervisor: Prof. Athina Markou, University of California at San Diego) will be presented showing that BHF177, a GABAB receptor PAM, decreased the reinforcing and motivational effects of nicotine in rats from the general population and in high/low impulsive rats in a similar manner and dose-dependently and selectively blocked cue-induced reinstatement of nicotine seeking, a putative animal model of relapse in humans. Thus, BHF177, or similar GABAB receptor PAMs, could be useful therapeutics for the treatment of different aspects of nicotine dependence, by assisting both in smoking cessation by decreasing the reinforcing effects of nicotine, as well as in preventing relapse to smoking in the general population and/or in high/low impulsive individuals. A brief introduction of the research focus of my newly established research group at DCU will be presented during my talk.

S2.4: Glutamate, stress and the adolescent brain: impact on the rewarding effects of cocaine

Richard M. O'Connor^a, Rachel D. Moloney^a, Jeffrey Glennon^b, Styliani Vlachou^c and **John F. Cryan^a**

^a*Department of Anatomy and Neuroscience, University College Cork, Ireland*

^b*APC Microbiome Institute, University College Cork, Ireland*

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Adolescence marks a critical time when the brain is highly susceptible to pathological insult yet also uniquely amenable to therapeutic intervention. It is during adolescence that the onset of the majority of psychiatric disorders, including substance use disorder (SUDs), occurs. It has been well established that stress, particularly during early development, can contribute to the pathological changes which contribute to the development of SUDs. Glutamate as the main excitatory neurotransmitter in the mammalian CNS plays a key role in various physiological processes, including reward function, and in mediating the effects of psychological stress. We hypothesised impairing glutamatergic signalling during the key adolescent period would attenuate early-life stress induced impaired reward function. To test this, we induced early-life stress in male rats using the maternal-separation procedure. During the critical adolescent period (PND25-46) animals were treated with the glutamate transporter activator, riluzole, or the NMDA receptor antagonist, memantine. Adult reward function was assessed using voluntary cocaine intake measured via intravenous self-administration. We found that early-life stress in the form of maternal-separation impaired reward function, reducing the number of successful cocaine-infusions achieved during the intravenous self-administration procedure as well impairing drug-induced reinstatement of cocaine-taking behaviour. Interestingly, riluzole and memantine treatment reversed this stress-induced impairment. These data suggest that reducing glutamatergic signalling may be a viable therapeutic strategy for treating vulnerable individuals at risk of developing SUDs including certain adolescent populations, particularly those which may have experienced trauma during early-life.

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S2.5: Ion channels as neuroprotective targets in multiple sclerosis

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Multiple sclerosis (MS) is the most frequent inflammatory disease of the central nervous system (CNS). MS has been attributed to a breakdown of immune tolerance to self-antigens in CNS myelin resulting in focal immune cell infiltration, demyelination, axonal and neuronal degeneration, which eventually leads to long-term disability. Axonal and neuronal loss occur already early in the course of the disease and are decisive for clinical deficits in the patients. A growing body of evidence has suggested that the inflammatory insults in MS determine neurodegeneration by causing axonal and neuronal mitochondrial dysfunction, energy failure and alterations of ion exchange mechanisms. Here I report on the pathophysiology of neurodegeneration during chronic CNS inflammation with a particular focus on neuronal ion channel dysregulation that commend as target molecules for neuroprotective treatment strategies. We recently identified two ion channels (ASIC1 and TRPM4), which crucially contribute to maladaptive cation handling under inflammatory conditions. Moreover, it has been postulated by circumstantial evidence that inflammatory demyelination results in redistribution and upregulation of Na⁺ channels Na_v1.2 (*Scn2a*) and Na_v1.6 (*Scn2b*) along the denuded axolemma with disturbed axonal ion homeostasis and subsequent axonal degeneration. We investigated this long-standing hypothesis by generating a novel transgenic mouse that allowed us to directly investigate the contribution of Na⁺ channel currents to neurodegeneration in an animal model of MS.

S2.6: The soluble IL-2 receptor in MS; more than a biomarker?

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Interleukin-2 is a critical mediator of T cell tolerance through its ability to enhance Treg responses while inhibiting the development of pathogenic Th17 type responses. These mechanisms underscore the strong association of mutations at the *IL2 receptor alpha chain (CD25)* gene locus and susceptibility to a number of T cell driven autoimmune diseases such as multiple sclerosis. Interestingly, the presence of certain *CD25* susceptibility alleles has been correlated with significantly increased levels of the soluble form of CD25 (sCD25) in the serum of MS patients. However, the functional consequences, if any, of this observation are unknown. We have demonstrated that sCD25 significantly enhanced the development of Th17 type responses *in vitro* without any effects on Th1 or iTreg type responses. sCD25 exerted these effects early during the Th17 developmental programme, through inhibiting signalling downstream of the the IL-2R. Although, sCD25 did not interact with the T cell surface, it greatly inhibited the detection of secreted levels of IL-2 demonstrating its ability to act as an IL-2 ‘sink’ in the T cell microenvironment. Importantly, systemic elevation of sCD25 also led to enhanced antigen specific Th17 responses *in vivo* as well as an earlier onset and increased severity of experimental autoimmune encephalomyelitis. These data identify a novel function of sCD25 in the development of pathogenic T cell responses and reveal a previously unappreciated mechanism through which the IL-2 receptor can regulate peripheral T cell tolerance.

S2.7: Neuronal Kv1.1 channels as promising targets for a novel selective blocker to normalise impaired conduction in demyelinated axons mimicking that in multiple sclerosis

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Members of the voltage-gated K⁺ channel subfamily (Kv1), involved in regulating transmission between neurons or to muscles, are associated with certain human diseases and, thus, could serve as putative targets for neurotherapeutics. This is especially applicable to tetramers containing Kv1.1 α subunits which become elevated in murine axons of optic nerve after demyelination, appear abnormally at inter-nodes and underlying defective neural conduction. To overcome this dysfunction related to debilitation in multiple sclerosis, a small inhibitor selective for the culpable hyperpolarising Kv1.1 currents was discovered, using chemi-informative synthesis and electrophysiological recording of its blockade of recombinant Kv1 channels, expressed in mammalian cells. Modelling of interactions with the extracellular pore region in a derived Kv1.1 structure identified a dipyrromethane scaffold with optimised alkyl-ammonium side chains as being suitable. This compound potently and selectively blocked Kv1.1 channels, accompanied by a positive shift in the voltage-dependency of activation and slowing of activation kinetics, complementary accentuating effects. Although it reduced a Kv1.3-mediated K⁺ current to a lesser extent, preferential inhibition was observed of Kv1 homomer and heteromers containing 2 or more Kv1.1 subunits, regardless of their positioning in concatenated tetramers. These collective findings highlight the therapeutic potential of this Kv1.1 inhibitor and warrants its *in vivo* evaluation, using models of multiple sclerosis.

S2.8: MicroRNAs as treatment targets in epilepsy

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Molecular Physiology and Neuroscience, Physiology & Medical Physics, RCSI

Temporal lobe epilepsy is a common, chronic neurologic disorder characterized by recurrent spontaneous seizures. Understanding the molecular mechanisms regulating gene expression may lead to novel approaches to treat or prevent epilepsy. MicroRNAs (miRNAs) are small, non-coding RNAs that regulate post-transcriptional expression of protein-coding mRNAs. A particularly interesting feature is their multi-targeting capability, meaning a single miRNA can exert effects on several genes, including within the same pathway. Research by a number of teams including our own has identified miRNA dysregulation in experimental and human epilepsy. We have characterized altered expression of miRNAs and explored their functional contribution. We have focused most on miR-134, a brain-specific, activity-regulated miRNA implicated in the control of dendritic spine morphology. Silencing of miR-134 expression *in vivo* has strong anticonvulsant effects and can substantially reduce the occurrence of epileptic seizures. In emerging work we have turned our attention to miRNA that regulate the expression of ion channels and neuroinflammation. These results demonstrate an important layer of gene expression control that may be targeted to treat or prevent epilepsy.

S2.9: Law and Neuroscience 2.0

Francis X. Shen

University of Minnesota

Brain science is rapidly becoming central to our understanding of how we make decisions, why we act, and why we sometimes act in ways that we wish we would not. Law and public policy have taken notice of this neuroscience revolution.

Lawyers and courts across the globe are already integrating neuroscience research into their arguments and opinions on questions such as: What are adolescents thinking? Why does emotional trauma for victims of abuse last so long? Why is eye-witness memory so poor? And much more. Legislators are also listening, as they craft policy to address mental health, addiction, dementia, prenatal care, education, and a host of other social policies.

But what will come of this momentum? Will the field of neurolaw continue to expand, or will neuroscience fail to bring about significant change in law?

This talk will address such questions by exploring the past, present, and future of neurolaw, laying out thoughts for what will constitute Law and Neuroscience 2.0.

Better understanding of brain function offers great promise but also great peril. The talk will thus cover the principles by which cognitive neuroscience should (and should not) be embraced by courts, legislatures, and us as citizens. The talk will touch briefly on topics such as criminal culpability, adolescent brain development, brain-based lie detection, cognitive enhancement, emotions, and decision making.

S2.10: The use of neuroscientific evidence by those accused of criminal offences in England and Wales 2005-2012

Lisa Claydon¹ and Paul Catley²

¹Open University and Council Member of the European Association of Law and Neuroscience

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Whilst discussion about the use and potential use of neuroscientific evidence in the courts has been widespread, there has been little empirical evidence as to how it is actually used. Much of the discussion has concerned the possible exploitation of such evidence by defendants arguing: “my brain made me do it”. The presenters have researched reported cases in England and Wales and identified 204 reported cases in which neuroscientific evidence has been used by those accused of criminal offences during the eight year period from 2005 – 2012 which challenges this stereotype as to how it might be used. The use of neuroscientific evidence has been varied: being used to quash convictions, to lead to convictions for lesser offences and to lead to reduced sentences. In addition cases have been identified where neuroscientific evidence is used to avoid extradition, to challenge bail conditions and to resist prosecution appeals against unduly lenient sentences. The range of uses identified is wide: including challenging prosecution evidence as to the cause of death or injury, challenging the credibility of witnesses and arguing that those convicted were unfit to plead, lacked *mens rea* or were entitled to mental condition defences. The acceptance of such evidence reflects the willingness of the courts in England and Wales to hear novel scientific argument, where it is valid and directly relevant to the issue(s) to be decided. The research parallels similar research being undertaken by colleagues in the USA, Canada, the Netherlands, Malaysia and Singapore.

S2.11: Neuropsychological assessment of mental capacity and decision-making with vulnerable adults.

Simone Carton

Principal Clinical Psychologist, National Rehabilitation Hospital, Dublin

The developments in neuroscience have substantially improved our understanding of the brain and the neural processes and interconnections that influence cognitions, emotions and behaviour. The interface between the neurological and the psychological is comprised of an intricate web of genetics, neurons, biochemistry and experience. These factors in turn shape motivations, preferences, choices and decisions. Clinical Neuropsychology attempts to understand these variables and how they can improve our understanding of patients with neurological disease.

The legal fraternity are also aware of the developments in neuroscience and their responsibility to incorporate this knowledge into legal practice. This is especially illustrated by the increasing requests for neuropsychology expertise in relation to assessing the impact of brain injury and illness to for example, the person's ability to live independently and or to make decisions about their treatment and or financial affairs. Similarly, governments are aware of their obligation to ensure that the laws are responsive to changes in knowledge and social and cultural values. This is especially highlighted in the proposed changes in the Irish legislation regarding mental capacity and decision making.

This talk will focus on (1) The contribution of neuropsychology to the assessment of mental capacity and decision-making in vulnerable adults with neurological illness/injury and how despite obvious neuropsychological compromise, they can be supported to exert their preferences. (2) How this clinical understanding is reflected in the proposed changes in legislation

S2.12: The ethical and legal implications of the neuroscience of self-regulation in understanding criminal culpability, prediction and rehabilitation of criminal behaviour

Lorraine Boran

School of Nursing and Human Sciences, DCU, Dublin

Self-regulation refers to the ability to alter one's affective and cognitive responses to environmental and internal demands. It emerges from the interplay between a top-down reflective executive control system and a bottom-up automatic socio-emotional system underpinning automatic responses to environmental rewards. Since self-regulation failure is a significant driver of antisocial behaviour, understanding its neurocognitive underpinnings offers some possibilities for the development of novel brain-based assessments and neurocorrective tools. In this talk, consideration will be given to the legal and ethical issues related to cognitive liberty, coercion, and incentivisation associated with the potential for neurocognitive assessments and neurocorrective interventions to inform appraisal of criminal culpability, predict recidivism, and modulate deviant behaviour at the neurological level.

Day 2

**Tom Connor Distinguished
Investigator Award Lecture
Abstract**

New insights into the mechanisms of nicotine addiction

Prof. Paul J. Kenny

Experimental Therapeutics Institute, New York

Habitual tobacco use is the leading cause of premature death and disease worldwide. Nicotine is the major addictive component of tobacco responsible for establishing and maintaining the habit. Nicotine acts in the brain at nicotinic acetylcholine receptors (nAChRs), which are pentameric ligand-gated ion channels. nAChR containing $\alpha 4$ and $\beta 2$ nAChR subunits are densely expressed in the ventral tegmental area (VTA) and other components of the brain reward system. Stimulatory effects of nicotine on these nAChRs are thought to underlie the motivational properties of the drug. Recently, allelic variation in *CHRNA5*, the gene encoding the $\alpha 5$ nAChR subunit, was shown to increase vulnerability to tobacco dependence and smoking-associated diseases. nAChRs comprised of these subunits are densely expressed in the medial habenula-interpeduncular nucleus (MHb-IPN) pathway. Our laboratory has established that $\alpha 5$ -containing nAChRs regulate the stimulatory effects of nicotine on the MHb-IPN system. Moreover, we found that the MHb-IPN system regulates aversive but not rewarding properties of nicotine, and thereby exerts an inhibitory effect over nicotine intake. More recently, we have found that prolonged exposure to self-administered nicotine induces shrinkage of the MHb and degeneration of the fiber connection between the MHb and IPN (fasciculus retroflexus). We observe similar structural deficits in the MHb-IPN of human smokers. Together, these findings identify the MHb-IPN system as a key brain pathway controlling nicotine intake. Genetic variation that decreases the responsiveness of this pathway, or dysfunction that occurs as a result of nicotine intake, may facilitate the transition to occasional to habitual smoking behavior.

Poster Presentation Abstracts

**Poster Topic Area 1:
Cognitive and Behavioural
Neuroscience**

P1.01. Genetic variation in cholinergic muscarinic receptor-2 gene and its role in intelligence, attention & spatial working memory in bipolar disorder

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An investigation of two datasets involved 1) healthy controls (HC; n=54, mean age±SD, 42±9, 50% female), and BD (n=51, 42±10, 49%); and 2) HC (n=189, 35±12, 51.9%) and BD (n=129, 45±11, 48.8%). Participants underwent genotyping (rs324650, HWE p range=0.12-0.87) and neuropsychological testing to assess intelligence quotient (National adult reading test, NART, Wechsler adult intelligence scale, WAIS-III), attention (sustained attention to response task, SART) and spatial working memory (Cambridge automated neuropsychological test battery spatial working memory task, CANTAB SWM) performance.

There was a main effect of genotype for the SNP rs324650 in attention (F=4.7,p=0.01), but not for SWM (F=0.93,p=0.39) and IQ (F=0.71,p=0.49). A significant interaction between genotype (rs324650) and diagnosis was detected for the total number of correct responses measured in the SART task of attention (F=4.46,p=0.013). A main effect of diagnosis was detected confirming existing literature showing lower attention (F=39.5,p=2.9E-9), and spatial work memory performance (F=35.9,p=7.2E-9) in BD relative to the control group.

These findings suggest a role for the TT-genotype of the rs324650 SNP of the CHRM2 gene in explaining reduced attention in BD. Despite several studies previously implicating rs324650 to IQ, we did not observe this relationship in the present data for the control (F=67.4,p=0.19) or the BD group (F=185.8,p=0.83).

Acknowledgements: This study is possible by the gracious support by Galway Neuroscience Centre, NCBES, NUI Galway Millennium Research Fund, College of Science PhD Scholarship (SA), & Health Research Board (HRB) grant.

P1.02. Behavioural and neurochemical effects of natural plant-derived alkaloid and/or flavonoid compounds in naïve and nicotine-dependent rats: a comparative study

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Tobacco smoking is considered one of the most serious worldwide health problems, causing several hundred thousand deaths per year and numerous secondary health problems; current pharmacotherapies are considered largely insufficient, with only a small percentage of smokers still being abstinent one year after cessation. Recent studies suggest that alkaloid or flavonoid components of plant-derived compounds (e.g., harmine) could mediate therapeutic effects in drug dependence and other CNS disorders. Although studies have focused on the potential therapeutic effects of plant-derived compounds on dependence to cocaine, morphine and alcohol, there have not been studies investigating the effects of harmine and/or other alkaloid compounds on the different phases/aspects of nicotine dependence, including the behavioural (i.e., reinforcing, reward-enhancing) and cognitive-enhancing effects of nicotine. Thus, this PhD research project aims to use a combination of behavioral and neurochemical procedures in rats to investigate the effects of alkaloid and/or flavonoid compounds on: 1) cognitive and attentional performance, impulsivity and reward, 2) the reward-facilitating, cognitive-enhancing and attentional performance effects of nicotine and 3) several neurotransmitter systems of the basal forebrain (such as the cholinergic, dopaminergic, GABAergic systems) implicated in nicotine effects. Results generated by these studies may have a strong translational value and lead to the development of new medications and treatments for nicotine dependence.

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P1.03. Multimodal validation of facial expression detection software for real-time monitoring of affect in patients with suicidal intent

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High risk for suicide is typically assessed by clinicians using questionnaires and interviews (Swann, Dougherty et al. 2005, Dougherty, Mathias et al. 2009). Although useful in a wide range of clinical settings, this assessment approach has many disadvantages e.g., misinterpretation of subtle differences in meanings of words used in emotional scales, objective and subjective biases and difficulties in reliably assessing the intensity of the emotion (Hooley and Parker 2006, Balon 2007, Furukawa 2010, Hall 2011). Most significantly, these cues can be missed with catastrophic consequences. In this context, we suggest that novel, non-intrusive facial affect detection technology could play a role in the clinical evaluation of suicidal intent. We report on the acquisition of discrete emotional states (i.e., fear, sadness, joy, anger, disgust and surprise) while the patient is participating in a standardised task utilising the presentation of emotionally challenging images.

The present project extends the validation of facial affect data using well established measures such as electroencephalography (EEG), event related potentials (ERP), galvanic skin response (GSR) and heart rate variability (HRV). Altogether, we suggest that the computerised detection of facial affect during participation in mood challenging tasks could play an important role in the evaluation of suicide risk.

P1.04. Effects of exercise on learning and memory throughout the lifespan: the role of new neurons and cognitive reserve hypothesis

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Trinity College Dublin

Introduction: Age-related cognitive decline has been associated with decreased hippocampal neurogenesis¹. Studies have suggested that physical exercise can counteract molecular modifications related to hippocampal dysfunction in Alzheimers disease (AD) and ageing and increases hippocampal neurogenesis during the process of ageing^{2,3}.

Objective: To investigate the effects of chronic exercise on memory and learning throughout the lifespan.

Materials and Methods: Young male mice (n=18) are undergoing 1 hour of treadmill running 3 times per week for a period of 8 months. At the end of this period, the young mice will be middle-aged (11 months). They will then cease exercise and be housed until old age (20 months). All mice are tested every 2 months for non-spatial (Novel Object Recognition-NOR) and spatial (Object Displacement-OD) memory. We have tested animals in NOR and OD tasks at 5 and 7 months, after 2 and 4 months undergoing treadmill running, respectively.

Results: As preliminary results, we observed that at 5 months old, there was no difference between exercise group (Ex) and sedentary group (Sed) in the NOR task ($p=0.0694$). However, we observed a difference between Ex and Sed exploration time in the OD task ($p < 0,05$). Interestingly, at 7 months old, after 4 months of moderate exercise, we found differences between Ex and Sed exploration time in both tasks, NOR and OD ($p < 0,05$).

Conclusion: These data suggest that at 7months old mice do not present cognitive deficits, however, 4 months of exercise facilitates spatial and non-spatial learning and memory compared to sedentary animals.

P1.05. Examining the Effects of Dim Light-at-Night on affective Behaviours in C57Bl/6 mice

Michael Cleary-Gaffney, Andrew N. Coogan
Maynooth University

Rates of major depression have increased substantially in recent years, although it is not currently clear what the factors behind such increases are. Environmental factors may be important, and it has recently been postulated that dim nocturnal light may contribute to depression symptoms in humans and in rodents. Sex is also a very important factor in affective disorders, with prevalence rates of major depression twice as high in females than in males. We set out to test the hypothesis that dim-light would interfere with the circadian rhythm of C57Bl/6 mice and induce depressive-like behaviours and that there would be sex-specific differences. Animals were either singly or group housed for three weeks where locomotor activity was measured and then tested on a range of tests of emotional behaviours. Animals were subsequently placed into either 12 h light: 12h dim nocturnal light (~5 lux) cycle or back in a 12:12 light dark condition and retested on the behavioural battery after three weeks. Brains of the same animals were used to measure stem cell proliferation in the dentate gyrus using the biomarker Ki-67. Exposure to dim light-at-night did not lead to significant circadian disruption nor to significant changes in any of the parameters examined, and no sex-dependent effects were detected. Levels of Ki-67 were significantly decreased in the dentate gyrus of light-at-night animals. These results indicate that species and strain differences may be important in assessing potential impact of dim nocturnal light on circadian and affective systems in rodents.

P1.06. Social Jetlag, chronotype, personality and glycaemic control in type II diabetes

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Circadian rhythms are endogenously generated daily cycles that may be influenced by external cues such as light, and such rhythms are important in the temporal regulation of metabolism. One expression of inter-individual differences in circadian rhythms is the expression of chronotypes, in which individuals may exhibit differences in diurnal preferences (eg. morningness of eveningness) for certain activities. Further, given the societal demands of working schedules there may be a misalignment between internal circadian time and externally imposed time cues, a phenomenon which has been termed social jetlag. The aim of this study was to investigate the impact of chronotype on glycaemic control in type II diabetes, and to investigate if any effects might be mediated through social jetlag or personality domains. The Munich Chronotype Questionnaire was administered to outpatients at the diabetes centre in Connolly Hospital, Dublin (n=120). The Big Five Inventory was also administered to assess personality type. Clinical measures were also obtained, specifically HbA1c levels as a measure of glycaemic control. There was a moderate positive correlation between the mid-sleep and HbA1c ($r = 0.237$, $p=0.009$). There was also a positive medium correlation between HbA1c levels and social jetlag was revealed ($r = 0.344$, $p < 0.001$), as was a correlation found between the neuroticism domain of the Big Five and HbA1c levels ($r=0.267$, $p=0.007$). Partial correlation reveals that controlling for neuroticism does not affect the relationship of social jetlag and HbA1c levels, suggesting that the influence of social jetlag and personality domains on glycaemic control are independent of each other.

P1.07. Schizophrenia-associated SNPs linked to neurotransmission genes impact memory and social cognition in patients and controls

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Schizophrenia (SZ) is a highly heritable disorder with positive, negative and cognitive symptoms. Genome-wide association studies (GWAS) have been carried out to compare the DNA sequences of SZ patients and healthy controls. The functions of the genes identified in GWAS are very diverse, making the establishment of the functional effects of these risk variants a priority.

On average, people with SZ score lower than healthy controls on measures of memory, IQ and attention. These abilities are strongly associated with functional outcome. Current pharmacological treatments for SZ can improve the positive symptoms but are less successful at treating the negative symptoms and cognitive deficits. Studying the influence of SZ-associated risk variants on neuropsychological measures may indicate genetic origins and biological pathways that contribute to these cognitive deficits.

Genetic loci within genes linked to neurotransmission were chosen for analysis from the most recent SZ GWAS. The effect of risk SNP burden on cognitive test scores in patients and controls was examined using linear regression analyses.

The SNP rs1339227 within the gene RIMS1 was found to have a significant effect on scores of Reading the Mind in the Eyes ($p=0.032$); rs7893279 within the gene CACNB2 on the Hinting Task ($p=0.016$); and rs2007044 within the gene CACNA1C on CANTAB Spatial Working Memory ($p=0.026$). The effect of rs2007044 risk SNP burden on memory was also significant in an independent replication sample ($p=0.03$).

The genes RIMS1, CACNA1C and CACNB2 are linked to critical processes for neurotransmitter release in a manner not specific to any one neurotransmitter. The size of the genetic effects here are modest, consistent with previous findings, and point to mechanisms in neurotransmission that may contribute to these deficits.

P1.08. Are there gender differences in the Olfactory Bulbectomy model of depression?

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Depression is a neuropsychiatric disorder that affects roughly twice as many more women than men. Sex differences in neurobiology are thought to be one of the major causes of this preponderance of females suffering from depression. In pre-clinical behavioural research there is an inadequate use of female test subjects due to the belief that their baseline behaviour is more variable than that of males. The aim of this study is to examine a commonly used animal model of depression, namely the olfactory bulbectomized (OB) rat in regards to whether there are any differences in the behavioural profile between male and female Sprague-Dawley rats. Following olfactory bulbectomy (or sham) surgery, rats were allowed a 3-week period before behavioural testing commenced which consisted of the open field (OF), elevated plus maze (EPM), forced swim test (FST) and Morris Water Maze (MWM). Significant OB-related changes were found in the OF and EPM, regardless of gender, whilst there was a significant OB-related reduction in time spent in the target quadrant in the MWM, an effect also seen in both female groups. There were no OB or gender-related differences in the FST behaviour. It can be concluded that in the tests that have a significant locomotor component that the magnitude of the OB-related deficit is equivalent between male and female rats and thus suggests that an equally valid result would be obtained. The cognitive differences between the genders in the MWM calls into question the utility of this test for assessing OB-related effects.

P1.09. Peripheral Inhibition of FAAH attenuates formalin-evoked nociceptive responding in a mouse model of IFN- α -induced hyperalgesia

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Side effects of interferon-alpha (IFN- α) treatment include depression and painful symptoms, effects we have recently replicated in a preclinical animal model. Anandamide (AEA) modulates emotional and nociceptive processing; however it is unknown if AEA tone is altered in response to IFN- α administration, and if this underlies the hyperalgesia observed. This study investigated if repeated IFN- α administration alters AEA, or the related N-acylethanolamines, PEA and OEA, levels in the descending pain pathway and paw tissue, in the presence and absence of inflammatory pain. Furthermore, the effect of inhibiting the AEA, PEA and OEA catabolising enzyme FAAH, on formalin-evoked nociceptive responding was examined. Repeated IFN- α administration for 8 days did not alter AEA levels in the periaqueductal gray, rostral ventromedial medulla (RVM), spinal cord or paw tissue but reduced PEA levels in the spinal cord, when compared with saline-treated counterparts. IFN- α -treated mice that received intraplantar injection of formalin (1%; 20 μ l) exhibited enhanced formalin-evoked nociceptive responding, when compared to saline-treated counterparts, an effect associated with enhanced AEA levels in the RVM. Intraplantar formalin administration tended to increase AEA, PEA and OEA levels in the paw tissue of saline-treated animals, an effect not observed in IFN- α -treated mice. Intraplantar (1 μ g/10 μ l), but not systemic (10mg/kg), administration of the FAAH inhibitor PF-3845 reduced formalin-evoked nociception and increased PEA and OEA levels in the paw tissue of IFN- α -treated animals, an effect not observed in saline-treated animals. In conclusion, these data highlight a possible role for peripheral N-ethanolamine(s) in mediating IFN- α -induced hyperalgesia.

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P1.10. Lentiviral overexpression of interleukin-1 β in the hippocampus induces neurogenesis-associated cognitive deficits in adult male rats

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Previous studies have demonstrated that elevated levels of the pro-inflammatory cytokine interleukin-1 β (IL-1 β) in the hippocampus, has detrimental effects on memory and cognitive function, as well as on the proliferation and survival of newly born neurons. The current study aimed to assess whether long-term lentiviral-mediated overexpression of IL-1 β would alter performance in a series of hippocampal-dependent tasks including pattern separation, which has previously been demonstrated to be dependent on hippocampal neurogenesis. A lentivirus overexpressing IL-1 β (3.7×10^3 TU) or mCherry as a control was bilaterally injected into the dorsal hippocampus of adult male Sprague-Dawley rats. Three weeks after injection a battery of behavioural tests were carried out. Hippocampal tissue was collected 4 days following behavioural testing for analysis by real-time RT-PCR for changes in gene expression levels of IL-1 β and neurogenesis-related markers. Increased mRNA expression of IL-1 β was confirmed in the hippocampus following lentiviral IL-1 β overexpression. In the pattern separation task, rats overexpressing IL-1 β in the dorsal hippocampus were not able to pattern separate in the small separation condition, but were able to do so with a large separation, suggesting hippocampal neurogenesis-associated dysfunction. The current results indicate that long-term hippocampal exposure to the pro-inflammatory cytokine IL-1 β has detrimental effects on the neurogenesis-associated pattern separation cognitive task. Thus, the ability to pattern separate may be more susceptible to the detrimental effects of chronic inflammation than other hippocampal-dependant functions such as working memory and location recognition memory.

P1.11. MMNs using natural speech in aphasia post stroke

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Background: This experiment sought to investigate MMN responses in individuals with aphasia and controls using natural speech stimuli. Recent studies have demonstrated correlations between MMN responses and clinical language assessments in individuals with aphasia. However, no MMN study has used natural speech stimuli that include a fricative-acoustic change to investigate such correlations.

Aims: (1) To determine if natural speech stimuli can elicit robust MMNs in both individuals with aphasia and control participants. (2) To correlate the aphasic MMN data with language performance on a range of language assessments, such as the Western Aphasia Battery (WAB) and the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA).

Methods: MMN responses from individuals with aphasia (n=5) and controls (n=5) using natural speech stimuli were recorded, and correlated with language assessment scores.

Results: Robust MMN responses to the natural speech stimuli were not obtained from both individuals with aphasia and controls. Visual inspection of the ERP waveform components did show MMNs present for controls and not aphasic individuals. Moreover, no correlations were found in general, however, a weak correlation was observed between the MMN responses to the real word deviant and the aphasia quotient of the WAB.

Conclusion: These findings imply that natural speech may be similar to artificial speech when evoking MMNs in individuals with aphasia.

P1.12. Genotype-dependent exacerbation of nerve injury-induced pain, anxiety and depressive behaviour in rats

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Wistar-Kyoto (WKY) rats are an inbred rat strain that demonstrate a depressive and anxiogenic phenotype and enhanced nociceptive responding compared with Sprague-Dawley (SD) rats (Burke et al., 2010, Rea et al., 2014). The aim of this study was to investigate if WKY rats, as a model of trait negative affect, exhibit altered nociceptive behaviour and affective behaviour following peripheral nerve injury, compared with SD counterparts. L5 spinal nerve ligation (SNL) resulted in prolonged (up to 30 days) mechanical and cold allodynia in adult male SD and WKY rats as measured by the von Frey and acetone drop tests, respectively. Prolonged SNL-induced heat hyperalgesia in the Hargreaves test was only observed in WKY, but not SD rats. Baseline testing showed that WKY rats displayed increased anxiety-like behaviour (reduced time in centre zone of the open field) compared to the SD rats. Post-SNL, both SD and WKY rats displayed increased anxiety-like behaviour compared to sham counterparts, but levels of anxiety-like behaviour were higher in WKY rats than in SD rats. WKY-sham rats spent more time immobile in the forced swim test versus SD-sham rats, indicating increased depressive-like behaviour. Immobility was greater in the WKY-SNL group versus the WKY-sham group, while no difference in immobility was observed between SD-sham and SD-SNL groups. In conclusion, these data suggest increased sensitivity to noxious heat, and increased anxiety- and depressive-like behaviour following peripheral nerve injury in a genotype (WKY) predisposed to negative affect.

P1.13. Motor simulation as a window into depression: Mental rotation, specific and non-specific motor imagery performance as an implicit measure of depression

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According to the WHO depression is a major challenge to all health systems despite being treatable. It is estimated that up to 50% of people with symptoms do not seek treatment and this is attributed to a combination of treatment avoidance due to stigma, a lack of services and the inability of staff to identify the issue. Even when people with depressed symptoms are assessed, stigma can lead to biased or socially desirable responses on traditional inventories (e.g., BDI). A novel alternative is to explore the potential of augmenting self-report measures of depression with measures of psychomotor retardation, or bradyphrenia, and often over-looked feature of depression. We present initial findings on the use of motor simulation (e.g., mental travel and mental rotation tasks) as a measure of depression. Prior research has indicated the potential for mental simulations as a measure of depression (Bennabi et al., 2013). Our approach is unique in that we focus upon a pre-selected athletic sample in which mental health stigma is typically high and where mild to moderate depression is a consistent outcome of injury. In this context, times for both executed and simulated action for an injured effector limb may be slowed due to the injury. Consequently, a combination of hand, foot and object rotations will be used to draw inferences on the affective state of an athlete post-injury. The potential for the application of motor simulation as a means of assessing depression states among athletes will be discussed.

P1.14. The effects of Z-score Neurofeedback on procedural learning

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Neurofeedback training (NFT) is becoming increasingly popular as a method of brain training. In the past, single electrode NFT has been shown to enhance procedural learning in a serial reaction time task (SRTT). This study investigates if previous findings can be replicated using LORETA Z-score NFT (LZNFT). Twenty participants were randomly assigned to the experimental group who received LZNFT, or to the control group who received sham feedback (SFB). All sessions consisted of six separate EEG recordings, 30 minutes of LZNFT or SFB, and the computer-based SRTT. Previous findings indicate a single session of NFT directly prior to completion of the SRTT results in a faster reduction of reaction times across trial blocks when compared to completion of the SRTT without NFT. This study replaced traditional NFT with LZNFT and introduced a SFB control group. It was found there was no difference between groups on the SRTT post intervention which suggests that a single session of LZNFT does not have the same enhancing effects on procedural learning as traditional single electrode NFT.

P1.15. Chronotype, social jetlag, and sleep quality: exploring symptoms of adult attention-deficit hyperactivity disorder (ADHD)

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There is substantial evidence pointing to disturbed circadian clock function and late circadian typology in ADHD. Where often eveningness has been associated with individual symptoms such as impulsivity and inattention it is seldom the relationship between chronotype and day-to-day environment is examined. We hypothesise that factors such as social jetlag and sleep quality may too have a meaningful impact on symptoms of ADHD.

A study sample of 335 participants (74.1% female) were recruited among university students from Ireland and Romania. Participants had a mean age of 24.67 ± 7.53 (range 18-58) and were absent of any physiological/psychological illness or engaged in shift-work. We measured chronotype parameters (MSFsc, social jetlag in hours) using the Munich Chronotype Questionnaire (MCTQ) and sleep quality using the Pittsburgh Sleep Quality Inventory (PSQI). Participants also completed the adult ADHD Self-Report Scale (ASRS-v1.1), Barratts Impulsivity Scale (BIS-11), and Cognitive Failures Questionnaire (CFQ) to assess domains of attention and impulsivity.

Our main findings report that respondents with high-risk of ADHD accumulated greater social jetlag compared to low-risk respondents, $F(1, 333)=7.66$, $P<.05$, $\eta^2=.02$, and also had greater sleep disturbances, $F(1, 333)=13.82$, $P<.001$, $\eta^2=.04$. Differences in chronotype between groups were not found.

We suggest that social jetlag and sleep quality may be important predictors of symptom severity in ADHD and might mediate the relationship between circadian typology and the disorder which other studies have found. Our findings highlight the deleterious health consequences of living against the clock and underscore the importance of the circadian involvement in disorders such as ADHD.

P1.16. Midbrain dopamine and the modulation of hippocampal firing activity associated with memory

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Central to the understanding of memory function in the brain is a detailed understanding of the processes contributing to how some information is retained as memories yet other information is not. Relevant to this is the question, does value and saliency information coded by dopamine neurons in the ventral tegmental area (VTA) affect hippocampal memory function and how might this arise? We present evidence that a dopaminergic projection from the midbrain to the hippocampus can modulate hippocampal memory function.

We performed tetrode recordings in the hippocampus and ventral tegmental area of DAT-IRES-Cre mice injected (in the VTA) with a Cre activated viral construct coding for channelrhodopsin. Mice explored familiar and novel open fields and performed a spatial memory task. We found that activity in midbrain dopaminergic nuclei can respond to the sustained value related stimulus of spatial novelty. Axonal segments of transfected midbrain dopaminergic neurons were found in the CA1 subfield of the dorsal hippocampus. Photostimulation of this projection during exploration (or learning in the memory task) produced increased hippocampal reactivation of waking firing activity in subsequent sleep, a process thought important for memory consolidation. Furthermore, this was followed by increased stability of the associated representations along with enhanced behavioural performance in a memory probe test.

Increased understanding of the activity and mechanisms involved in dopaminergic modulation of hippocampal associated memory may provide important insights into the aberrant memories associated with drugs of addiction or the relapse of addicts on exposure to a specific context.

P1.17. Postnatal oxytocin intervention reverses selective behaviour and physiological effects of birth by caesarean section in mice

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An individual's microbiota is normally acquired during delivery through the mother's birth canal. However, birth by Caesarean section (C-section) results in a different pattern of bacterial colonisation. Simultaneously, the neuropeptide oxytocin (OXT) is released during birth, which activates the newborn immune and central nervous system. However, mechanistic insights into the long lasting consequences of C-section on brain-gut axis and behaviour remain largely unexplored.

The aim of the present study was to assess the effects of the mode of delivery on mouse behaviour and brain-gut axis throughout their lifespan, and to investigate whether early postnatal OXT can prevent it. We applied a multi-disciplinary approach using a mouse model of C-section, followed by several behavioural assays and subsequent brain and immune analyses.

In early-life, animals born by C-section exhibited maternal attachment deficits. In adulthood, C-section born animals exhibited stereotyped behaviour, anxiety-like behaviour, deficiencies in social memory, abnormal hypothalamic-pituitary-adrenal axis responsiveness to stress, disrupted gastrointestinal motility. In early-life, OXT administration reversed C-section-mediated maternal attachment impairments. Remarkably, in adulthood, OXT selectively restored social memory deficits, stereotyped behaviour and disrupted gastrointestinal motility.

Taken together, these results demonstrate that birth by C-section induces long-term changes in behaviour mice across the brain-gut axis and behaviour. Moreover, postnatal treatment with oxytocin ameliorates some of the behavioural and physiological effects of birth delivery by C-section.

P1.18. Exercise and its effects on cognitive decline, neurogenesis and inflammation in the APP/PS-1 mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is a chronic neurodegenerative disease characterised by progressive cognitive decline and significant hippocampal pathology. Neurogenesis, which occurs only in the hippocampus and olfactory bulb, plays an important role in the formation of new memories and decreased neurogenesis has been observed in mouse models of AD. Neuroinflammation, which has been detected in human and animal model AD brains, negatively modulates hippocampal neurogenesis and induces deficits in cognitive function. Since exercise positively modulates hippocampal neurogenesis and cognition and may also exert antiinflammatory effects, in this study the effects of exercise on cognitive function, neurogenesis and neuroinflammation in APP/PS-1 mice was investigated.

APP/PS-1 mice (3 months old) have been divided into sedentary and exercising groups. Exercising mice are trained on a treadmill for 30min per day, while sedentary mice are placed on a stationary treadmill. Mice are maintained in their respective conditions for 6 months until sacrifice and recognition and spatial memory function is assessed every two months. At 9 months old, mice will be sacrificed and tissue analysed to assess exercise-induced effects on hippocampal neurogenesis, microglial activation and a panel of neuroinflammatory markers.

Data thus far (mice are five months old) show that three month old WT and APP/PS-1 mice display intact recognition and spatial memory, while exercising APP/PS-1 mice perform better in tests of recognition and spatial memory compared to their sedentary counterparts. Post-mortem analysis of hippocampal tissue should confirm whether long-term exercise can prevent cognitive decline in APP/PS-1 mice by maintaining neurogenesis and decreasing neuroinflammation.

P1.19. Microalgal Omega 3 polyunsaturated fatty acids (PUFAs) effects on cognition, sociability, depressive-like behaviour and brain fatty acid composition in C57BL/6 mice

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Essential omega-3 polyunsaturated fatty acids (n-3 PUFAs) play a critical role in brain development and function, especially during perinatal development and early postnatal period. Using dietary interventions, we assessed the effects of n-3 PUFAs supplementation in pregnant mice on the behavioural phenotypes of their offspring in cognitive, depressive-like and sociability tests, and later assessed brain lipid composition.

P1.20. Interaction of ghrelin and the monoamine system in the regulation of associative memory

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Ghrelin is an orexigenic gastric peptide, with its function in food intake, energy and body weight homeostasis being thoroughly characterized. Primarily synthesized within the stomach, ghrelin is also produced within the limbic system involved in emotional memory e.g. amygdala and hippocampus. Since its discovery in 1999, the extra-hypothalamic function of ghrelin has become more evident, including its effect in learning, memory, reward, neuroprotective and mood regulations. Furthermore, the G-coupled protein receptor responsible for ghrelin's effect, Growth hormone secretagogue receptor 1a (GHSR) has been demonstrated to form heterodimers with members of the monoamine system. These include neurotransmitters: dopamine and serotonin. These monoamines have a well-established role in appetite and satiety, reward, mood, learning and memory. Thus, investigation into the interaction between these hormonal and neurotransmitter systems in higher cognitive function is warranted.

In this study we put forward behavioral and in-vitro electrophysiology evidence in the interaction of both these systems in the formation of associative memory. By employing fear conditioning as the testing paradigm for associative learning, we show an impairment in the formation of hippocampal dependent memory. We show, to our knowledge for the first time, using multi-electrode arrays the effect of ghrelin on synaptic transmission within areas involved in memory. These results, in conjunction with previous data show the diverse action of ghrelin and may be important for the future pharmacological targeting of the GPCRs involved in learning and memory.

P1.21. The Effects of Z-Score Neurofeedback Training on Response Inhibition

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Response inhibition (RI) is a vital executive function (EF) that allows individuals to engage in control of their initial responses, permitting adaptive and flexible behaviour. Thus, RI is crucial for many everyday functions and is thought to be related to a range of psychological disorders. Through the use of stimulation techniques it has been shown that RI can be facilitated through the reduction of theta frequency in the right inferior frontal gyrus (rIFG). However, due to the limitations of stimulation techniques for therapeutic purposes, this study investigated the effect of Z-score Low Resolution Electromagnetic Tomography (LORETA) Neurofeedback Training (NFT) in the regulation of theta frequency in the rIFG on scores of RI ability (n=9). The Stop-signal task (SST) was used to measure RI ability and a control group (n=9), receiving NFT in an area unrelated to RI, the rAG, were assessed also. Furthermore, to ensure that possible observed effects are RI-specific, two additional measures of different EFs were employed (the Switcher task and the Letter Number Sequencing task). It was found that Z-score LORETA NFT did not produce facilitation of RI on the SST in either NFT group. However, improvement for the rIFG on the Switcher task, a task measuring cognitive flexibility and task switching, was observed. Implications of the findings of this study and possible future directions are discussed.

P1.22. Cognitive analysis of schizophrenia risk genes: focus on genes with epigenetic function

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Schizophrenia is a psychiatric disorder characterised by positive and negative symptoms as well as cognitive impairment. Disrupted epigenetic processes are observed in complex and single gene brain disorders that exhibit cognitive deficits, and have been recently studied as potential targets of pharmaceutical intervention for the treatment of cognitive deficits. Genome wide association studies (GWAS) have identified 108 chromosomal regions associated with risk of schizophrenia, implicating 350 genes. The aim of this study was to identify risk genes for schizophrenia with epigenetic functions and test these genes for association with cognitive deficits in schizophrenia. Cross-referencing 535 epigenetic genes with 350 GWAS genes identified 5 candidate genes: RERE, SATB2, EPC2, EP300 and KDM3B. The effect of risk single nucleotide polymorphisms (SNPs) in these genes on cognition was examined using a dataset of psychosis cases ($n = 905$) and controls ($n = 330$) who had completed tests in 5 areas of cognition: IQ, working & episodic memory, attention and social cognition. Regression was carried out using a linear model. For RERE, there was association between the schizophrenia risk allele and attention ($p = 0.03$). For SATB2, there was association with social cognition ($p = 0.003$). For EPC2, an association was found with full scale IQ ($p = 0.004$) and performance IQ ($p = 0.001$). An association was found between the schizophrenia risk allele for KDM3B and verbal IQ ($p = 0.038$). This initial analysis provides support for our hypothesis that risk genes with epigenetic functions contribute to cognitive deficits in schizophrenia.

**Poster Topic Area 2:
Diseases and Disorders of the
Nervous System**

P2.01. The cellular and molecular consequences of maternal immune activation on the development of the rodent spinal cord

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In recent years epidemiological studies have implicated maternal immune activation (MIA) in neurological disorders including schizophrenia, epilepsy, cerebral palsy and autism spectrum disorder. Investigations using rodent models have suggested that the effect of MIA on the developing nervous system may be temporally and spatially regulated. It has been reported that maternal Poly(I:C) treatment at mid-gestation (E9) but not late gestation (E17) suppressed exploratory behaviour in adult mouse offspring. In addition, treatment at E9 but not at E17 significantly reduced the number of reelin-positive neurons in the striatum. Foetal cytokine response to MIA has also been reported to differ depending on the timing of insult. Further elucidation of the cellular and molecular consequences underlying the effect of MIA on the developing nervous system is necessary.

This project investigates the effect of MIA on the development of the rodent spinal cord. Time-mated dams will receive injections of low-dose (50µg/kg) lipopolysaccharide (LPS) to induce a subclinical inflammatory response at different gestational time points (E12, E14, E16 and E18). Spinal cords of offspring will be analysed at both early and late time points post injection. mRNA and microRNA levels will be investigated at each time point through expression profiling and particular attention will be paid to factors associated with the immune response such as cytokines and chemokines, as well as to a number of transcription factors, growth factors and signalling molecules which we have identified as part of an in-silico investigation into the interaction between inflammation and microRNA expression.

P2.02. Effect of aerobic exercise on cognition and quality of life in multiple sclerosis

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Multiple Sclerosis (MS) is a progressive neurological disorder of the central nervous system (CNS). Cognitive disturbances affect 40-65% of MS patients and contributes to disability status. Presently there is no cure or effective cognitive treatments for MS. Exercise is neuro-protective, improving memory and promoting hippocampal neurogenesis in rodents and it may also enhance cognitive function in humans. In this study, we investigate whether an aerobic training program has therapeutic potential in individuals with MS by ameliorating cognitive disturbances.

Healthy volunteers and MS patients attending outpatient clinics at Cork University Hospital and the Mercy University Hospital were recruited for this study. Written informed consent was obtained from each participant and the study received ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals. Assessments were performed pre- and post-training, including disability status, depression, quality of life and cognitive performance which was assessed using the Cambridge Neuropsychological Test Automated Battery. The Astrand 6 minute cycle test measured individual fitness. Participants cycled for 30 minutes at 60-75% VO₂max and this training session was repeated twice a week for 8 weeks. Peripheral blood mononuclear cells and plasma were prepared from whole blood and stored for future assessment of cytokines/chemokines.

We determined that quality of life was reduced among MS patients, with a reduction in both physical health ($p = 0.0016$) and mental health ($p = 0.0427$). Preliminary data indicates that aerobic training is associated with improvements in fitness levels ($p = 0.0038$), quality of life and cognitive parameters in both groups. Our findings also indicate that ergometry training improves disability scores in MS patients. Further analysis will correlate cognitive improvements with inflammatory signatures in peripheral blood.

P2.03 Network abnormalities in bipolar disorder: optimizing anatomical sensitivity

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Introduction: Structural maps of the brain reveal that regions are linked by a multitude of connections, organised as a network. One measure of connectivity is the rich-club phenomenon—a group of structures more highly connected to each other than the rest of the network. There is no obvious focal anatomical deficit in bipolar disorder, rather it is associated with impairments in many brain regions. To date the rich-club has been studied using atlases such as the AAL-90. Herein we attempted to extend this to a subject-based parcellation method using freesurfer with the goal of improving anatomical accuracy.

Methods: Structural (MP-RAGE) and diffusion-weighted MR images (64 directions, $b=1300$ s/mm², Siemens 1.5T MRI scanner) were acquired from 18 bipolar disorder and 27 age and gender matched healthy control participants from the Galway Bipolar Study. Connectivity matrices were generated following grey matter parcellation using Freesurfer (v5.0.1) to define nodes and recursively calibrated constrained spherical deconvolution based tractography (ExploreDTI v4.8.4) to define edges. Statistical analysis was completed using SPSS.

Results: There was no significant difference between diagnostic groups in either nodal degree or mean rich-club connection density (mean \pm SD, freesurfer: 49.1 \pm 12.0, AAL-90 62.9 \pm 3.4). Lower values and greater variance (freesurfer SD was 24% of mean, AAL-90 was 0.05%) were observed in the rich-club derived from the freesurfer parcellation.

Conclusions: This novel application of subject-based parcellation in brain network analysis may increase anatomical and subject-specific sensitivity. However, currently the loss in statistical sensitivity due to generating a connectivity matrix using freesurfer based parcellated volumes outweighs any potential gains expected in future more compatible iterations.

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P2.04 Prebiotics selectively reduce anxiety in mice via modulation of short-chain fatty acids production

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Prebiotic fibres such as short-chain fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) are known to selectively modulate the composition of the intestinal microbiota, and to stimulate proliferation of lactobacilli and bifidobacteria in the gut. Prebiotics are commonly used in infant milk formula to alter the gut microbiota, and are associated with lower stool pH and increased levels of faecal short-chain fatty acids (SCFAs). The role of prebiotics for psychiatric disorders is less investigated.

This study's objective was to test whether FOS and GOS altered behaviour in animal tests of anxiety, depression, cognition, stress response and social behaviour. Adult male mice were administered with FOS, GOS, a combination of FOS and GOS, or water for the duration of the 10-week study; 3 weeks prior to – and 5 weeks during behavioural testing. Mice were culled two weeks after the last behavioural test.

The administration of combination of FOS and GOS decreased depressive-like behaviour in a number of behavioural models including the tail suspension and forced swim tests. Similarly, the administration of GOS and the combination of FOS and GOS decreased anxiety in a number of tests such as the open field test and elevated plus maze and displayed lower corticosterone concentrations after acute stress. This prebiotic-induced antidepressant and anxiolytic-like phenotype was associated with increased caecal acetate and propionate and reduced i-butyrate concentrations.

These data show that these two prebiotics were actively influencing gut physiology, and positively modulating anxiety, depression and other behaviours in healthy naive mice. These findings strengthen the role of gut microbiota supplementation as psychobiotic-based strategies for stress-related brain-gut axis disorders and cognition opening new avenues in the field of neurogastroenterology.

P2.05. The involvement of panx-1 in amyloid-induced neurodegeneration and the protective effect of the endocannabinoid system

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Alzheimer's disease is an age-related neurodegenerative disease characterized by the progressive deterioration of cognition and memory resulting from synaptic loss and neuronal death. The accumulation and aggregation of amyloid- β ($A\beta$) leads to chronic activation of the immune response and neuronal apoptosis. The endocannabinoid system has emerged as a viable therapeutic target for the treatment of neurodegenerative disease. The aim of this study was to investigate the role of the ubiquitously expressed PanX1 membrane channel in $A\beta$ -induced neurodegeneration and endocannabinoid neuroprotection.

In primary rat cortical neurons exposed to $A\beta$ (10 μ M) both the inhibition of cannabinoid degradation, through URB597 (5 μ M), and of PanX1, probenecid (1 mM), reduced apoptosis to control levels. Furthermore, URB597 significantly reduced expression of the apoptotic effector molecule caspase-3 which is known to regulate the PanX1 channel. The release of chemoattractant signals from dying neurons was blocked by URB597 and 10panx (200 μ M), a PanX1 mimetic peptide, as indicated by a 115% decrease in microglial migration after exposure to medium from $A\beta$ -primed neurons. Treatment of BV2's with both URB597 and probenecid was shown to reduce ATP-induced microglial migration. LPS-induced IL-1 β release was also reduced by treatment with either URB597 or 10panx indicating a protection against NLRP3 inflammasome activation.

These results have highlighted the protective role of endocannabinoid signalling against $A\beta$ -induced apoptosis and inflammation. Furthermore they identify the PanX1 membrane channel as a possible mediator of endocannabinoid mediated neuroprotection.

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P2.06. An investigation into the role of the putative cannabinoid receptor GPR55 in regulating neuroinflammation and neurodegeneration

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Alzheimer's disease (AD) is a progressive neurodegenerative disease associated with neuronal loss and cognitive decline. A neuropathological feature of AD is the deposition of β -amyloid ($A\beta$) which is proposed to contribute to neuroinflammation and neuronal cell death. A therapeutic approach that can halt the actions of $A\beta$ is attractive as this is a strategy likely to impede disease progression. The orphan G-protein coupled receptor GPR55 is responsive to cannabinoids and is widely expressed in the neurons and glia of the brain. This study aims to examine the role of GPR55 and its signalling mechanisms in the regulation of neuroinflammation and neuronal cell death in an in vitro model of AD.

Cultured primary rat cortical neurons were treated with LPI (1 μ M & 10 μ M) in the presence or absence of $A\beta$ (10 μ M) for 72 hours. The medium was then applied to the BV2 microglial cell line and the subsequent migration of BV2 cells was achieved using a Boyden chamber assay. Neuronal DNA fragmentation was assessed using terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL). The data obtained in this study suggests that LPI (10 μ M) downregulates microglial migration and neuronal apoptosis evoked by $A\beta$, whereas a lower micromolar concentration of LPI (1 μ M) appears to increase levels of migration evoked by $A\beta$.

This data demonstrates a possible role for GPR55 receptor ligands in the regulation of microglial migration and neuronal apoptosis in an in vitro model of AD.

P2.07. Mismanagement of iron homeostasis proteins in iron-loaded ex vivo slice cultures

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Recent studies have shown alterations in iron distribution and the expression of iron-related molecules in multiple sclerosis amongst other neurodegenerative diseases. A clearer picture of this metabolic dyshomeostasis of iron might be gained by establishing an ex vivo slice culture model of aberrant CNS iron homeostasis. Here, we examined the molecules involved by iron-loading organotypic rat hippocampal slice cultures. Firstly, we demonstrated that iron content, as measured by a ferrozine colorimetric assay, in slice cultures after 10 days in culture ($5.61 \pm 0.66 \text{ nmol/mg}$) replicates iron content in age-matched tissue samples ($5.99 \pm 1.03 \text{ nmol/mg}$; $p > 0.05$). Secondly, we demonstrated differential iron uptake and toxicity after 12 hr exposure to $10 \mu\text{M}$ (a supraphysiological concentration) ferrous ammonium sulfate, ferric citrate or ferrocene. Thirdly, we showed that $1 \mu\text{M}$ ferrocene causes maximal iron loading, producing a 1.6-fold increase in iron content (4.97 ± 0.57 to $8.05 \pm 0.98 \text{ nmol/mg}$; $p < 0.05$) with minimal impact on culture viability (as assessed by LDH and MTT assays). Furthermore, iron treatment led to significantly higher levels of ferritin light-chain (an iron storage molecule) transcripts ($p < 0.05$). The expression of ferritin protein was also characterised by immunohistochemistry. In summary, ferrocene loading perturbs iron metabolism in our hippocampal slice culture system. This model of iron loading appears to be a promising platform for studying iron regulation in the CNS.

P2.08 Comparison of Toll-like receptor expression in toxin and inflammatory models of Parkinson's disease

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Toll-like receptors (TLRs) are emerging as potential targets for anti-inflammatory intervention because of their pivotal role in the innate immune response. Although the resident immune surveillance cells in the brain, the microglia, express several TLRs including the bacterial responsive TLR4 and the viral responsive TLR3, changes in their expression in inflammatory models of Parkinson's disease remains unexplored. Therefore, the aim of this study was to characterise the timecourse of TLR expression after intra-striatal administration of the bacterial inflammagen, lipopolysaccharide (LPS), the viral mimetic, Poly I:C, the catecholaminergic neurotoxin, 6-hydroxydopamine (6-OHDA) or the pesticide, rotenone. Male Sprague Dawley rats were given a single intra-striatal injection of LPS (10 µg), Poly I:C (20 µg) or 6-OHDA (10 µg) and corresponding vehicle on the other side, and were sacrificed on Days 1, 4, 14 and 28 post surgery (n=7 per treatment, per time-point). Changes in several inflammatory genes including TLR3, TLR4 and cytokines were examined using qRT-PCR. Following injection of LPS, we found that expression of the viral-sensing TLR3 and the bacterial-sensing TLR4 genes were significantly increased in the inflamed striatum. In the Poly I:C, 6-OHDA and rotenone models, TLR 3 and 4 were significantly increased, but had a different pattern of expression to the LPS model. In addition to the changes in TLR expression, we also found similar elevations in both pro-inflammatory (e.g. TNF-α and IL-6) and anti-inflammatory (e.g. IL-10) cytokines in LPS, Poly I:C and rotenone-injected striatum, but these changes were not seen in 6-OHDA-injected models. This study highlights the pattern of changes in TLR expression in four models of Parkinson's disease and further strengthens the rationale for targeting TLRs for anti-inflammatory intervention in this neurodegenerative disease.

P2.09. Investigation of microtubular protein levels in human plasma as a potential bio-marker for depression: A pilot study

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Neuronal microtubules represent a promising target for intervention in depressive disorders. Previous preclinical research has linked altered microtubule dynamics to the pathogenesis and treatment of depressive disorders (Bianchi et al. 2012, PNAS 109:1713-8). Furthermore, one third of depressed patients are unresponsive to antidepressant drugs, constituting a population known as treatment resistant depression (TRD). Wistar Kyoto (WKY) rats display a depressive-like phenotype resistant to Selective Serotonin Reuptake Inhibitors (SSRIs) and represent a model of TRD. By measuring the expression of microtubular proteins in plasma obtained from WKY and TRD patients, a potential biomarker for TRD may be identified.

Plasma was obtained from a group of TRD patients (n=10) and healthy non-depressed participants (n=10). Samples were analysed using Infrared Western Blotting. The expression of acetylated alpha-tubulin (Acet-Tub; marker of stable microtubules), tyrosinated alpha-tubulin (Tyr-Tub; marker of dynamic microtubules), and detyrosinated alpha-tubulin (Glu-Tub; marker of stable microtubules) was analysed.

Despite a low sample size, certain trends were apparent in the data. First, an increase in Acet-Tub expression was observed in the TRD group compared to healthy controls ($p=0.2941$). Second, a decrease in the Tyr-Tub/Glu-Tub ratio in TRD patients was observed when compared to healthy controls ($p=0.1089$). These findings are consistent with recent work in WKY, which overexpress plasma Acet-Tub ($p=0.0001$) compared to healthy Sprague-Dawley rats.

These changes are indicative of microtubular alterations and decreased microtubular dynamics, thus analysis of microtubular proteins may represent a potential biomarker of TRD. Future investigations are currently being planned that include larger sample sizes.

P2.10. An injectable collagen hydrogel for the delivery of primary dopaminergic neurons into the Parkinsonian brain

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Primary dopaminergic neurons derived from fetal ventral mesencephalon tissue have been shown to integrate and function after transplantation into the adult Parkinsonian brain. However, their use as a routine therapeutic procedure is limited by poor graft survival with only ~5% of transplanted cells surviving the transplantation procedure. Therefore, the aim of this study was to determine the neural cytocompatibility of a biomaterial scaffold composed of cross-linked collagen in order to establish its potential as a scaffold to improve the outcome of reparative cell therapies in Parkinson's disease. Injectable collagen hydrogels were fabricated from type 1 bovine collagen (2 mg/ml) and cross-linked with 4s-StarPEG (6, 12 or 24 mg/ml). These were incubated with rat fetal ventral mesencephalon, primary astrocyte and mesenchymal stem cell cultures for 48 hours after which cell viability was assessed using alamarBlue® and LIVE/DEAD® assays. The effect on neurite outgrowth and dopaminergic viability was evaluated in ventral mesencephalon cultures using β III-tubulin and tyrosine hydroxylase immunocytochemistry respectively. We found that the different cross-linked collagen hydrogels were cytocompatible with all cell types and they did not impede neurite outgrowth or negatively affect dopaminergic viability in ventral mesencephalon cultures. In vivo analysis is underway to assess the survival of cells encapsulated in collagen hydrogels and transplanted into the striatum. In conclusion, collagen hydrogels of all cross-linker concentrations were highly cytocompatible and this supports the hypothesis that collagen scaffolds could be used to improve the outcome of ventral mesencephalon cell therapy in Parkinson's disease.

Acknowledgements: This work was funded through a Government of Ireland Postgraduate Scholarship from the Irish Research Council to Niamh Moriarty.

P2.11 Node Definition using Atlas versus Subject Specific Parcellation & Connectivity in Bipolar Disorder

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Introduction: Left-right decoupling causing integration deficits, alongside longer paths and reduced global efficiency have been reported in euthymic bipolar subjects (Leow,2013;GadelKarim,2014). Complex network analysis combines structural and diffusion magnetic resonance to generate brain network graphs (Bullmore & Sporns,2009; Rubinov & Sporns,2010). Node definition is a critical step that is likely to influence the statistical and anatomical sensitivity with which network abnormalities can be detected. To date no study has compared atlas-based and subject-based methods of node definition for structural connectivity analyses.

Methods: Euthymic bipolar subjects (n=26) and healthy controls (n=32) underwent structural and diffusion MRI. Subject-based parcellation was achieved using FreeSurfer, atlas-based using AAL-90 atlas and edges were defined using constrained spherical deconvolution based tractography (ExploreDTI,Brain Connectivity Toolbox,MATLAB). We quantified brain network integration and segregation using global metrics: nodal degree, characteristic path length, betweenness centrality, global efficiency, and local metrics: clustering coefficient and local efficiency.

Results: Using subject-based parcellation, global differences were absent while lower clustering coefficient (p=0.003) was identified in the left precentral gyrus. These metrics, while anatomically more precise to the sample, had close but slightly larger variance across local (CC: 12,6%-15,0%; Elocal: 11,6%) and marked increased variance across global (13.8%-35.5%) metrics relative to atlas-based results (CC:9,8%-10,3%; Elocal: 9,9%; global: 5.0%-9.5%)

Discussion: These findings suggest left-lateralized dysconnectivity of the posterior border of the frontal lobe, where the central executive network is located. Subject-based methods of parcellation may provide anatomical sensitivity at a local level but benefits appear to be negated at the global level by reduced statistical sensitivity.

P2.12. Electroencephalographic (EEG) Signatures of Impairment in Cognitive, Sensory and Motor Networks in Amyotrophic Lateral Sclerosis (ALS)

Bahman Nasseroleslami, Kieran Mohr, Parameswaran M. Iyer, Edmund C. Lalor, Orla Hardiman

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease of upper and/or lower motor neurons, primarily manifested through clinical motor symptoms. There is, however, emerging evidence of impairment beyond corticospinal pathways in both motor and non-motor brain networks, which demands further characterisation. We therefore recorded high density EEG in two experimental paradigms: first, in resting state, and second, during an auditory oddball paradigm. Comparing patients (n=66) with controls (n=17) revealed that patients displayed auditory evoked potentials (AEP) of lower amplitude and longer latency to deviant tones. Furthermore, the difference between standard and deviant AEPs, (Mismatch Negativity, MMN) was smaller and emerged later for patients than for controls. The average MMN amplitude did not differ between spinal, bulbar, cognitive or C9orf gene-carrier ALS subgroups. Resting-state brain connectivity, as assessed through partial coherence and partial directed coherence of scalp-recorded EEG (sensor space), shows a general decrease of connectivity in patients (n=9) vs. controls (n=8), especially above the primary motor cortical areas. The changes in AEP and MMN imply that the cognitive networks responsible for discrimination and probably part of the auditory sensory network have been affected in ALS. The inter-cortical connectivity patterns imply the decreased connectivity of superficial cerebral areas (including the primary motor regions), but may also reflect increased connectivity between deeper brain regions. The above-mentioned EEG signatures can elucidate the characteristics of the affected motor and non-motor brain networks in ALS and can be of practical utility in developing diagnostic and prognostic biomarkers in future studies.

P2.13 Exacerbation of motor dysfunction in the AAV- α -synuclein model of Parkinson's disease after intra-striatal infusion of the pesticide rotenone

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Although Parkinson's disease is thought to arise as a result of complex interactions between underlying genetics and environmental factors, it is widely modelled in experimental animals using a single genetic or neurotoxic insult. Unfortunately, this has produced models that fail to reliably recapitulate the clinical condition, and this has led to a drive to develop more relevant models with improved validity. One such approach is to combine different risk factors for the disease in order to generate relevant gene-environment interaction models. In this context, the aim of this study was to assess the behavioural impact of exposing rats with a high intra-cerebral load of α -synuclein (delivered using AAV vectors) to the Parkinson's disease-associated pesticide, rotenone. Male Sprague Dawley rats were assigned to four groups of 10 rats: 1) Control, 2) AAV- α -synuclein, 3) Rotenone, and 4) AAV- α -synuclein & Rotenone. The relevant groups then received unilateral intranigral infusion of either AAV2/6- α -synuclein or AAV2/6-GFP control. Rats were then tested for 9 weeks on a variety of tests of lateralised motor function after which the relevant groups received a unilateral intrastriatal infusion of either rotenone (3.6 μ g) or its vehicle. Behavioural testing resumed one week after rotenone surgery and continued for 8 weeks. We found that unilateral intranigral infusion of AAV2/6- α -synuclein resulted in a significant contralateral motor impairment across all behavioural tests and the subsequent rotenone challenge significantly exacerbated these motor impairments. These results indicate that incorporating both a genetic and an environmental challenge is a valid approach to modelling the motor dysfunction associated with Parkinson's disease.

P2.14 An investigation of white matter tracts in familial pure bipolar disorder

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Numerous studies investigating white matter organization in bipolar disorder (BD) have been conducted to understand the pathophysiological mechanism behind BD. Structural integrity is altered in intra- and inter-hemispheric tracts, showing a genetic background for the disorder¹. Increased genetic liability is associated with reduced fractional anisotropy (FA)². White matter organization has emerged as a potential endophenotypic marker for BD³.

We used diffusion-weighted MRI to determine FA in 31 BD participants, 14 with a first or second degree family member with BD [fBD] (mean age \pm SD, % females; 41.2 ± 3.1 , 30.1%) and 17 without [nfBD] (41.2 ± 2.4 , 11%), and 43 healthy controls (42.5 ± 1.5 , 8.2%). Tract-based spatial statistical analysis (TBSS)⁴ was used with a sample-specific template and threshold free-cluster enhancement correction ($p < 0.05$) to assess group difference in FA across the three groups.

fBD was associated with significantly reduced FA relative to nfBD and controls in the right anterior thalamic radiation, the right superior longitudinal fasciculus, right corticospinal tract, and the corpus callosum (genu, body and splenium) as well as the left uncinate fasciculus and reduced additionally in fBD relative to nfBD in the left cingulum. No significant differences in FA were found between nfBD and controls.

Abnormal white matter structure in major association, commissural and limbic circuits appears to be more markedly reduced in organization in familial pure BD specifically. The precise role or precipitants of these abnormalities and their significance still remains unclear and further investigation of the heritable features of BD is likely to be fruitful regarding the pathophysiology of the disorder.

P2.15. The Bladder Pain Disorder as a peripheral sensory disorder: the effect of lidocaine on urodynamic parameters

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Bladder Pain Syndrome (BPS) is a disease of unidentified aetiology. Precise pain perception in this disease is not understood. Is this a peripheral pathology with pain of peripheral origin or has the pain become centralized? We hypothesise pain centralization with severe and chronic cases.

To study the effect of alkalized lidocaine on pain perception using urodynamics in BPS patients.

21 female BPS patients referred to the Urodynamic Department of the Cork University Maternity Hospital (CUMH). Written consent was given and the King's Health Questionnaire completed. Urodynamic assessment was completed. Participants completed a Visual Analogue Scale (VAS) at maximum cystometric capacity and cystometric capacity. The bladder was emptied and a pain score recorded. Participants were randomly assigned to 'lidocaine' or 'control' groups; 'lidocaine' participants received 20mls of 2% alkalized lidocaine, while the 'control' participants received 20mls normal saline. These solutions were allowed to remain in-situ for 10 minutes and saline urodynamic protocol repeated.

Lidocaine administration resulted in a decrease in pain perception, leading to an improvement in the second urodynamic recording. In addition, patients reported significantly lower pain post void after lidocaine treatment. However, there was a lack of analgesic effect in 4 of the 16 patients who received lidocaine, with a corresponding deterioration in their urodynamic parameters.

By using urodynamics, we have demonstrated an objective assessment of lidocaine treatment on BPS. We failed to see an analgesic effect in 4 patients. This suggests pain centralisation may be a contributing factor in BPS, thus making exclusive peripheral treatment strategies ineffective.

P2.16. The effects of viral priming on neurotoxin induced neurodegeneration and synapse dysfunction in cell culture models relevant to Parkinson's disease

Laura K. Olsen and Declan P. McKernan

Department of Pharmacology and Therapeutics, College of Medicine

Parkinson's disease (PD) is a neurodegenerative disease characterized by motor dysfunctions (resting tremors, unstable posture, bradykinesia, and rigidity) and sometimes dementia. Dopaminergic (DA) neurodegeneration in the substantia nigra causes cortical-striatal motor pathway impairment in PD. This neurodegeneration is correlated with alpha-synuclein aggregation, oxidative stress, and chronic neuroinflammation. Toll-like receptor 3 (TLR3) recognizes pathogen-associated molecular patterns (PAMP), specifically viral nucleotides. Neuronal TLR3 activation leads to pro-inflammatory cytokine expression and microglia activation. Chronic viral infection has been identified as a risk factor for developing PD. Further investigation into this innate immune response in neurons is needed to determine the role of neuroinflammation in PD pathology.

The effects of TLR3 activation on degeneration in the presence of 6-OHDA, rotenone, and MPP⁺ (established neurotoxins used for modelling PD) were assessed. Using the SH-SY5Y neuronal cell line, cell death and synaptic/axonal transport protein expressions were examined. Neuronal loss was observed for poly I:C (0-100 µg/ml), 6-OHDA (0-50 µM), rotenone (0-500 nM), and MPP⁺ (0-1,000 µM). Poly I:C (20 µg/ml), 6-OHDA (20 µM), rotenone (250 nM), and MPP⁺ (1 mM) treatments led to alterations in synaptophysin and PSD-95 proteins. Pre-treatment with poly I:C (10 µg/ml) was found to be neuroprotective or increase neurodegeneration depending on the cellular environment following PD related neurotoxin treatment. These disparities may be due to the downstream effects of TLR3 activation (cytokine expression). Neuroprotective inflammatory processes may instead lead to exacerbation of neurodegeneration in PD due to the changes in the microenvironment for DA neurons.

P2.17. The roles of glycosylated neural precursors in central nervous system formation

Aisling O'Malley, Denis Barry
Trinity College Dublin

LewisX (LeX) is a glycan motif associated with glycoproteins and glycolipids that are present on neural stem and progenitor cells. LeX is expressed in discrete subpopulations of neuroepithelial and radial glial cells in the spinal cord throughout development and into postnatal life. Patterns of LeX expression indicate roles in axon guidance in the spinal cord and cell proliferation in the brain. Radial glial cells have already shown potential in facilitating axon growth and are known to give rise to both neurons and glial cells in the brain.

In this study, we present a biopolymer polycaprolactone (PCL) scaffold that can support the growth of radial glial cells for use in transplantation scenarios to repopulate the central nervous system (CNS) after degeneration, and restore connectivity. In addition, the distribution of LeX in the healthy CNS and in organotypic spinal cord slice culture injury model has been characterised. We have investigated the potential of using electrospun PCL scaffolds as transplant conduits to deliver radial glial cells and neurons to the injury site and determine their potential in regenerating the CNS and the roles of LeX in mediating this process.

P2.18. Free water elimination and mapping from diffusion MRI in chronic schizophrenia

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Introduction: Relating brain tissue properties of subjects with DTI is limited when a voxel contains partial volume of brain tissue with free water. We investigate standard FA and FA of tissue (FAT) with free water eliminated amongst chronic schizophrenic patients.

Methods: Diffusion weighted data (64 direction, $b=1300$ s/mm², Siemens 1.5T) was acquired for 19 participants (14M,5F, Mean Age=36.69±9.69) with chronic schizophrenia and 19 controls (14M,5F, Mean Age=38.21±10.29). Tract Based Spatial Statistics (TBSS)[1] was previously performed [2] and extended herein to examine separately the free water maps and tissue FA (FAT) maps generated using a bi-tensor model implemented in house using Matlab software (v7.11.0), as previously developed by Pasternak et al [3].

Results: The chronic schizophrenic group showed widespread increased cerebral free water compared to healthy controls, overlapping with previously reported areas of decreased FA ($P<0.05$)[2]. Focal areas (including genu and splenium of the corpus callosum) demonstrated decreased FA in the absence of increased free water. Pearson's correlation showed a negative correlation of median FA in the genu and number of psychotic episodes ($r=-0.602, p=0.018$), and median FAT in the splenium was positively correlated with positive symptoms (SAPS)[4] ($r=0.55, p=0.037$).

Discussion: Our findings suggest that colossal FA deficits are partially due to a tissue effect, extending our previous work and corroborating with Pasternak et al [2][5]. The free water increases are consistent with a neuroinflammatory response, while regions of reduced FA and normal free water is suggestive of white matter degeneration – both features of chronic schizophrenia. Finally, correlations with clinical measures contribute to our understanding of acute and chronic effects of the disorder.

[1]Smith et al.,(2006)NeuroImage,31(4),pp.1487-1505.

[2]Holleran et al., (2013)Neuropsychopharmacology,39(4),pp.944-954.

[3]Pasternak et al.,(2009)Magn. Reson.Med.,62(3),pp.717-730

[4]Andreason.,(1984)Iowa,Iowa University Press.

[5]Pasternak et al.,(2015)Schizophrenia_Research,161(1),pp.113-118

P2.19 Investigation of white matter alterations in familial bipolar disorder

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Numerous studies investigating white matter organization in bipolar disorder (BD) have been conducted to understand the pathophysiological mechanism behind BD. Structural integrity is altered in intra- and inter-hemispheric tracts, showing a genetic background for the disorder¹. Increased genetic liability is associated with reduced fractional anisotropy (FA)². White matter organization has emerged as a potential endophenotypic marker for BD³.

We used diffusion-weighted MRI to determine FA in 31 BD participants, 14 with a first or second degree family member with BD [fBD] (mean age \pm SD, % females; 41.2 ± 3.1 , 30.1%) and 17 without [nfBD] (41.2 ± 2.4 , 11%), and 43 healthy controls (42.5 ± 1.5 , 8.2%). Tract-based spatial statistical analysis (TBSS)⁴ was used with a sample-specific template and threshold free-cluster enhancement correction ($p < 0.05$) to assess group difference in FA across the three groups.

fBD was associated with significantly reduced FA relative to nfBD and controls in the right anterior thalamic radiation, the right superior longitudinal fasciculus, right corticospinal tract, and the corpus callosum (genu, body and splenium) as well as the left uncinate fasciculus and reduced additionally in fBD relative to nfBD in the left cingulum. No significant differences in FA were found between nfBD and controls.

Abnormal white matter structure in major association, commissural and limbic circuits appears to be more markedly reduced in organization in familial pure BD specifically. The precise role or precipitants of these abnormalities and their significance still remains unclear and further investigation of the heritable features of BD is likely to be fruitful regarding the pathophysiology of the disorder.

P2.20. Plasma microRNA profiles identify adults with temporal lobe epilepsy

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There is an important and unmet need for biomarkers of epilepsy to identify patients at risk of epilepsy development, progression or remission. Epilepsy biomarkers could also support decisions on when and how to treat epilepsy patients. Imaging and EEG biomarkers are both time-consuming and expensive. A blood biomarker would help solve this problem. microRNAs are endogenous, non-coding RNA molecules that regulate gene expression by inhibiting translation of target mRNA. microRNAs have been identified in various body fluids. Their stable expression in biofluids as well as their dysregulation in disease conditions opens up a new field for biomarker studies.

The aim of this study was to determine whether plasma microRNA can be used as diagnostic biomarkers of human epilepsy. Blood samples from 20 temporal lobe epilepsy patients during in-patient video-EEG monitoring, along with blood from 20 age and gender-matched healthy volunteers were profiled using the OpenArray miRNA analysis platform run on a 12K Flex QuantStudio PCR. Over 100 microRNAs were consistently called present in control plasma, confirming high specificity of the profiling platform. There were expected high levels of known plasma microRNAs including miR-16, miR-24, miR-150 and miR-484 and low or undetectable levels of brain-expressed microRNAs. Our results showed that, 31 microRNAs were significantly differentially dysregulated in epilepsy patients compared to controls. Among those are a number of brain-specific microRNAs implicated in epilepsy pathogenesis. These results support the benefits of microRNAs in epilepsy diagnosis and their potential use as novel epilepsy biomarkers.

P2.21. Peripheral Akt activity: a potential biomarker for Parkinson's disease

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Defective PI3-kinase/Akt signalling is strongly implicated in the neurodegenerative process of Parkinson's disease (PD) and our previous work has shown Akt activation is decreased in dopaminergic neurons in the brains of patients with PD. There is an urgent need for peripheral biomarkers, particularly blood biomarkers, for improved diagnosis and therapeutic monitoring in PD. There is rationale to support the translation of defects in Akt from brain to blood systems in PD due to the primary function of this signalling system in cellular survival in response to stress and inflammation in the disease. We investigated the activity of Akt, and Akt isoform expression in peripheral blood mononuclear cells (PBMCs), lymphocytes, CD14+ monocytes, M1 and M2 macrophages prepared from (1) control non-PD individuals (n = 10); patients with PD that were not on any medication for the disease (n = 10) and patients with PD on dopamine modifying drug treatment (n = 10). Results revealed a specific and selective increase in Akt activation (phospho Ser473 Akt/Akt ratio) in M1 and M2 macrophages, in PD patients (both treated and untreated groups) compared to matched controls. Levels of Akt isoforms (1, 2, 3) did not differ significantly in blood cells when comparing control and disease groups. The results support the potential of the Akt system as a novel peripheral biomarker for PD, which we are presently investigating in larger patient groups along with α -synuclein the major pathogenic protein in PD.

Poster Topic Area 3:
Integrative Systems:
Neuroendocrinology,
Neuroimmunology and
Homeostatic Challenge

P3.01. TLR3-induced inflammatory responses in the rat hypothalamus are attenuated by FAAH, but not MAGL, substrates

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The endocannabinoid system has emerged as an important target for the modulation of immune responses. However, while several lines of evidence have demonstrated that endocannabinoids regulate TLR4-induced inflammation, there is a paucity of data investigating their effects on inflammation associated with the activation of other TLRs. Thus, the present study examined the effects of enhancing endogenous 2-AG and/or anandamide tone, on TLR3-induced peripheral and central inflammatory responses. Female Sprague-Dawley rats were systemically administered the MAGL inhibitor MJN110 (5mg/kg), the FAAH inhibitor URB597 (1mg/kg) or the dual FAAH/MAGL inhibitor JZL195 (15mg/kg) prior to the systemic administration of the TLR3 agonist poly I:C (3mg/kg) or saline. Animals were sacrificed 4hrs post poly I:C/saline challenge, the spleen and hypothalamus excised and stored at -80°C. Concentrations of endocannabinoids and inflammatory gene expression were determined using LC-MS-MS and qRT-PCR respectively. Systemic administration of MJN110 and URB597 increased 2-AG and anandamide levels respectively in the spleen and hypothalamus, while JZL195 increased levels of both endocannabinoids. Poly I:C induced an increase in IP-10 and TNF- α expression in the spleen; an effect not altered by MJN110, URB597 or JZL195. In comparison, poly I:C-induced increase in IP-10 and TNF- α expression in the hypothalamus was attenuated by URB597 and JZL195, but not MJN110. These data suggest an important role for FAAH substrates including anandamide, but not 2-AG, in the modulation of TLR3-induced inflammatory responses in the hypothalamus. As such, increasing levels of FAAH substrates may be an important therapeutic target for neuroinflammatory responses following viral infection.

Acknowledgments: This study was supported by funding from the Hardiman Postgraduate Scholarship, the Discipline of Physiology and by Science Foundation Ireland Research Frontiers Project (Grant no. 11/RFP/NES/3175).

P3.02. Pharmacological Inhibition of FAAH attenuates TLR4-induced increases in NF- κ B -inducible inflammatory genes in the Frontal cortex; effects partially mediated by central TRPV1 receptors

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The contribution of the brain's endocannabinoid system in mediating TLR-induced neuroinflammation is not fully understood. As such, this study examined the effects of inhibiting FAAH, the enzyme which preferentially metabolises AEA, on neuroinflammation following systemic administration of LPS. Furthermore, the potential role of endocannabinoid receptor targets within the brain in mediating such responses was examined. Rats received systemic (10mg/kg) or central (500nmoles) administration of the FAAH inhibitor PF3845 or the corresponding vehicle, 15 (i.c.v.) or 30 (i.p.) minutes prior to systemic administration of LPS (100 μ g/kg). In a separate experiment, rats received i.c.v. administration of selective antagonists, 15 minutes prior to PF3845, followed 30 minutes later with LPS. Animals were sacrificed 2h later, frontal cortical tissue excised, and expression of cytokines and concentrations of AEA, OEA and PEA were determined. Data were analysed using a one-way ANOVA followed by Fisher's LSD post-hoc test or unpaired two-tailed t-test. $p < 0.05$ was deemed significant. Systemic and central administration of PF3845 significantly increased frontal cortical levels of AEA, PEA and OEA, and attenuated the LPS-induced increases in cortical expression of NF- κ B-inducible inflammatory mediators, when compared to vehicle-LPS-treated counterparts. Prior i.c.v. administration of AM251 or AM630 failed to alter the PF3845-induced attenuation of cytokine expression following LPS. However, prior i.c.v. administration of the TRPV1 receptor antagonist IRTX significantly attenuated the PF3845-induced decrease in cortical expression of IL-6. Increasing FAAH substrate levels directly within the brain potently attenuates TLR4-induced neuroinflammatory responses independent of central CB1 and CB2 receptor activation but rather is partially mediated via central activation of TRPV1.

Acknowledgements: Funding provided by Science Foundation Ireland Research Frontiers Project (Grant no. 11/RFP/NES/3175).

P3.03. Astrocytes are primed by chronic neurodegeneration to produce exaggerated chemokine and cell infiltration responses to acute stimulation with the cytokines IL-1 β and TNF- α

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Microgliosis and astrogliosis are standard pathological features of neurodegenerative disease. Microglia are primed by chronic neurodegeneration such that toll-like receptor agonists, such as lipopolysaccharide (LPS), drive exaggerated cytokine responses on this background. However, sterile inflammatory insults are more common than direct CNS infection in the degenerating brain and these insults drive robust IL-1 β and TNF- α responses. It is unclear whether these pro-inflammatory cytokines can directly induce exaggerated responses in the degenerating brain. We hypothesised that glial cells in the hippocampus of animals with chronic neurodegenerative disease (ME7 prion disease) would display exaggerated responses to central cytokine challenges. TNF- α or IL-1 β were administered intrahippocampally to ME7-inoculated mice and normal brain homogenate-injected (NBH) controls. Both IL-1 β and TNF- α produced much more robust IL-1 β synthesis in ME7 than in NBH animals and this occurred exclusively in microglia. However, there was strong nuclear localisation of the NF κ B subunit p65 in the astrocyte population, associated with marked astrocytic synthesis of the chemokines CXCL1 and CCL2 in response to both cytokine challenges in ME7 animals. Conversely, very limited expression of these chemokines was apparent in NBH animals similarly challenged. Thus, astrocytes are primed in the degenerating brain to produce exaggerated chemokine responses to acute stimulation with pro-inflammatory cytokines. Furthermore, this results in markedly increased neutrophil, T-cell and monocyte infiltration in the diseased brain. These data have significant implications for acute sterile inflammatory insults such as stroke and traumatic brain injury occurring on a background of aging or neurodegeneration.

P3.04. Gut microbiome alterations in major depressive disorder: relevance to pathophysiology

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The biological mechanisms underlying the pathophysiology of Major Depressive Disorder (MDD) involve immune, endocrine and neurotransmitter dysregulation. Preclinical findings suggest that the gut microbiota can modulate brain development, function and behaviour by recruiting the same neuroimmune, neuroendocrine and neural pathways of the brain-gut-microbiome-axis which are considered dysfunctional in MDD. However, the extent to which these preclinical findings translate to clinical populations is currently unknown.

Methods: Thirty four patients with DSM-IV MDD were recruited, together with 33 healthy subjects matched for gender, age and ethnicity. CRP and a panel of cytokines were measured using ELISA. Salivary cortisol levels for assessment of the cortisol awakening response (CAR) were determined by ELISA. Plasma tryptophan and kynurenine were determined by HPLC. Faecal samples were collected for 16s rRNA gene sequencing to determine bacterial community structure and diversity.

Results: Preliminary analysis demonstrated significant differences in the gut microbiota in the MDD group. In parallel patients with MDD showed significantly higher plasma levels of IFN- γ , IL-8, IL-6, IL-1 β , TNF- α and CRP. In addition, there was a significantly higher CAR and an elevated kynurenine: tryptophan ratio in patients with MDD.

Conclusion: Alterations in the gut microbiota in patients with MDD are pronounced and may drive the prominent pathophysiological features of this disorder. The mechanisms underpinning these effects require further investigation but may be related to perturbations to intestinal barrier function. Ultimately, these findings may pave the way for therapeutic targeting of the gut microbiome as a viable strategy for novel antidepressant development.

P3.05. WKY rats exhibit a reduced homecage locomotor activity response to chronic restraint stress

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Stress is known to be a predisposing factor in the development or exacerbation of a number of medical conditions, the response to which is determined by genetic factors. The Wistar Kyoto (WKY) rat is a genetically stress-hypersensitive strain of rat which exhibits an anxiety- and depressive-like phenotype. We have recently demonstrated that the WKY rat exhibits a blunted locomotor response and HPA axis activity following an acute immune challenge. This study examined the effect of chronic repeated restraint stress on locomotor activity (LA) in WKY rats in comparison to the less stress-sensitive Sprague-Dawley (SD) strain. Baseline behavioural testing revealed that WKY rats spent less time in the centre of the open field, and more time in the centre platform of the elevated plus maze, indicating anxiety-like phenotype, an effect accompanied by reduced LA in both arenas. Homecage LA monitoring revealed that WKY rats exhibit reduced LA when compared to SD counterparts. Both SD and WKY rats exhibit enhanced homecage LA for 1 hr following exposure to 2 hours of restraint stress, an effect maintained over a period of 10 consecutive days. The magnitude of the increase in homecage LA activity following restraint stress was significantly blunted in WKY rats when compared to SD counterparts. The data indicate that WKY rats exhibit an anxiety-like phenotype and reduce locomotor activity both at baseline and in response to chronic stress exposure. In conclusion, this data provides further evidence of altered behavioural responses to stress in the WKY rat strain.

Acknowledgements: Work supported by College of Medicine, postgraduate fellowship and Discipline of Physiology, NUI Galway.

P3.06. Myelinating white matter tracts display differential activation of the unfolded protein response in postnatal rat cerebellum

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Membrane protein and lipid synthesis primarily occurs in the endoplasmic reticulum, an organelle which can initiate the Unfolded Protein Response (UPR) when under stress. We hypothesise that the UPR is activated in white matter tracts during myelination in order to expand the ER capacity of oligodendrocytes.

Critical myelination time points were identified by immunohistochemistry in rat cerebellum and these were correlated to peaks in ER stress signalling by staining for activated UPR transducers (pIRE1, ATF6 and pPERK) and associated downstream molecules (peIF2alpha, PDI, GRP78, GRP94, CHOP and calreticulin) in cerebellar tracts III and IV. Gene expression in developing cerebellum was assessed by qPCR.

Actively myelinating tracts displayed differential expression of pIRE1, pPERK and ATF6 as well as classical UPR targets GRP78, GRP94 and PDI. Activated pIRE1-positive cells were widespread at P14 and P17, during myelination and at significantly higher numbers than other stages ($p < 0.05$ and 0.01). Nuclear-localised ATF6 (indicative of the active transcription factor) peaked at P10, concurrent with the initial phase of myelination ($p < 0.01$). Downstream targets GRP78, GRP94 and PDI were significantly upregulated at P17 compared to P7 ($p < 0.01$, 0.001 , 0.01) and remained significantly elevated in adults ($p < 0.001$, 0.01 , 0.05). The majority of cells positive for these markers were oligodendrocytes as confirmed by dual-labelling. Although gene expression of GRP78, GRP94 and PDI did not change significantly over time, ATF6 and XBP1s both showed significant fold changes between early and late timepoints.

This data helps promote understanding of events occurring during developmental myelination and may have implications for the development of reparative treatments in diseases such as multiple sclerosis.

P3.07. Pharmacological inhibition of MAGL enhances TLR-3-induced increases in Type I Interferon- and NF-κB-inducible inflammatory genes in the rat hippocampus

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Several lines of evidence have demonstrated that the endocannabinoid 2-arachidonoylglycerol (2-AG) exerts potent immunoregulatory effects on TLR4-induced neuroinflammation, however, there is a paucity of data investigating the effect of 2-AG on inflammation associated with the activation of other TLRs including TLR3. As such, the present study examined the effects of inhibiting MAGL, the enzyme which preferentially metabolises 2-AG, on TLR3-induced neuroinflammation.

**Poster Topic Area 4:
Neural Excitability, Synapses
and Glia: Cellular Mechanisms**

P4.01. Regulation of myelination in the prefrontal cortex by the microbiome

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Background: Myelination is a critical but vulnerable dynamic feature of normal brain development with implications for mental health and disease ranging from neurodegenerative to chronic stress disorders and multiple sclerosis. In particular, normal cognition and social functioning appear to be contingent on intact myelination in the prefrontal cortex (PFC), a brain region implicated in multiple psychiatric disorders. Interestingly, social isolation stress results in a decreased myelination in the (PFC). Growing evidence points to a role for the gut microbiome in regulating brain function and behaviour. Studies in germ-free (GF) animals, have highlighted the impact the microbiota can have on neurodevelopment with GF animals demonstrating decreased sociability. Given these overlaps, we aimed to investigate whether GF mice displayed altered myelination in adulthood in this brain region. Methods: We assessed both at the ultrastructural and transcriptional level changes in myelin sheath thickness and functional myelin sheath components using transmission electron microscopy and qRT-PCR. Results: Ultrastructural analysis revealed hypermyelination within the PFC of GF mice as indicated by decreased g-ratio compared to conventional mice. These mice also displayed increased expression of six myelin genes only within the PFC. However, colonisation post-weaning normalised the expression of these myelin component genes. Coinciding with this, GF mice displayed altered expression of oligodendrocyte regulating genes within the PFC. Conclusion: This is, to our knowledge, the first demonstration that the gut microbiota can regulate myelination. This effect is brain-region specific. Moreover, our results suggest that the microbiota can be successfully targeted later in life to modulate myelination patterns, at least at the transcriptional level. This raises the possibility that targeting the gut microbiota during critical time windows could be a viable approach for treating disorders associated with abhorrent myelination patterns.

P4.02. Characterisation of LNX family E3 ubiquitin ligases

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Ligand of numb protein X1 (LNX1) and LNX2 are E3 ubiquitin ligases. LNX proteins arose early in metazoan evolution and are conserved in all vertebrate lineages², yet our understanding of LNX protein function *in vivo* is very limited. Lnx mRNAs are prominently expressed in the nervous system³, suggesting that LNX proteins play a role in neural development. This hypothesis remains unproven, however, largely because LNX proteins are present at very low levels *in vivo*. Here, we provide explanations for the low levels of LNX proteins detected *in vivo*. Using luciferase reporter assays, we show that the 5' untranslated region of the mRNA that generates the LNX1p70 isoform, strongly suppresses protein production. This effect is mediated in part by the presence of upstream open reading frames (uORFs). By contrast, uORFs do not negatively regulate LNX1p80 or LNX2 expression. Instead, we find some evidence that protein turnover via proteasomal degradation may influence LNX1p80 levels in cells. To gain functional insights into the LNX family, we have characterised and compared the LNX1 and LNX2 interactomes using affinity purification and mass spectrometry. We identified a large number of novel LNX-interacting proteins, some shared by LNX1 and LNX2, others isoform specific, and have mapped several of these interactions to individual LNX domains. We have also shown a number of these interactions to be substrates for LNX dependent ubiquitination. Furthermore, we report here the generation of LNX1p70^{-/-}/LNX2^{-/-} knockout mice. The first biochemical and behavioural characterization of these double knockout mice will be described.

P4.03. The microbiota regulates amygdaloid volume and dendritic length

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Germ-free mice (GF; microbiota deficient from birth) have provided critical insights into the role of the microbiota in the regulation of brain and behaviour. GF mice display altered hypothalamic-pituitary-adrenal axis signalling, anxiety-like behaviours as well as deficits in social cognition, responses which are amygdala-mediated. While the mechanisms underlying this behavioural and physiological repertoire remain to be determined, it is possible that the microbiota recruits structural aspects of the amygdala to mediate its effects at the level of the central nervous system. Therefore, the aim of the present study was to determine if the volume and dendritic morphology of the amygdala differ in GF compared to conventionally colonized (CC) mice. Stereological measures of well-defined subregions of the amygdala revealed significant expansions of the basolateral (BLA), lateral (LA) and central (CeA) nuclei in GF versus CC mice. We also investigated the effect of GF status at the level of single excitatory (pyramidal-like) and inhibitory (stellate) neurons in the BLA by measuring the dendritic length, branching and spine density of single neurons. In GF mice, stellate neurons exhibited significant increases in both length and branching. Pyramidal-like neurons from GF mice were significantly longer but did not differ in branching compared to controls. Spine density was increased over the entire dendritic arbour of pyramidal-like neurons from GF mice. These findings suggest that the gut microbiota is critical for normal neurodevelopment of the amygdala and that this neural remodelling could contribute to the altered stress responsivity and behavioural profile documented in GF mice.

P4.04. Early life stress and the oestrogen interact to influence both spinal and cortical glutamate metabolism

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Early life stress is a recognised risk factor for chronic pain disorders including fibromyalgia and visceral pain. Anterior cingulate cortex (ACC) and lumbosacral spinal cord have been shown to play important roles in modulation of visceral pain, both in affective component and motor planning. Moreover oestrus cycle related fluctuating sex hormone have been linked with alternating pain sensitivity.

Here we evaluate whether oestrus cycle and maternal separation (model of early life stress) have any influence on metabolism of glutamate-an excitatory neurotransmitter, in both spinal cord and ACC.

Maternally separated and non-separated Sprague Dawley adult female rats were assessed in all stages of oestrus cycle (n=10). ACC and lumbosacral-cord slices were incubated with tritium-labeled aspartate to allow uptake across glutamate transporters (EAATs). Function of EAATs was measured in terms of intracellular radioactivity normalized to measured protein value of slices.

In non-separated rats, both the spinal and cortical EAAT function varied across the oestrus cycle-being inhibited in high estrogen states i.e. proestrus and oestrus ($P < 0.05$).

In maternally separated rats, spinal EAAT function was similar to that seen in non-separated rat. However, cortical EAAT function in maternally separate rats was inhibited in low oestrogen state i.e. diestrus rather than high oestrogen states ($P < 0.05$).

Our data shows that cortical and spinal EAAT function is dependent on phase of oestrus cycle. Moreover, cortical EAATs are sensitive to effects of early life stress. Drugs enhancing EAAT function may have an important role in counteracting the inhibitory effect of early life stress on glutamatergic system.

Poster Topic Area 5: Neuropharmacology

P5.01. An integration of preclinical tests to assess acute anxiolytic and chronic antidepressant effects of diazepam and desipramine in rats

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Although there is a high degree of comorbidity between depression and anxiety, it is not common for antidepressant and anxiolytic effects of drugs to be evaluated in a combined manner. Thus, this study aimed to integrate preclinical tests of anxiety [elevated plus maze (EPM) and open field (OF)] and depression (forced swim test, FST), in a single study design using the standard antidepressant desipramine (DMI, 0, 2.5, 5 and 10 mg/kg) or the anxiolytic diazepam (DZP, 0.5, 1 and 1.5 mg/kg). Male Sprague-Dawley rats received daily subcutaneous injections of the drugs; controls received vehicle injections. Thirty minutes after the first injection, rats were assessed in the EPM, followed immediately by the OF. After a further 13 days drug treatment, the antidepressant effects in the FST were examined; home cage locomotor activity (HCA) was measured in the hour preceding the test swim. Data were analysed using One-Way ANOVA, followed where appropriate by post hoc SNK; $p < 0.05$ was deemed statistically significant.

DZP had acute anxiolytic effects, and significantly affected ethological parameters in the EPM. DZP decreased distance moved (cm) in the OF. In the FST, chronic DMI significantly decreased immobility and increased climbing in a dose dependent manner. Both DZP and DMI decreased HCA in the hour prior to the FST.

This study has demonstrated that both antidepressant and anxiolytic effects of drugs can be successfully integrated into a single experimental design, and thus can be proposed as a cost and time-effective approach for assessing these properties for novel compounds.

P5.02. Descending effect on spinal nociception by amygdaloid glutamate varies with the submodality of noxious test stimulation

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Amygdala has an important role in the processing of primary emotions, such as fear. Additionally, amygdala is involved in processing and modulation of pain. While the amygdala, particularly its central nucleus (CeA), has been shown to contribute to pain control, the descending pain regulation by the CeA is still only partly characterized. Here heat and mechanical nociception was tested in both hind limbs of healthy rats with a chronic guide cannula for microinjection of glutamate into the CeA of the left or right hemisphere. The aim was to assess whether the descending pain regulatory effect by glutamate in the amygdala varies with the submodality or the body side of nociceptive testing, brain hemisphere or the amygdaloid glutamate receptor. Motor performance was assessed with the Rotarod test. Amygdaloid glutamate, independent of the treated hemisphere, produced a dose-related heat and mechanical antinociception that varied with the submodality of testing. Heat antinociception was short lasting (minutes), bilateral and not reversed by blocking the amygdaloid NMDA receptor with MK-801. In contrast, mechanical antinociception lasted longer (>20 min), was predominantly contralateral and reversed by blocking the amygdaloid NMDA receptor. At an antinociceptive dose, amygdaloid glutamate failed to influence motor performance. The results indicate that independent of the brain hemisphere, the spatial extent and duration of the descending antinociceptive effect induced by amygdaloid glutamate varies with the amygdaloid glutamate receptor and the submodality of pain.

P5.03. A pilot study on using the 5-Choice Serial Reaction Time Task (5-CSRTT) boxes to test effects of drugs on attentional performance, impulsivity and compulsivity in rats

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Nicotine and cannabis are among the most widely abused drugs and are often used in combination or as a progression in addictive substance use, particularly among adolescents and young adults. Clinical and preclinical studies have suggested functional brain interactions between nicotine and natural or synthetic cannabinoid compounds in relation to reward-related processes and cognitive deficits. Our project aims to assess interactions between nicotine and/or cannabinoid exposure during adolescence and impulsivity levels and/or reward/reinforcement during adulthood in high and low impulsive Sprague-Dawley rats. In order to achieve these aims, it was necessary to conduct a pilot study to ensure that new 5-CSRTT boxes, used to assess attentional performance and impulsivity, are functioning appropriately. Eight male Sprague-Dawley rats were trained in the 5-CSRTT boxes. Paired samples t-tests and a Wilcoxon signed-rank test were performed to discern whether rats performed worse on various parameters of the 5-CSRTT during a challenge session compared to a three-day baseline, as would be expected if the equipment was functioning correctly. There was a significant difference in response accuracy ($p < 0.5$) and percentage of correct responses ($p < 0.01$) between the three-day baseline and challenge session. However, there were no significant differences in premature and time-out responses. Overall, findings indicate that the 5-CSRTT boxes, essential equipment for proposed future experiments, are functioning correctly. Proposed future experiments using this procedure may have implications for the prevention/ treatment of nicotine and cannabis abuse.

*Authors have equally contributed to this work.

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P5.04. Pharmacological targeting of the cannabinoid type-2 (CB₂) receptor protects the nigrostriatal pathway against inflammation-driven neurodegeneration in the LPS rat model of Parkinson's disease

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The cannabinoid type-2 (CB₂) receptor has recently emerged as a potential anti-inflammatory target in neurodegenerative diseases. Indeed, we have recently shown significant CB₂ receptor upregulation, concomitant with microglial activation, in the inflammation-driven lipopolysaccharide (LPS) rat model of Parkinson's disease (Concannon et al., 2015). Therefore, the aim of this study was to determine if pharmacological activation of CB₂ receptors can prevent inflammation-driven Parkinsonism in this model.

Male Sprague Dawley rats were assigned to four groups: [1] LPS lesion & CB₂ agonist (n=10), [2] LPS lesion & Vehicle (n=10), [3] Naive & CB₂ agonist (n=4), [4] Naive & Vehicle (n=4). Animals in the lesion groups received a unilateral, intra-nigral LPS lesion (10 µg in 2 µl). Animals were injected with either CB₂ agonist (JWH-133, 1 mg/kg i.p.) or vehicle 2 hr prior to surgery, and daily for a further 13 days. Animals underwent twice daily behavioural testing for motor dysfunction and were sacrificed 14 days post-surgery. Quantitative immunohistochemical analysis was performed to assess neuroinflammation and neurodegeneration.

Injection of LPS into the rat substantia nigra caused significant motor dysfunction, which was underpinned by significant nigral microgliosis and nigrostriatal neurodegeneration. Chronic JWH-133 attenuated LPS-induced dopaminergic neurodegeneration but this did not ameliorate motor dysfunction. Interestingly, the CB₂ agonist did not reduce microglial infiltration/proliferation indicating that the protective effects of JWH-133 may involve other anti-inflammatory mechanisms.

Overall, this study has shown that pharmacological targeting of the CB₂ receptor protects against inflammation-driven dopaminergic neurodegeneration without reducing the level of microgliosis, indicating the CB₂ receptor may represent a viable target for anti-inflammatory disease modification in Parkinson's disease.

P5.05. The Endocannabinoid system in the anterior cingulate cortex is required for the termination of fear-conditioned analgesia in rats

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Background: Fear-conditioned analgesia (FCA) is the profound suppression of pain upon re-exposure to a context previously paired with an aversive stimulus. The endocannabinoid system in brain regions including the periaqueductal grey, amygdala and ventral hippocampus mediates FCA.

Aims: The aim of the present study was to investigate the role of the endocannabinoid system in the anterior cingulate cortex (ACC) in formalin-evoked nociceptive behaviour and FCA in rats.

Methods: Cannulae were implanted into the ACC of male Lister-Hooded rats. On the conditioning day, animals received footshock (10 x 1s, 0.4mA), while controls did not. 23.5 hours later, animals received intraplantar injection of formalin (2.5%) into the right hindpaw. 15 min later, rats received intra-ACC injection of vehicle, the fatty acid amide hydrolase inhibitor URB597 (0.1mM/0.3 μ L), the CB1 receptor antagonist AM251 (2mM/0.3 μ L), or a combination of URB597+AM251 and 15 minutes later were re-exposed to the conditioning arena for a period of 30 minutes during which nociceptive behaviour was assessed. Data were analysed by ANOVA and Fisher's LSD post-hoc test.

Results: Re-exposure to the context previously paired with footshock reduced formalin-evoked nociceptive behaviour in the first 20 minutes of the trial, confirming the expression of FCA. AM251 prolonged the expression of FCA towards the end of the trial, an effect that was not affected by co-administration of URB597.

Conclusions: These findings suggest that pharmacological blockade of CB1 receptors in the ACC prolongs FCA, suggesting a role for the endocannabinoid system in the ACC in the termination of FCA.

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P5.06. Superior behavioural recovery after status epilepticus with midazolam compared to lorazepam treatment in mice

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Status epilepticus (SE) occurs as a result of a failure of the normal mechanisms to terminate seizures and constitutes a neurological emergency that can result in permanent brain damage. Benzodiazepines are the first line of treatment for SE; however, debate remains regarding drug of first choice and delivery route. Although lorazepam remains the most common treatment for SE, midazolam has become a popular alternative, particularly as it can be given non-intravenously. Anticonvulsants are also commonly used to terminate SE in animal models. Here, we aim to determine the efficacy of midazolam, in comparison to lorazepam, as a pharmaco-therapeutic for SE in an experimental model of epilepsy. SE was induced by intra-amygdala kainic acid injection in 8 week old C57Bl/6 mice. Forty-minutes after kainic acid, mice were treated with an intraperitoneal injection of either lorazepam or midazolam (8 mg/kg). EEG activity, histology and behavioural tests assessing recovery of function were evaluated and compared between groups. Treatment with either lorazepam or midazolam resulted in similar patterns of reduced EEG epileptiform activity for up to 1 h after drug administration. Damage to the hippocampus and presentation of post-insult anxiety-related behaviour did not significantly differ between drug groups. However, recovery of normal behaviours such as grooming, levels of activity and the overall welfare of treated mice were all superior at 24 h in mice given midazolam compared to lorazepam. Our results suggest that midazolam is as effective as lorazepam as an anticonvulsant while also providing early recovery after SE in this model.

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P5.07. Novel functional crosstalk of the ghrelin receptor in the central regulation of food reward

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The ghrelin receptor (GHS-R1a) plays a key role in mood, appetite and reward-related behaviours, including the hedonic aspects of food intake and food addiction. In addition, the serotonergic system, specifically the 5-HT_{2C} receptor, has also shown to be of critical importance in the regulation of appetite and satiety. We recently showed compelling evidence for a functional interaction between the GHS-R1a and the 5-HT_{2C} receptor and demonstrate that this GHS-R1a/5-HT_{2C} receptor interaction translates into a biological significant modulation of ghrelins orexigenic effect.

Specifically, in vitro we show co-localized receptor expression using confocal microscopy, demonstrate ligand-mediated co-internalization of the GHS-R1a/5-HT_{2C} receptor pair and show that the GHS-R1a/5-HT_{2C} dimer attenuates ghrelin-mediated calcium mobilization. The 5-HT_{2C} and GHS-R1a receptors were also co-expressed ex-vivo in cultured primary hypothalamic- and hippocampal rat neurons, suggesting a physiologically relevant interaction between these receptors in a biological system. We further demonstrated that when 5-HT_{2C} receptor signalling is blocked in mice, ghrelins orexigenic effect is potentiated. In contrast, the specific 5-HT_{2C} receptor agonist lorcaserin, recently approved in the US for the treatment of obesity, attenuates ghrelin-induced food intake as well as ghrelin mediated sucrose preference.

These in vivo data support our in vitro findings of 5-HT_{2C} receptor-mediated attenuation of GHS-R1a receptor activity in the homeostatic as well as hedonic regulation of food intake. Overall, the findings of this study highlight the potential of a novel combined GHS-R1a/5-HT_{2C} receptor treatment strategy in weight management, which may also be applicable in the rewarding and motivational aspects of food intake (ie food addiction).

P5.08. Real-time changes in oxygen and local field potential in the brains of freely-moving rats following NMDA receptor antagonism

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Using amperometric sensors, it is possible to monitor real-time changes in oxygen in the rat brain in a manner that is directly comparable to changes observed in the blood-oxygen-level-dependent (BOLD) signal in fMRI. Using spectral analysis, it is also possible to extract changes in the local field potential (LFP) from the oxygen signal, allowing the direct comparison of a BOLD-like signal with electrophysiological information in behaving animals. Recording in the striatum and hippocampus of male Wistar rats, comparisons in tissue oxygen and LFP were made between different behavioural states and pharmacological interventions. Exploratory behaviour was associated with significant increases in tissue oxygen and in alpha power (9-12 Hz) in both the striatum and the hippocampus. There was also a significant increase in striatal gamma power (50-100 Hz). Administration of non-competitive NMDA receptor antagonists (ketamine; MK-801; phencyclidine [PCP]) was associated with hyperlocomotion accompanied by significant increases in striatal and hippocampal oxygen. In the striatum, there was a significant increase in high frequency oscillatory power (140-180 Hz) that was absent in the hippocampus. In the hippocampus, there were significant increases in theta (6-8 Hz) and gamma power and significant decreases in delta (1-4 Hz) and alpha power that were absent in the striatum. This data suggests that NMDA antagonists act on these two brain regions through different physiological mechanisms. Furthermore, the extracted LFP data allows for a deeper understanding of neuronal oxygen supply and utilisation.

P5.09. The consequences of acute or intermittent methamphetamine exposure in utero on neonatal development in rat offspring

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In pregnant females there are many patterns of methamphetamine (MA) use, and correspondingly such patterns of use may lead to different outcomes for the neonate. The severity of effects on the neonate is related to the frequency and quantity of MA that the foetus is exposed to. There is a paucity of studies investigating different patterns of exposure for pregnant females taking MA, either clinically or in laboratory animals. To date, our previous work has focused on chronic use of MA during pregnancy or lactation.

**Poster Topic Area 6:
Novel Methods and Technology
Development**

P6.01. Cerebral oxygenation in preterm infants less than 32 weeks during the first 48 hours of life

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Introduction: Preterm birth (< 32 weeks gestation) is a strong determinant of neonatal brain injury or mortality. Near Infrared Spectroscopy (NIRS) is a tool that can monitor neonatal cerebral oxygenation (rSO₂). However, normative values of rSO₂ with a neonatal probe have yet to be established. Therefore, this study aims to determine such values and explore the relationship between these values and outcome.

P6.02. Standardisation of *Xenopus laevis* as a model to study spinal cord regeneration

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Vertebrate amphibian tadpoles of *X. laevis* have a remarkable capability to recover from spinal cord injury (SCI). Although the *Xenopus* model has been used to study regeneration, the specific procedure for spinal cord transection and a method to quantify behaviour post-surgery has not been standardized. In the present study, a reproducible surgical protocol for *X. laevis* SCI was established yielding consistent spinal cord transection. Furthermore, we developed a behavioural test for assessment of swimming ability following SCI to monitor the success of the surgery and functional recovery. Swimming ability of spinal cord-injured and uninjured stage 50 *X. laevis* tadpoles was assessed by measuring vibration induced motor responses. Uninjured tadpoles (pre-surgery) responded strongly to vibration at all-time points whereas injured tadpoles did not initially respond but gradually recovered responsiveness. To monitor spinal regeneration at the cellular level, the regenerating axons were observed at different time points uncovering the stages of axonal regeneration. Axons appeared to cross the injury site associated with BLBP+ radial glia suggesting that these cells create a permissive environment for axons to regenerate. In summary, a surgical protocol to reproducibly perform spinal cord injury in *X. laevis* tadpoles was developed. In addition, a standardized method to evaluate the success of the surgery and restoration of locomotor ability of tadpoles was introduced. With these refinements, *X. laevis* now provides a paradigm for studying recovery from spinal cord injury, which will further help in the identification of pathways and components of neuroregeneration.

P6.03. A new approach to SCI rehabilitation

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In order to maintain postural and locomotor control the central nervous system requires a critical level of proprioceptive sensory input from the lower limbs on the timing and level of load-bearing. Recent research in spinalised animal models has shown that full weight-bearing stepping can be recovered in the presence of spinal epidural stimulation and pharmacological modulation using serotonergic agonists. It has also been observed that progressive increase daily lower limb load-bearing, can further enhance recovery of standing potential, in spinalised rats and in a small number of human spinal cord injury patients. The mechanism whereby motor function recovers with these interventions is slowly being elucidated from a perspective of spinal network responses to combinations of neuromodulatory interventions, utilising implanted or transcutaneous electrical stimulation, exoskeletal robotic entrained walking systems and pharmacological modulation. The aim of this independent case study in one human participant is to further evaluate the potential of exoskeletal bipedal loadbearing, lumbosacral electrical stimulation and a pharmacological intervention in restoration of standing and autonomic nervous system responses after complete paralysis due to spinal cord injury. The participant is currently undergoing baseline pre-intervention medical tests and extensive neurophysiological and biomechanical evaluation during supported standing and robotically assisted ambulation. The participant will then undergo four week intervention phases commencing with exoskeletal walking and standing training alone, followed by walking/standing training in combination with transcutaneous electrical stimulation and a pharmacological intervention. Preliminary baseline and Phase I intervention data will be discussed as well as the use of emerging technologies in SCI rehabilitation.

P6.04. Computational discovery of plasma microRNA profiles as biomarkers of temporal lobe epilepsy

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Epilepsy is a common neurological disorder affecting approximately 1% of the population and is characterised by recurrent unprovoked seizures. The lack of a clinically accepted biomarker for epilepsy diagnosis as well as the incomplete and vague history often provided by the patient is responsible for up to 30% misdiagnosis. MicroRNAs are a class of small non-coding RNA that regulate gene expression at a post-transcriptional level. MicroRNAs are important contributors to brain function and emerging animal and human data suggest microRNAs control multiple pathways in epilepsy. MicroRNAs are also detectable in various body fluids and their stability as well as links to disease mechanism makes them potentially ideal molecular biomarkers of epilepsy.

We determined plasma levels of 754 microRNAs collected from 20 healthy volunteers and 20 epilepsy patients using high-throughput real-time quantitative reverse transcription PCR. Computational analysis included normalisation, clustering, differential expression analysis, target prediction and pathway analysis. A number of significantly differentially expressed microRNAs were identified between control and epilepsy samples including known brain-expressed microRNAs implicated in epilepsy. Furthermore, we applied feature selection with machine learning algorithms, N-to-1 Neural Networks, to build a microRNA-based predictor of epilepsy, validated on an independent test set. This analyse showed that these classifiers may be useful in supporting the existence of a set of microRNAs implicated in disease pathogenesis that may be biomarkers of human epilepsy.

P6.05. In vitro and in vivo analysis of valproic acid-loaded nanoemulsion

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Brian Patrick Kirby, Johnson Stanslas, Hamidon Basri

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OBJECTIVE: To investigate, both in vitro and in vivo, the potential of formulated valproic acid-encapsulated nanoemulsion (VANE) to penetrate the blood-brain barrier.

**Poster Topic Area 7:
Other**

P7.01. Bifidobacterium Longum: A psychobiotic that modulates brain activity, the stress response and neurocognitive performance in healthy volunteers

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Methods: 22 healthy male volunteers completed the study in a repeated-measures design. Participants ingested (2.16 +/-0.20) X 10⁹ CFU of B. longum NCIMB 41676 or placebo daily for four weeks each. Participants completed study visits pre-placebo, post-placebo and post-probiotic. Acute stress was assessed in response to the socially evaluated cold pressor test, and daily stress was assessed online via the Cohen

Perceived Stress Scale. CNS activity was assessed via resting electroencephalography (EEG), and cognitive performance using a test battery from the CANTAB platform.

Results: B. longum NCIMB 41676 attenuated the acute stress response in terms of reduced cortisol output as well as blunted increases in subjective anxiety. During daily consumption of the probiotic, self-reported daily stress was lower. Post-probiotic, central EEG theta power was lower and mobility was heightened. There was a subtle improvement in visuospatial memory performance in paired associate learning.

Conclusions: Daily consumption of B. longum NCIMB 41676 is associated with attenuated psychological and physiological stress, altered EEG and a modest improvement in cognitive performance. Further research is warranted to investigate the mechanisms of this putative psychobiotic and its effect in relevant stress-related conditions.

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P7.02. Altered expression of P2Y receptors following status epilepticus and chronic epilepsy in mice

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Royal College of Surgeons in Ireland

Epilepsy is a chronic neurological disorder characterized by recurrent seizures affecting 1% of the general population. Despite the existence of numerous AEDs, 30%-40% of patients do not respond to treatment. There exists an urgent need for novel therapeutics.

ATP has emerged as a potential contributor to SE and specific inhibitors of ATP-gated ion channels have shown anticonvulsive and neuroprotective properties. The P2YR are beginning to be implicated in brain diseases and altered expression of some P2YR has been reported.

To study the induction and expressional changes of the P2YR after seizures we used our mouse model of epilepsy. SE was induced by intra-amygdala microinjection of KA and after a short latency period epilepsy was developed. The animals were sacrificed at different time-points after SE (1h, 4h, 8h, 24h and 20days) and the hippocampus was analyzed by Western blot and quantitative PCR.

An exhaustive analysis of mRNA and expressional changes of the different P2YR after SE and epilepsy in the hippocampus revealed receptor-specific changes. P2YR2, P2YR4 and P2YR6 mRNA levels were up-regulated while P2YR1, P2YR12, P2YR13 and P2YR14 were down-regulated. P2Y1R, P2Y2R, P2Y4R, P2Y13R and P2YR14 proteins levels revealed a trend to be increased and P2YR11 and P2YR12 to be decreased after SE. During epilepsy, mRNA levels of P2Y1R, P2Y2R, P2Y4R, P2Y6R, P2YR12 and P2YR13 showed a tendency to be increased whereas protein levels of P2YR1, P2YR2 and P2YR12 were up-regulated and P2YR11 was down-regulated.

P2Y specific alterations in hippocampus can be induced by SE and during epilepsy.

P7.03. Semaphorin6A mediates sensory afferent projection into the developing spinal cord

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During vertebrate development, sensory axons project from the peripheral nervous system into the spinal cord at the dorsolateral margin via the dorsal roots. They then synapse with interneurons to elicit reflex responses or ascend to the brain in separate tracts depending on sensory modality. This segregation of sensory axons is essential for appropriate conscious somatic sensation and unconscious proprioception. Radial glial cells support the formation of ascending tracks by forming scaffolds which channel various axon fasciculi through the spinal cord along the rostrocaudal axis (Barry et al., 2014). Semaphorins are the largest family of axon guidance cues expressed during central nervous system (CNS) formation. Class 6 semaphorins are found throughout the developing CNS and play vital roles in the guidance of growing axons in the brain, yet their roles in the spinal cord are relatively unknown.

We investigated the roles of Semaphorin6A (Sema6A) and its receptor PlexinA2 during spinal cord development by comparing the organisation of radial glia and axon tracts, in particular sensory axons, in wild type, Sema6A^{-/-} and PlexinA2^{-/-} mice.

P7.04. Application of a weighted burden test to whole exome sequence data for obesity and schizophrenia

David Curtis

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Whole exome or whole genome sequencing produces genotypes for very large numbers of variants. For biological and statistical reasons it makes sense to combine information at the level of the gene. A priori, one may wish to give more weight to variants which are rare and which are more likely to affect function.

A combined weighting scheme, implemented in the SCOREASSOC program, was applied to whole exome sequence data for 1392 subjects with schizophrenia and 982 with obesity from the UK10K project.

A t test comparing average scores was mildly anticonservative when considering obese subjects as cases but otherwise results conformed fairly well with null hypothesis expectations and no individual gene was strongly implicated. However a number of the higher ranked genes appear plausible candidates as being involved on one or other phenotype and may warrant further investigation. These include MC4R, NLGN2, CRP, DONSON, GFAP, GTF3A, IL36B, ADCYAP1R1, ARSA, DLG1, SIK2, SLAIN1, ZNF507, CRHR1, NSF, SNORD115, GDF3 and HIBADH.

Some individual variants in these genes have different frequencies between cohorts and could be genotyped in additional subjects. For other genes, there is a general excess of variants at different sites so attempts at replication would be more difficult. Overall, the weighted burden test provides a convenient method for using sequence data to highlight genes of interest.

P7.05. High-fat diet impacts on spinal pain processing pathways

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Obesity rates are approaching epidemic proportions and are a significant factor in annual health care costs. In addition, to cardiovascular comorbidities, the presence of chronic pain is extremely high in this population of individuals. It is now well accepted that the glutamatergic system is involved in pain processing. Recently, it has been demonstrated that a high-fat (HF) diet leads to neurochemical alterations in glutamatergic neurotransmission pathways, in terms of clearance and metabolism. The excitatory amino acid transporters (EAATs) clear glutamate from the synapse. Interestingly, their function has been demonstrated to be altered within the hippocampus of HF fed animals.

P7.06. Rab coupling protein (Rab11-FIP1C), Rab14 and endosomal recycling in neuritogenesis

Mary W. McCaffrey, **Andrew J. Lindsay**

University College Cork

Rab GTPases and their effector proteins serve important roles in synaptic function, neurite growth/remodelling and nervous system development. Furthermore, Rab dysfunction has been linked to a number of neurological disorders such as Parkinson's, Alzheimer's, Charcot-Marie Tooth and Huntington's diseases. Rab11 and its major family of effector proteins, the Rab11-Family Interacting Proteins (Rab11-FIP) are central regulators of the endosomal recycling pathway and serve multiple roles in neuronal function. Rab11 and Rab11-FIP2 have been implicated in AMPA receptor trafficking in dendritic spines during long-term potentiation (LTP) (Wang et al. 2008), while Rab11-FIP5 has recently been implicated in long-term depression (LTD) (Bacaj et al. 2015). Rab11 and RCP have been implicated in the directional trafficking of cell surface proteins, such as $\alpha 1$ integrin, during neurite outgrowth (Eva et al. 2010). We will present data demonstrating that RCP cooperates with Rab14, during the formation of neurites in N2A mouse neuroblastoma cells (Lall et al. 2015).

P7.07. Disrupted anatomical integration and rich club connectivity in euthymic bipolar disorder

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Introduction: Euthymic bipolar disorder has been relatively unexplored using complex network analysis^{1,2}. Complex network analysis combines structural and diffusion magnetic resonance imaging (MRI) to model the brain as a network and evaluate topological properties of brain structure^{3,4}. Most recently, a group of highly inter-connected high density structures termed the 'rich-club' represents a particular group of structures in integrated brain functioning⁵. We hypothesized global dysconnectivity as well as rich club effects to present as a feature of the disorder due to widespread white matter microstructural alterations previously identified in this cohort^{6,7}.

Methods: This cohort of 42 individuals diagnosed with euthymic bipolar disorder and 43 healthy volunteers underwent diffusion MRI scans. Network metrics were generated using the Brain Connectivity Toolbox through MATLAB. Global metrics were derived to investigate properties of integration. Metrics of degree, clustering coefficient, characteristic path length, global efficiency, betweenness centrality and the rich club coefficient were investigated in this analysis.

Results: Analysis of global metrics revealed group differences across measures of characteristic path length ($p=0.017$), global efficiency ($p=0.015$) and clustering coefficient ($p=0.047$). The rich club connectivity effects were significant for k density values 55 and 56 before FDR multiple comparison correction. $k=55$ ($Z = -2.24$, $p\text{-value} = 0.024$) & $k= 56$ ($Z = -2.65$, $p\text{-value} = 0.0067$). After correction of 28 p -values, $k=56$ demonstrated a trend effect. Rich club structural differences between groups suggest impaired integration of the right superior frontal gyrus and left thalamus in the bipolar group rich club network.

Discussion: Deficits in rich club connectivity in the bipolar group highlight the reduced capacity for global brain communication, as suggested by the relationship detected between global efficiency and rich club connectivity. Differentially affected rich club organization may explain for reductions in whole brain communication.

P7.08. The effects of the stress hormone corticosterone on neural progenitor cells derived from specific areas of the longitudinal axis of the hippocampus

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Adult hippocampal neurogenesis plays important roles in learning, memory, anxiety and the response to stress and antidepressants. How adult hippocampal neurogenesis regulates these diverse functions is currently unclear. Accumulating evidence suggests that the hippocampus is functionally segregated along its longitudinal axis such that the dorsal hippocampus (dHi) plays a preferential role in spatial learning and memory, while the ventral hippocampus (vHi) plays a preferential role in anxiety and the stress response. We have reported that stress preferentially affects neurogenesis in the vHi rather than the dHi, but the underlying mechanisms remain unknown. Thus, the aim of this study was to determine whether neural precursor cells (NPC) derived from specific areas along the longitudinal axis of the hippocampus differentially respond to the stress hormone, corticosterone. To this end, NPCs from rats (P28) were prepared from dHi, vHi and intermediate hippocampus (iHi) and the effects of several doses of corticosterone (0.5, 1 and 5 μ M) on their proliferation was examined by labelling with BrdU. All corticosterone doses reduced the number of proliferating NPCs irrespective of the region the NPCs were derived from. MTT assays showed that corticosterone-induced reductions in NPC proliferation were not due to reduced cell viability. Current studies are investigating whether NPCs from dHi, iHi or vHi exhibit differential sensitivity to corticosterone-induced reductions in neuronal differentiation. The current data suggest that region-specific effects of stress on neurogenesis are not due to differential sensitivity of region-specific NPCs to corticosterone but are likely due to regional differences in stress-induced afferent neural activity.

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