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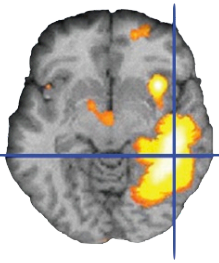

NEUROSCIENCE Ireland

Young Neuroscientists Symposium

Dublin, Ireland

Saturday, 20th September 2014

Trinity Biomedical Sciences Institute,

Trinity College Dublin

Lilly

CAMI Centre for Advanced Medical Imaging

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Welcome Note

Dear Colleagues,

It is with great pleasure that I welcome you to the inaugural Young Neuroscientists Symposium (YNS). Through the hard work of the organising committee, this first YNS has an excellent scientific programme to offer delegates covering topics from across the neurosciences. We have 10 local speakers, over 70 posters, two data blitz sessions, two international keynote speakers, a lecture by the winner of the 2014 Neuroscience Ireland Early Career Investigator Award and a career development workshop all showcasing the cutting edge in neuroscience. On the social side of things, we will have a wine reception followed by a social night – it can't all be work!

On behalf of Neuroscience Ireland and the YNS organising committee, I would like to thank Trinity College Dublin for hosting the event at the Trinity Biomedical Sciences Institute. I would also like to thank Frontiers in Neuroscience for providing an official platform for publishing the abstracts from this meeting. Of course, without financial assistance this day would not be possible so I must extend my gratitude to Science Foundation Ireland for supporting YNS and also to our many sponsors who have allowed us to make the best event possible for our delegates.

We hope that YNS will recur every two years, giving early career neuroscientists the opportunity to present their work to their peers in a friendly and scientifically engaging environment. Looking forward, our aim is to engage with those working on brain-related outside of traditional neuroscience research, such as computer scientists and engineers, and bring them into contact with the core molecules-to-mind investigators. By encouraging interdisciplinary collaborations now, Ireland's young neuroscientists will have a great advantage in their careers by embracing new methods and ways of approaching the many challenges that face brain research. We expect to see many of today's early career neuroscientists become the leaders of their respective fields in the years to come.

Dr. John Kealy,
Chair of the YNS Organising Committee.

YNS Organising Committee

Dr. John Kealy (Chair; Maynooth University)
Dr. Nikita Burke (NUI Galway)
Dr. Danielle Corbett (UCD)
Ms. Erin Dolan (UCC)
Ms. Francesca Farina (Maynooth University)
Ms. Kate Forte (Maynooth University)
Dr. Lorna Lopez (RCSI)
Ms. Roisin McManus (TCD)
Ms. Michelle Naughton (NUI Galway)
Mr. Marc Nugent (DCU)
Ms. Deirdre Twomey (TCD)

Dr. Richard Roche (Neuroscience Ireland President, Maynooth University)

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Conference Programme

08:30-9:00	**Registration** Trinity Biomedical Sciences Institute, Trinity College Dublin
09:00-9:10	**Opening Address** Dr. Richard Roche (Maynooth University)
	Morning Scientific Session *Chairs: Dr. Keith Murphy (UCD) and Dr. Caroline Herron (UCD)*
09:10-10:00	**Prof. Alan Sanfey**, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Netherlands *Fairness, Trust, & Cooperation: Insights from Decision Neuroscience*
	Oral session 1
10:00-10:15	**Olivia Bilbollet-Bahena (TCD)** *Cell-cell communication during thalamocortical development in mice*
10-15-10:30	**James Reynolds (RCSI)** *Proteomic analysis of epileptic tolerance identifies Ubiquitin carboxyl-terminal hydrolase isozyme L1 as a novel contributor to hippocampal neuroprotection*
10:30-10:45	**Keeley Baker (Maynooth University)** *The Development of a Choline Biosensor for Real-Time In-Vivo Monitoring*
10:45-11:00	**Edel Hennessy (TCD)** *Astrocytes are primed by chronic neurodegeneration to produce exaggerated chemokine and cell infiltration responses to acute stimulation with the cytokines IL-1β and TNFα.*
11:00-11:20	**Coffee break**
	Career Development Workshop *Chair: Dr. Yvonne Nolan (UCC)*
11:20-12:00	Dr. Niamh O' Sullivan (UCD) Dr. Dara Dunican (SFI) Industry representative - To be confirmed

	Afternoon Scientific Session *Chairs: Dr. Áine Kelly (TCD) and Dr. Redmond O'Connell (TCD)*
	Oral session 2
12:00-12:15	**Andrew Patrick Allen (UCC)** *Biomarkers of ketamine efficacy in treatment-resistant depression: Focus on BDNF*
12:15-12:30	**Tom Burke (TCD)** *Cognition and Emotional Processing in Amyotrophic Lateral Sclerosis*
12:30-12:45	**Azadeh Beizaei (UCD)** *Isolating rearing decreased midkine expression in hippocampus while its level up-regulated by galanthamine and dopamine*
	Data blitz 1 *Chairs: Dr. Áine Kelly (TCD) and Dr. Redmond O'Connell (TCD)*
12:45-12:50	Donna Cosgrove (NUIG)
12:50-12:55	Luke Alvey (UCD)
12:55-13:00	Éadaoin Griffin (TCD)
13:00-14:00	**Lunch and poster session**
14:00-14:50	**Prof. Michael Heneka,** University of Bonn, Germany *Does Inflammation contribute to neurodegenerative disease?*
14:50-15:20	**Early Career Award winner** Dr. Eva Maria Jimenez Mateos (RCSI) *MicroRNAs in epileptogenesis and epilepsy*
15:20-15:40	**Coffee break**
	Data blitz 2 *Chairs: Prof. Oliver Dolly (DCU) and Dr. Colm Cunningham (TCD)*
15:40-15:45	Elizabeth Kehoe (TCD)
15:45-15:50	Sinead Kinsella (RCSI)
15:50-15:55	Niamh Connolly (RCSI)

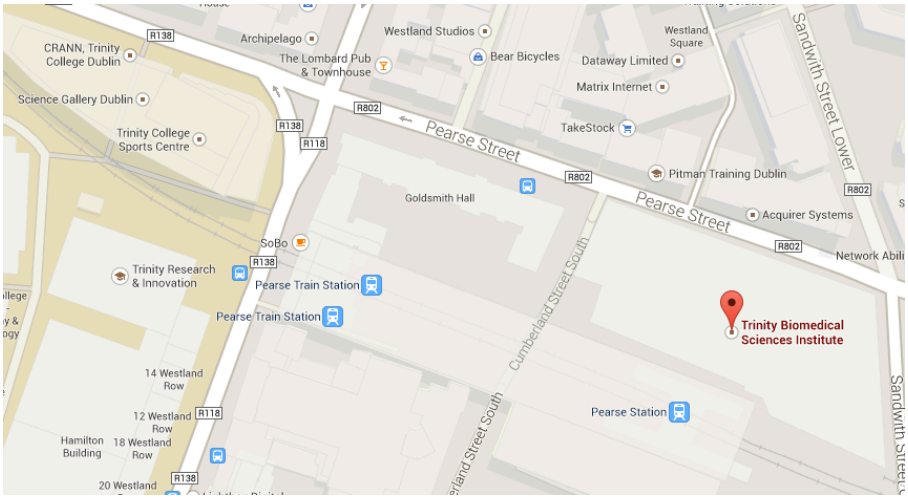
	Oral session 3 *Chairs: Prof. Oliver Dolly (DCU) and Dr. Colm Cunningham (TCD)*
15:55-16:10	**Elizabeth Walshe (Maynooth University)** *Falling Head Over Heels: Investigating the higher-cognitive and electrophysiological processes underlying gait and falls*
16:10-16:25	**Ruth M. Concannon (NUIG)** *Pronounced upregulation of the microglial CB2 receptor in an inflammation driven rat model of Parkinson's disease: Implications for anti-inflammatory disease modification*
16:25-16:40	**Johangir Sajjad (UCC)** *Sex hormones modulate glutamate reuptake by spinal excitatory amino acid transporters in the rat spinal cord*
16:40-17:00	**Closing address and prizes**
17:00-18:30	**Wine reception and finger food**
18:30	**Social event at the Ginger Man**

Venue Information

Trinity Biomedical Sciences Institute,
Trinity College Dublin,
152-160 Pearse Street,
Dublin 2.

Ph: +353-1-8963989 (Reception)

https://www.tcd.ie/biosciences/visiting/



Keynote Speakers

Prof. Michael Heneka, University of Bonn, Germany
14:00-14:50

Michael Heneka is Professor of Clinical Neurology at the University of Bonn, Germany. In addition to this role, he is also Head of the Neuroinflammation Group at the German Center for Neurodegeneration (DZNE), Head of the Neurodegeneration Outpatient Unit at the Klinischen Behandlungs- und ForschungsZentrums für neurodegenerative Erkrankungen (KBFZ) and an Adjunct Professor at the Department of Medicine, University of Massachusetts Medical School, USA. His research covers a wide range of topics in neuroimmunology including neuroinflammation, neurodegeneration, nuclear hormone receptor biology, aminergic neurotransmitter systems, neuronal network function, physiology and pathophysiology of microglia and astrocytes.

Does inflammation contribute to neurodegenerative disease?

Generation of neurotoxic amyloid-ß peptides and their deposition along with neurofibrillary tangle formation represent key pathological hallmarks in Alzheimer's disease (AD). Recent evidence suggests that inflammation may be a third important component which, once initiated in response to neurodegeneration or dysfunction actively contributes to disease progression and chronicity. Microglia is being activated by binding of aggregated proteins or aberrant nucleic acids to pattern recognition receptors which elicit an innate immune response. The latter is characterized by the release of inflammatory mediators including complement activators and inhibitors, chemokines, cytokines, radical oxygen species and enzyme systems. Exogenous as well as endogenous factors may promote and facilitate neuroinflammation in the AD brain. Thus, degeneration of aminergic brain stem nuclei including the locus ceruleus and the nucleus basalis of Meynert may drive inflammation in their projection areas given the antiinflammatory and neuroprotective action of their key transmitters norepinephrine and acetylcholine. Inflammation may not just occur secondary to degeneration, but actively drive amyloid beta aggregation and APP processing. Inhibition of the microglia driven innate immune response at key signalling steps may provide protection. Therefore, antiinflammatory treatment strategies should be considered. Data on microglial activation in AD along with suggestions to modify and alter the pro- into an antiinflammatory phenotype will be reviewed and discussed.

Prof. Alan Sanfey, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Netherlands
09:10-10:00

Alan Sanfey is a Principal Investigator at the Donders Institute for Brain, Cognition and Behavior at Radboud University Nijmegen, the Netherlands. Previously he held positions as Associate Professor of Psychology at the University of Arizona, and as a postdoctoral research fellow at Princeton University. He holds a Ph.D. in Cognitive Psychology from the University of Colorado, and an undergraduate degree in Psychology from University College Dublin, Ireland. He currently heads the Decision Neuroscience group at the Donders Institute, with his research studying both individual and interactive decision-making by combining the methods of behavioral experiments, functional neuroimaging, and formal economic models. A further goal of his group is to use the knowledge gleaned from these studies to inform public policy debates.

Fairness, Trust, & Cooperation: Insights from Decision Neuroscience

Abstract: Our lives consist of a constant stream of decisions and choices, from the mundane to the highly consequential. The standard approach to experimentally examining decision-making has been to examine choices with clearly defined probabilities and outcomes, however it is an open question as to whether decision models describing these situations can be extended to choices that must be made by assessing the intentions and preferences both of oneself and of another social partner. This class of social decision-making offers a useful approach to examine more complex forms of decisions, which may in fact better approximate many of our real-life choices. I will present both behavioural, pharmacological, and neural data from several experiments where we have used existing and novel economic games to observe how players decide in real, consequential, social contexts, and will discuss how we can use these brain insights to build better models of human social preferences, incorporating both psychological and neurobiological constructs.

Early Career Investigator Award 2014

Dr Eva Jimenez-Mateos (RCSI)

Eva Jimenez-Mateos did her undergraduate degree in Biochemistry in the Autonoma University Madrid before undertaking a PhD in the mechanisms which regulate neuronal migration and differentiation in the early development under the supervision of Prof. Avila in the Centro de Biologia Molecular, Madrid. Following her PhD, she moved to Ireland and started to work in the laboratory of Prof. David Henshall in the RCSI, where she has focussed on the molecular mechanism of epilepsy, mainly the role of microRNAs in epileptogenesis and its implication as possible new therapeutics targets.

MicroRNAs in epileptogenesis and epilepsy

MicroRNAs (miRNA) are a class of short non-coding RNA which function as post-transcriptional regulators of gene expression, repressing and refinement protein translation. Injury to the brain as status epilepticus (SE) can cause damage to specific areas of the brain such as the hippocampus and results in the development of epilepsy. This original insult to the brain is predicted to impact levels of multiple proteins involved in neuronal morphology and function, gliosis, neuroinflammation, and cell death. In parallel, emerging work in animal models and human epilepsy has found selective miRNAs changes within the brain during epileptogenesis or in established epilepsy. Functional analysis by intracerebral delivery of chemically modified antisense oligonucleotides (antagomirs) has been shown to have potent, specific and long-lasting effects on brain levels of miRNAs. We have recently reported that blocking a neuronal-specific miRNA (miR-134) has a neuroprotective effect, reduced seizure severity during status epilepticus and reduced the later emergence of recurrent spontaneous seizures.

Career Development Workshop

The Career Development Workshop is an interactive panel discussion where representatives from academia, industry and funding institutions will talk about career choices available to neuroscientists based in Ireland. Audience members are strongly encouraged to ask questions and engage in a conversation with the panel members in order to find out what their options are in the next stages of their careers. Are you a postgrad looking to do a postdoc? Are you a postdoc thinking of making the move to industry? This is the workshop for you.

Dr. Niamh O'Sullivan (UCD)
Dr. Niamh O'Sullivan is a lecturer in neuroscience and genetics in UCD's School of Biomolecular and Biomedical Sciences. She is also a principal investigator studying the mechanisms underpinning human neurodegenerative disorders such as motor neuron disease and Alzheimer's disease. Her laboratory makes use of the experimental model organism the fruit fly (*Drosophila melanogaster*) to better understand the functions of genes linked to the human diseases. Niamh began her career with a degree in Genetics from Trinity College Dublin before moving to UCD where she undertook a PhD investigating the genetic events that occur during memory formation. She continued to work on this successful project before receiving a Marie Curie Fellowship to study neurodegeneration using the fruit fly at the University of Cambridge. Her work at Cambridge suggested a new explanation as to why neurons are dying in some forms of human disease. Niamh received a Junior Research Fellowship from Imperial College London to continue her research before being appointed her academic position in UCD last summer.

Dr. Dara Dunican (SFI)
Dr Dunican graduated from NUIG with a BSc in Biochemistry before completing a PhD in Biochemistry in TCD in 1996 in the area of phospholipase signalling in glioma cells. Dr Dunican subsequently carried out postdoctoral research in the MRC Centre for Developmental Neurobiology in London, and the Research Institute of Molecular Pathology in Vienna, in the latter position working on the mechanisms of asymmetric cell division in *Drosophila* neuronal stem cells. After completing a post-doctoral position back in Ireland in TCD, Dr Dunican joined SFI as a Scientific Programme Officer in 2013. As a member of the Post award team in SFI Dr Dunican's current role includes the management of a portfolio of research awards in the Biomedical, Diagnostics and Pharmaceutical areas, and responsibility for a number of SFI Programmes including the Technology Innovation Development Award (TIDA) and the President of Ireland Young Researcher Award (PIYRA).

Oral Abstracts

1.1 Cell-cell communication during thalamocortical development in mice

10:00-10:15 – Molecular Biology and Genetics

Bibollet-Bahena O, Hokamp K, Yoshida Y, Fujisawa H, Mitchell KJ. Trinity College Dublin, Dublin 2, Ireland. bibolleo@tcd.ie

During the development of the mammalian brain, a staggeringly complex network of connections self-assembles between billions of neurons. The accuracy of this process is essential for the correct functioning of the nervous system, and defects in the wiring of the brain are thought to underlie many serious psychiatric and neurological disorders. Although different molecules involved in the guidance of neurons have been identified to date, it is speculated that many more are implicated. We are interested in guidance cues involved in thalamocortical connectivity to explore patterns of combinatorial gene expression in development. We used a bioinformatics approach to mine mouse expression data generated by the Allen Brain Institute in order to identify a list of genes encoding surface proteins that are differentially expressed across development in the thalamus (temporal clustering analyses), or across the thalamus in the adult brain (spatial clustering analyses). The cluster analyses identified novel proteins potentially involved in axon pathfinding and synaptogenesis. Among these surface proteins, we have discovered novel roles for Sema6B and PlexinA4 at the stage of thalamocortical axon (TCA) invasion into the somatosensory cortex (also known as the barrel cortex in rodents). Sema6B and PlexinA4 mutant mice have disrupted barrel organization with TCAs not clustering properly. Moreover, layer IV cells are found at abnormal positions within the hollows in Sema6B mutant mice. This study is providing new relevant candidates to explore in order to gather more insights into the proper genetic program of brain connectivity.

1.2 Proteomic analysis of epileptic tolerance identifies Ubiquitin carboxyl-terminal hydrolase isozyme L1 as a novel contributor to hippocampal neuroprotection

10:15-10:30 – Diseases and Disorders

Reynolds J, Jimenez-Mateos E, Miller-Delaney S, Cao L, Bian F, Zhou A, Henshall D. Royal College of Surgeons, Ireland, Dublin 2, Ireland. jamesreynolds@rcsi.ie

Brief, non-harmful seizures can render the brain temporarily resistant to cell death induced by prolonged, otherwise injurious seizures (epileptic preconditioning). Previous profiling work has identified coordinated mechanisms of neuroprotection associated with epileptic preconditioning including suppression of neuronal excitability-associated transcripts and reduced microRNA expression. We elaborated on these studies through quantitative mass spectrometry of ipsilateral hippocampal lysates at 3h and

24h following focal-onset status epilepticus (SE, 1µg intraamygdala kainic acid) in preconditioned (tolerance) and sham-preconditioned (injury) C57BL6/J mice. SE predominantly induced upregulation of proteins (63.9%-77.5% of regulated proteins) indicating a global translational response. Ontological analysis revealed functional clusters among changes in the proteome, including regulation of the cytoskeleton, protein localisation and trafficking, and vesicle/membrane dynamics. Profiling also noted divergences that may underpin endogenous neuroprotection in tolerance. We validated proteomic data using Western blotting and immunofluorescence, confirming that Ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL1), a deubiquitinating enzyme, is downregulated in the hippocampus at 24h following SE. Inhibition of UCHL1 depleted the hippocampus of monomeric ubiquitin and PSD-95. Inhibition prior to SE decreased Lorazepam responsivity, exacerbated seizure-induced neuronal death (at 24h) and increased hippocampal expression of p53 and cleaved MDM2 (at 4h). SE was associated with a downregulation of antisense Uchl1 (AsUchl1), a pro-translational lncRNA targeting Uchl1 mRNA, at 8h, with no observed change in Uchl1 transcription. These data suggest that the post-transcriptional loss of UCHL1 following SE is deleterious to neuronal survival and are considered in light of rapamycin therapy, of which AsUchl1 is a putative target.

1.3 The Development of a Choline Biosensor for Real-Time In-Vivo Monitoring.

10:30-10:45 - Other

Baker K, Bolger F, Lowry J. National University of Ireland Maynooth, Maynooth, Co. Kildare, Ireland. Keeley.l.baker@nuim.ie

Choline is the precursor and metabolite of the neurotransmitter acetylcholine. The availability of choline influences acetylcholine synthesis and release which is involved in learning and short term memory. The dysregulation of the cholinergic system is recognised as a determinant of cognitive decline in age-related neurodegeneration. Long term in-vivo electrochemistry (LIVE) facilitates the direct sampling of the brain extracellular environment of freely moving animals through the implantation of microvoltammetric/amperometric sensors. LIVE involves the application of a potential across an electrode-solution interface to oxidise or reduce species close to the electrode surface in order to generate a faradaic current. This allows the change in concentration of a particular species to be measured continuously. Here we report the development of a biosensor for the detection of choline where characterisation in-vitro has determined the sensitivity and selectivity of the sensor towards choline and potential endogenous interferents. The sensor also characterised in the in-vivo environment has successfully monitored neurochemical fluctuations in choline levels in freely-moving animals.

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

10:45-11:00

Hennessy E, Cunningham C. Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland. hennesed@tcd.ie

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-1β 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-1β were administered intracerebrally to ME7-inoculated mice and normal brain homogenate-injected (NBH) controls. Both IL-1β and TNF-α produced robust IL-1b synthesis in ME7 microglia but this was very limited in NBH animals. In addition there was strong nuclear localisation of the NFkB 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 neutrophils, macrophage/microglia and T cells in the diseased brain and increased CNS cellular proliferation. 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.

2.1 Biomarkers of ketamine efficacy in treatment-resistant depression: Focus on BDNF

12:00-12:15 – Diseases and Disorders

Allen AP, Naughton M, Clarke G, Dowling J, Walsh A, Ismail F, Shorten G, Scott L, Cryan JF, Dinan TG. Biosciences Institute, University College Cork, Cork, Ireland. andrewallen@ucc.ie

Brain derived neurotrophic factor (BDNF) is a potential biomarker of ketamine's antidepressant efficacy in treatment-resistant depression (TRD). However, although the clinical response to ketamine can persist for one week or longer, it is unknown if changes in BDNF are stable over this time period, or following multiple infusions. Age- and gender-matched patients with TRD (N = 17) and healthy controls (HC; N = 20) were recruited. TRD patients received 1-3 ketamine infusions (0.5mg/kg) at visits one week

apart. Blood samples were collected at baseline in all participants, and within patients at 24 hours following first infusion and at 2 hours and 1 week following each infusion. Treatment response was defined at each timepoint as 50% + reduction in Hamilton Depression Rating Scale score. A majority of patients showed a clinical response to ketamine at all sampling time points. The TRD group had lower serum BDNF at baseline than healthy controls (TRD; M = 13.3 ng/ml, SD = 6.6, HC: M = 19.4, SD = 8.9, p = 0.03). Ketamine responders had increased serum BDNF at 1 week post first infusion (Mean change = 4.59, SD = 4.26, p = 0.03) but did not show this response at subsequent infusions-nor did they show a rapid response in BDNF (at 2 or 24 hours following any infusion). Lower serum BDNF at baseline in TRD patients compared to healthy controls may predict a sustained response to ketamine treatment, but BDNF may not show a rapid increase, nor increase following multiple ketamine infusions.

2.2 Cognition and Emotional Processing in Amyotrophic Lateral Sclerosis

12:15-12:30 - Cognitive and Behavioural - Human

Burke T, Hardiman O, Pender N. Academic Unit of Neurology, Trinity College Dublin, Dublin 2, Ireland. burket2@tcd.ie

Background: Executive dysfunction is known to occur in early stages of Amyotrophic Lateral Sclerosis (ALS). Social cognitive processes are considered by some to be subsumed by executive functions and brain atrophy is known to occur in cortical and subcortical regions involving cognitive functions in ALS, congruent with the neuroanatomical basis for social cognitive processes. Objectives The aims of this research were to investigate social-cognitive decline, relative to auxiliary cognitive decline. Methodology Participants were recruited as part of an ongoing population based study investigating cognitive heterogeneity in ALS. After removing patients whom were C9orf72 positive, participants were grouped based on whether patients had bulbar (n=20) or spinal onset (n=39) ALS. Gender, age, IQ and education matched healthy controls were used to generate culturally specific comparative data for within-patient analyses (N=59). Results On affective ToM, there was a significant difference between bulbar and spinal onset patients on this task (p= .001). Comparing bulbar and spinal patients standardized scores of executive function yielded no significant differences. Discussion and Conclusions Results indicate the presence of social-affective deficits within ALS, prior to characteristic executive and language dysfunction, for bulbar onset patients without comorbid deficits. These findings shall be discussed in relation to current research and cognitive theory, as well as ongoing population based ALS research. Acknowledgements: The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no (259867);the JPND SOPHIA project; Irish Health Research Board CSA2012/11 and the Irish Institute of Clinical Neuroscience (12549. 201616).

2.3 Isolating rearing decreased midkine expression in hippocampus while its level up-regulated by galanthamine and dopamine.

12:30-12:45 - Cognitive and Behavioural - Animal

Beizaei A, Chan C, Al Bayyari S, Murphy KJ. Conway Institute, University College Dublin, Dublin 4, Ireland. a.beizaee@gmail.com

Midkine (MK) is a heparin-binding cytokine that promotes growth, survival and migration of target cells. MK is widely expressed during the embryonic period where it likely plays a key role in promoting the survival and migration of neurons, neurite extension and enhancing neuronal differentiation. We previously have shown that MK is up-regulated in the rat hippocampus at mRNA and protein level following learning. Moreover, intracerebroventricular injections of MK enhanced memory consolidation and recall in water maze spatial learning and an odour reward discrimination task. Here, we have used isolation rearing to investigate if MK is affected by environmental insults associated with disruption of cognitive function. We have also used in vivo treatments and primary cell culture to investigate if MK is regulated by the pro-cognitive drug galanthamine or the neurotransmitters glutamate, dopamine and serotonin. We show that animals reared in isolation have significantly decreased mRNA levels of MK in the hippocampus and this effect was not seen in the prefrontal cortex. The Alzheimer's treatment, galanthamine, increased the levels of MK in the hippocampus of both social control and isolated adult Wistar rats. Finally, of the three neurotransmitters investigated only dopamine displayed the ability to up-regulate MK. Levels of MK in the hippocampus are shown to correspond with challenges that either enhance or impair cognitive function. In the future it may be possible to harness MK as a pro-cognitive therapy.

3.1 Falling Head Over Heels: Investigating the higher-cognitive and electrophysiological processes underlying gait and falls

14:00-14:15 - Cognitive and Behavioural - Human

Walshe E, Commins S, Roche RAP, PattersonM. Department of Psychology, John Hume Building, National University of Ireland Maynooth, Co. Kildare, Ireland. elizabeth.a.walshe@gmail.com

The role of cognition and cortical activity in walking gait and falls is increasingly evidenced by attentional demands in dual-task (DT) studies, and increased fall-risk in cognitively impaired clinical samples (Holtzer et al., 2007; Plummer-D'Amato, et al., 2008). However, the specific higher-level cognitive and neural processes need to be identified for effective clinical assessment and intervention. Experiment 1 compared changes in gait speed from normal walk to a range of cognitive DT trials (targeting motor processing, executive working memory, visuo-spatial executive processing, and simple language processing) in young (n=20) and older adults (n=17). Older adults were significantly slower at normal walking ($p<0.05$). Both groups evidenced decreased speed on all DT conditions, with the executive function domain tasks evidencing greater dual-task costs (evidenced more in the older group; $p<0.005$). Experiment 2 compared normal walking

characteristics, cognitive performances and associated EEG neural activity across 3 groups; young adults (n=20), older adults without a history of falls (non-fallers; n=13) and older adult fallers (n=7). Executive control, motor processing, multisensory integration and pre-attentive processing were assessed while sitting, with concurrent recording of EEG/ERPs. Age-related differences were evident on cognitive performances and reflected in ERP events, as expected, with the Stroop task revealing further latency differences between older fallers and non-fallers on the P3 component. Both studies evidence the role of executive function processing: this has implications for developing targeted screening assessments and interventions for those at risk in the community, as well as clinical populations. Research funded by the Irish Research Council.

3.2 Pronounced upregulation of the microglial CB2 receptor in an inflammation driven rat model of Parkinson's disease: Implications for anti-inflammatory disease modification.

14:15-14:30 - Neuropharmacology

Concannon RM, Okine BN, Finn DP, Dowd E. Department of Pharmacology & Therapeutics, National University of Ireland Galway, Galway, Ireland. r.concannon1@nuigalway.ie

The endocannabinoid system has recently emerged as a potential anti-inflammatory target to break the self-sustaining cycle of neuroinflammation and neurodegeneration that is associated with neurodegenerative diseases. However, in order to facilitate the investigation of cannabinoid drugs in neurodegenerative disease, the changes that occur in the endocannabinoid system in response to different degenerative triggers needs to be elucidated. Therefore, the aim of this study was to investigate and compare the changes that occur in the endocannabinoid system in neurotoxic and inflammation-driven models of Parkinson's disease. Male Sprague Dawley rats were given a single, intra-striatal injection of the dopaminergic neurotoxin, 6-hydroxydopamine, or the bacterial inflammagen, lipopolysaccharide (LPS). Animals underwent behavioural testing for motor dysfunction on Days 7, 14 and 28 days, and were sacrificed on Days 1, 4, 14 and 28 post-surgery (n=8 per treatment, per timepoint). Changes in the endocannabinoid system were investigated by qRT-PCR, mass spectrometry and immunohistochemistry. Following injection of 6-hydroxydopamine or LPS into the rat striatum, we found that expression of the cannabinoid type 2, (CB2) receptor was significantly elevated which correlated significantly with an increase in microglial activation. Interestingly, the increase in CB2 receptor expression in the inflammation-driven model was significantly more pronounced than that in the neurotoxic model. Moreover, elevation of striatal endocannabinoid levels was also observed in the LPS model but not the 6-hydroxydopamine model. Thus, this study has shown that the endocannabinoid system is dysregulated in different models of Parkinson's disease, and has also revealed significant differences between the models themselves. This study indicates that targeting the CB2 receptor may represent a viable target for anti-inflammatory disease modification in

Parkinson's disease. Acknowledgements: The authors gratefully acknowledge the support of Health Research Board Grant no. (HRA_POR/2012/12).

3.3 Sex hormones modulate glutamate reuptake by spinal excitatory amino acid transporters in the rat spinal cord.

14:30-14:45 - Neurophysiology

Sajjad J, Cryan JF, O'Mahony S. University College Cork, Cork, Ireland. 113221826@umail.ucc.ie

Introduction Females are more sensitive to pain, and some painful disorders including irritable bowel syndrome are more prevalent in women. Gender differences have been shown in many molecular targets along visceral pain pathways. In the spinal cord, Glutamate (an excitatory neurotransmitter) is regulated by excitatory amino acid transporters; EAAT1 & EAAT2 in spinal cord. Aim of Investigation Here we further explore potential sex differences in pain perception, originating from lumbosacral spinal cord. We studied glutamate reuptake levels across estrus cycle and investigated the effects of estrogen and riluzole (neuroprotective agent) on it. Methods Slices of lumbosacral spinal cord were taken from Sprague Dawley rats. These were incubated with tritium labelled aspartate. The function of spinal glial EAATs was measured in terms of intracellular radioactivity normalised to measured protein value of slices (Scintillation per minute/mg). Results Glutamate reuptake was similar in males and females, in diestrus phase of estrus cycle. Pre-incubation of cord slices with estrogen significantly reduced reuptake in males ($P<0.05$). In females reuptake was found to vary across the phases of the estrus cycle with lower levels in proestrus and estrus ($P<0.05$). Riluzole significantly enhanced reuptake in estrus phase only ($P<0.05$). Conclusions Taken together, our data shows that spinal EAATs are sensitive to the effects of estrogen and thus may play an important role in gender differences in pain. Thus drugs enhancing EAAT function such as riluzole may provide pain relief, by reducing synaptic glutamate, in high estrogen states.

Poster Abstracts

P01 Peripheral nerve striation frequency is higher and axonal path length is longer in Trembler-J mice.

Data Blitz 1: 12:50-12:55 - Diseases and Disorders

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Charcot Marie Tooth disease type 1A (CMT1A) occurs due to a mutation of peripheral myelin protein 22 (PMP22). The Trembler-J mouse has an identical spontaneous mutation, and is a model for CMT1A. In situ wild type (WT) mice sciatic nerves had a striation (band of Fontana) frequency of 7 ± 0.64 bands per mm but the Trembler-J mice appeared to lack nerve striations. Isolated WT sciatic nerves had a similar band frequency (8.1 ± 0.90 bands/mm; $p = 0.35$; $n = 5$), but the frequency of Trembler-J mice was much higher (21.2 ± 1.83 bands/mm; $p = 0.0002$; $n = 5$) (means ± S.E.M.; student's t-test). Confocal microscopy revealed that axons within sciatic nerves of WT mice follow a sinuous path, dictating band frequency. The median wavelength and amplitude of WT axons were 115.1μm ($n = 21$) and 7.99μm ($n = 37$) respectively. Axons within the sciatic nerves of Trembler-J mice followed a more irregular sinuous path, with a shorter median wavelength of 34.77μm ($n = 38$) and smaller median amplitude of 5.01μm ($n = 37$). Axonal length exceeded nerve length by 9% in WT animals and 34% in Trembler-J mice. In conclusion, the bands of Fontana are due to the sinuous undulating course of axons. The axons within WT peripheral nerves are longer than the nerves in which they are contained, and the axons of Trembler-J mice are longer than WT ones. The increased length of Trembler-J axons may contribute to the impaired conduction velocity seen in these animals.

P02 A Neurophysiological Metric for Derived Valence

Cognitive and Behavioural - Human

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Humans, through language, can react emotionally to arbitrary events in the absence of any direct conditioning histories. To date, research on valence-related frontal alpha asymmetry (FAA) effects typically involved gauging reactions to S-R procedures employing stimuli pre-established with emotional properties a priori and thus provide, at best, a partial explanation of the human's emotional repertoire. The presentation focuses on individualized upper alpha power asymmetries (IAA) computed over anterior regions as sensitive markers of shifts in derived valences established in vivo. The importance of examining derived valence from a neurophysiological perspective is discussed. Recently published examples of the IAA will be touched on.

P03 Characterization of the rat forced swim test as a model for detecting antidepressant activity

Neuropharmacology

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Although the rat forced swim test (FST) is the most extensively used preclinical test for antidepressant efficacy, there are several caveats that can affect the interpretation of the results. For example, treatment is typically subacute (i.e. 3 doses over 24h), whilst clinically antidepressant efficacy requires chronic administration. Furthermore, stimulant drugs are false positives due to general locomotor activation. The scoring method for the principal behavioural indices (i.e. immobility, climbing and swimming) also varies, either being scored continuously or in time bins. Thus, we examined subacute and chronic treatment with the tricyclic antidepressant desipramine (DMI, 10mg/kg, s.c.) and subacute treatment with the false positive amphetamine (AMP, 1mg/kg, s.c.) in young adult male Sprague-Dawley rats in the FST, using continuous and time sampling scoring approaches. Subacute treatment involved dosing at 24, 5 and 1h prior to the FST, whilst chronic treatment consisted of 14 daily doses, with the last dose occurring 1h before the FST. Home cage locomotor activity was measured in the hour preceding the FST. Data were analysed using One-Way ANOVA, followed where appropriate by a post hoc Student-Newman Keuls. All treatments reduced immobility and increased climbing, whilst subacute AMP also increased swimming, with similar effects regardless of scoring method. Locomotor activity was reduced with subacute and chronic DMI, whilst subacute AMP caused an increase in this parameter. In conclusion, this study demonstrated that significant effects can be found irrespective of scoring method, and that the FST can be refined to detect chronic antidepressant effects and false positive drugs.

P04 The effects of subacute administration of buprenorphine and the novel opioid modulator samidorphan on home-cage locomotor activity in rats

Neuropharmacology

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The opioidergic system regulates motivation, reward and mood. Complex alterations in ambulation are reported following administration of buprenorphine (BUP), a partial mu-opioid receptor agonist.[1,2] We examined the locomotor activity profile observed following administration of BUP alone, and in combination with samidorphan (SAMI, a novel mu-opioid receptor antagonist), in a rat home-cage tracking system.[3] Male Sprague-Dawley rats (250-350 g) received three subcutaneous injections mimicking the regimen typically employed for the forced swim test, i.e., 24, 5

and 1 hrs prior to the usual point of swim exposure. Rats (n=6-7/group) received saline (1 ml/kg), BUP (0.1 mg/kg), SAMI (0.3 mg/kg or 3 mg/kg) or a combination of BUP with either 0.3 mg/kg or 3 mg/kg SAMI. Home-cage locomotor activity (HCLA, distance moved) was tracked over 24 hrs. Data were analysed using ANOVA followed by Student Newman Keuls post-hoc test. $P \leq 0.05$ was deemed significant. BUP increased HCLA from 4-6 hrs, an effect attenuated by SAMI. BUP in combination with the lower dose of SAMI increased HCLA at 2 hrs post-injection. Following the second administration, SAMI alone reduced HCLA from 30-60 min (0.3-3 mg/kg). BUP alone elicited a time-dependent biphasic response, with decreased activity from 30-60 min followed by hyperactivity after 2 hrs; the hyperactive response was again attenuated by SAMI. Following the third administration, both BUP and SAMI reduced HCLA from 20-40 min, an effect not altered by the combination. In conclusion, BUP-induced increases in locomotor activity are subject to modulation by samidorphan, a mu-opioid receptor antagonist. Future studies will utilise this dosing regimen in the forced swim test, as the combination of these compounds does not elicit a stimulant effect at the usual time-point of swim exposure.

P05 Time to contact decision making with and without sensory evidence

Cognitive and Behavioural Neuroscience - Animal

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When trying to cross a road we have to detect and predict if an oncoming car will reach us or if it is safe to cross. This task is further complicated by the occlusion of the car by other vehicles. While we seamlessly make these decisions every day, little is known about the underlying neuronal processes. Furthermore, it is hypothesised that this process is less reliable in patients with Dystonia. Here, nine healthy participants performed a visual time to contact (TTC) task while electroencephalography (EEG) data was acquired. Participants were instructed to press a button when a looming ball reached two vertical lines on the screen. The initial size and velocity was manipulated to avoid habituation to the task. There were 3 trial types, 1) in which ball completed 100% of the trajectory and reached the target vertical lines; 2) in which the ball faded-out after 75% of the trajectory; 3) in which the ball faded-out after 50% of the trajectory. The response times showed that participants consistently overestimated the TTC. The response locked EEG analysis for the 100% trials showed that the amplitude accumulated until it peaked coinciding with the response, which is in line with previous EEG findings on decision making. The amplitude of the response locked EEG for the 50% and 75% trials accumulated in a similar fashion to the 100% trials but plateaus when the stimulus faded away. This could suggest that when the sensory signal is not present, participants perform a linear prediction.

P06 Light-at-Night and Mood: Examining the Role of Sex

Cognitive and Behavioural - Animal

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The idea that unnatural light exposure during the night may have deleterious health consequences has been termed the "light-at-night" hypothesis. It has recently been shown that exposure of rodent models to low-level night-time illumination elicits a number of behavioural and physiological changes, presumably mediated in part through alterations within the circadian timekeeping system. Amongst such changes are increases in depressive-like behaviours. This appears to be of particular interest as there is a long-recognised link between depression and circadian rhythm changes in patients. In this study we wish to expand on the findings to date and examine whether sex plays a role in the effects if light-at-night on mood in rodents. This is an important question as the prevalence of depression is higher amongst females than males, and there is an increasing awareness in biological psychiatry that rodent models of affective disorders must explicitly address the role of sex.

P07 Single-cell imaging of bioenergetic responses to neuronal excitotoxicity and oxygen and glucose deprivation

Data Blitz 2: 14:55-15:00 - Diseases and Disorders

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Excitotoxicity is a condition occurring during cerebral ischaemia, seizures, and chronic neurodegeneration. It is characterised by over-activation of glutamate receptors, leading to excessive Ca2+/Na+ influx into neurons, energetic stress and subsequent neuronal injury. We and others have previously investigated neuronal populations to study how bioenergetic parameters determine neuronal injury, however such experiments are often confounded by population-based heterogeneity and contribution of effects of non-neuronal cells. Hence, we here characterised bioenergetics during transient excitotoxicity in primary neurons at the single-cell level using fluorescent sensors for intracellular glucose, ATP, and activation of the energy sensor AMP-activated protein Kinase (AMPK). We identified ATP depletion and recovery to energetic homeostasis, along with AMPK activation, as surprisingly rapid and plastic responses in two excitotoxic injury paradigms. We observed rapid recovery of neuronal ATP levels also in the absence of extracellular glucose, or when glycolytic ATP production was inhibited, but found mitochondria to be critical for fast and complete energetic recovery. Employing an injury model of oxygen and glucose deprivation, we identified a similarly rapid bioenergetics response, yet with incomplete ATP recovery and decreased AMPK activity. Interestingly, excitotoxicity also induced an accumulation of intracellular glucose, providing an additional source of energy during and after excitotoxicity-induced energy depletion. We identified this to originate from extracellular,

AMPK-dependent glucose uptake and from intracellular glucose mobilisation. Surprisingly, cells recovering their elevated glucose levels faster to baseline survived longer, indicating that the plasticity of neurons to adapt to bioenergetic challenges is a key indicator of neuronal viability.

P08 Regulation of the transcription factor REST/NRSF and target genes by learning and glutamate in the rat hippocampus

Cognitive and Behavioural Neuroscience – Animal

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Memory consolidation requires glutamate-mediated hippocampal synaptic plasticity underpinned by de novo gene transcription. Previously in our laboratory a microarray study characterised the transcriptional profile in the first 24h post-learning. Bioinformatics analysis identified REST/NRSF, a master repressor of neuronal genes, as a putative transcription factor (TF) involved in memory. Here we found that basal REST is expressed in the adult rat hippocampus, with higher levels in pyramidal neurons than in granular neurons. Following passive avoidance (PA) animals showed learning-associated REST regulation that was time and region-specific. At 1h following PA, REST was upregulated in the three main regions of the hippocampus, the DG, CA1 and CA3. At 3h REST was downregulated in the DG and CA1. Next we cross-referenced our list of learning-associated genes with a list of REST target genes and found 88 coincident genes, mainly regulated at 2-6h post-learning. Three of these genes, Slitrk1-2 and Gabbr1, function in synaptic plasticity. Using qPCR we found that these three genes were downregulated at 2h following PA, and Slitrk1 was upregulated at 3h, agreeing with REST regulation at protein level. Lastly, we investigated whether memory-associated REST regulation could be driven by physiological increases in glutamate. In primary hippocampal neurons, REST was increased at 1-3h post-glutamate treatment. At 1h REST regulation was AMPA receptor-dependent while at 3h it was NMDA receptor-dependent. In conclusion, we propose a novel role for REST during memory consolidation as a regulator of learning-associated genes, possibly driven by glutamate via AMPA and NMDA receptors.

P09 Polygenic scores from the MiR137 pathway explain variability in cognitive performance patients with schizophrenia and controls.

Data Blitz 1: 12:45-12:50 - Cognitive and Behavioural - Human

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Genome-wide association studies (GWAS) have identified rs1622579, within an intronic region of MiR137, as a risk variant for schizophrenia. This variant is associated with deficits in verbal episodic memory and altered connectivity. As MiR137 interacts with several other GWAS variants (e.g. ZNF804A, TCF4, CACNA1C), we tested whether these cognitive effects were

associated with polygenic risk in a set of identified downstream targets of MiR137. Polygene scores were calculated by (1) selecting all identified downstream genetic targets of MiR137; (2) selecting risk SNPs within each of these genes based on risk estimates from the Psychiatric Genomics Consortium, (3) ascribing a score to each participant based on total number of risk alleles carried. To estimate these polygene effects on cognitive deficits associated with SZ (IQ, memory, attention, theory of mind) linear regression was performed. We carried out three separate analyses: all cases/controls (n=586), patients with a broad psychosis diagnosis (n=489) and patients with schizophrenia/schizoaffective disorder (n=379). MiR137 polygenic risk scores were significantly higher in the broad and narrow diagnosis groups compared to controls ($F(2,1081) = 5.52$, $p<0.01$). Poorer performance on measures of IQ, memory, and attention were each found to be associated with higher MiR137 polygene scores ($p<0.05$). The amount of variance explained on the measures varied between 1% and 2.6%. These data support a modest but significant influence of this MiR137 'pathway' on multiple measures of cognition. These effects were significantly more apparent when considered in combination with its interacting risk variants than when the risk variant was considered in isolation.

P10 Expression and functional analysis of nucleic acid sensors in astrocytes and microglia.

Neuroimmunology

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The recognition of nucleic acids is essential in combating viral and bacterial pathogens. The sensors and pathways involved in RNA/DNA detection have only recently been discovered and have expanded over the last number of years. TLR9 was the first DNA sensor to be discovered followed by the cytosolic DNA receptors which include members of the PYHIN family, DAI and the enzyme cyclic GMP-AMP synthase (cGAS). The PYHIN family are so called as they contain an N-terminal PYRIN domain and a C-terminal HIN domain. These proteins bind DNA directly via their HIN domains culminating in the production of anti-viral and pro-inflammatory cytokines. Microglia and astrocytes can respond to cytosolic poly(I:C), via RIG-like receptors, however the contribution of DNA sensors has not been fully explored in neuroimmune cells. Furthermore, the contribution of individual cell types, in particular astrocytes, has been confounded by difficulties in obtaining pure populations devoid of contaminating microglia. Finally, most studies reported to date have used poly(dA:dT) as a DNA mimetic, however this can be reverse transcribed to RNA by RNA pol III and is capable of activating RNA sensors. We have carried out extensive expression profiling of the newly described DNA sensors in purified astrocytes and microglia and have found that both cell types have the capacity to induce a strong anti-viral response in the presence of immune stimulatory DNA and RNA. Furthermore

we have found that key sensors are upregulated in a murine model of neurodegeneration and this is dependent on the type I interferon, IFN-β.

P11 Successful lipreading of silent speech strengthens the correlation between cortical activity and the corresponding speech envelope

Cognitive and Behavioural Neuroscience – Human

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Neuroimaging research has shown that the presentation of visual speech in the absence of auditory speech activates primary auditory cortex (Calvert et al., 1997; Pekkola et al., 2004). Recent electrophysiological work has demonstrated that an estimate of the acoustic envelope can be reconstructed from electroencephalography (EEG) data recorded during visual-only (V) speech (Crosse and Lalor, 2014). While the authors suggested that this effect was driven by the neural response to motion in the visual stimulus, it remains a possibility that auditory cortical activity tracks the amplitude envelope of the unheard acoustic signal during successful silent lipreading. Here we test this hypothesis by examining the effects of recalling a known speech passage during silent lipreading on EEG. Subjects were trained on a one-minute audiovisual (AV) speech stimulus prior to testing. They were then presented with 14 trials of the same AV stimulus, 14 trials of the same stimulus without the audio (V-trained) and 14 trials of different V stimuli with which they were not familiar (V-untrained). Subjects were instructed to recall the auditory speech in their head during the V-trained condition and to detect target words during each of the three conditions. Subjects performed this target word detection significantly better in the V-trained condition than in the V-untrained condition. Preliminary analysis of the EEG data suggests that cortical activity during the V-trained condition is more closely correlated with the acoustic envelope than the V-untrained condition. We interpret this as evidence of auditory cortex synthesising tracking of the acoustic envelope during silent lipreading.

P12 An investigation of the interaction between the CPP and the N400

Cognitive and Behavioural Neuroscience - Human

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In a decision-making scenario, the human brain goes through a process that leads up to the moment a decision is made. In electrophysiology, this neural process can be observed using standard time-locked averaging techniques; a centro-parietal positivity (CPP) increases steadily and peaks at the time of response. It was recently shown that the build-up of the CPP was observed even when participants failed to respond or falsely identified a target (O'Connell et al., 2012). It has long been established that when presented with a semantically unexpected stimulus, such as an anomalous word at the end of a sentence, a negative component with a similar topography to the CPP, known as the N400, is elicited (Kutas & Hillyard, 1980). Here we

investigate whether the processes underlying the CPP and N400 components interact with each other when they are elicited together. We recorded 128-channel EEG in 4 healthy participants whilst they read 200 English sentences. The last word of each sentence either made sense (sensical) or did not make sense (nonsensical), the latter of which elicited an N400. Immediately after each sentence, the participant responded to whether it was sensical or nonsensical, hence eliciting a CPP. Examination of the time-locked average response revealed that a CPP was produced, followed closely by a negativity, the N400, when the sentence did not finish as expected. Furthermore, the amplitude of the CPP was enhanced during nonsensical trials compared to sensical trials, suggesting an interaction between the processes manifested by the two components.

P13 Cytokine release inhibitor drug, CRID3, inhibits the NLRP3 inflammasome in glia.

Neuroimmunology

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Assembly of the cytosolic multiprotein complex, the NLRP3 inflammasome, results in activation of caspase 1 and processing of IL-1β to permit release of the active form of the cytokine. Recent findings indicate that a novel NLRP3 inhibitor, cytokine release inhibitor drug 3 (CRID3), effectively inhibits inflammasome activation in bone marrow-derived macrophages. The aim of this study was to investigate the effects of CRID3 on NLRP3 inflammasome activation in glia. Primary cultures of purified microglia, purified astrocytes and mixed glia, generated from neonatal mice, were pre-treated with lipopolysaccharide (LPS; 1μg/ml) for 4 hours and thereafter incubated with different concentrations of CRID3 for 30 minutes, after which time human Ab1-40 (4.3μM) + Ab1-42 (5μM) was added. Incubation continued for a further 24 hours. ELISA, RT-PCR and flow cytometry was used to assess cytokine expression and caspase 1 activity. Ab significantly increased release of IL-1β in LPS-pretreated microglia and astrocytes and this was significantly attenuated by CRID3 in a dose-dependent manner; CRID3 did not affect release of TNFα or IL-6 in either cell type. In parallel with the increase in IL-1b release, Ab also significantly increased expression of activated caspase 1 activity in LPS-treated microglia and astrocytes, represented by the CD11b+ and CD11b- populations in mixed glial cultures; this effect was significantly attenuated by CRID3. Consistent with a specific effect on IL-1b processing, CRID3 exerted no significant effect on the Ab-induced increase in mRNA expression of IL-1β, TNFα and IL-6 in LPS-pretreated microglia or astrocytes. These data show that CRID3 selectively inhibits inflammasome activation in both glial subtypes and identify it as a potential therapy for neurodegenerative disorders which are characterized by neuroinflammatory changes.

P14 Pushing the envelope: scalp recorded EEG encodes phonetic features of continuous speech.

Cognitive and Behavioural Neuroscience - Human
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How the human brain processes speech remains elusive. However, recent studies have shown that cortical activity tracks the temporal envelope of speech. Techniques based on regression methods have been developed for mapping this representation of speech to the recorded neurophysiological signal. Further results have been achieved using a spectro-temporal representation, which is obtained by partitioning the acoustic signal into a number of frequency-bands and calculating the envelope of each band. Although these methods are powerful tools that have addressed several previously unanswered questions, recent work with intra-cranial recordings (ECoG) has shown that high-gamma cortical activity tracks higher-order representations of speech based on the phonetic structure. Our research shows that a phonetic representation of speech can optimise the mapping to the low-frequency EEG signal. Specifically, 90 minutes of continuous, natural speech was presented to 10 subjects. Multivariate linear-regression was then employed on the recorded data and predictions of the electrophysiological signals were obtained using leave-one-out cross-validation. A model that combines phonetic and acoustic features was shown to be a better predictor of the EEG than the ones based only on the acoustic information for all subjects. Indeed, a phonetic representation carries higher-order information than both the temporal and spectro-temporal envelope representations and hence we discuss the nature of the improvement shown in light of this. In particular, we argue that our phonetic model accounts for important differences across phonemes, especially between the responses to vowels and non-vowels.

P15 First Onset Depression and the Hypothalamic-Pituitary-Adrenal Axis: An Investigation of State and Trait Biomarkers

Diseases and Disorders
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Depression is a major public health issue, effecting about 6% of late adolescents. Additionally, it is an extremely heterogeneous psychiatric disorder with many subgroups that we hope to identify through analysis of several biomarkers. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is the most robust and consistent finding in the search for the biological etiology of major depressive disorder, therefore our study hopes to identify links between alterations in the HPA axis and varying phenotypes of depression. With our samples, we hope to measure and identify HPA-axis dysregulation by examining cortisol levels in saliva and urine, altered tryptophan/kynuerenine ratios implicated in 5HT imbalance, altered brain activity in brain regions associated with depression such as the

hippocampus and amygdala during a functional neurogimaging task, and changes in the epigenome that have recently been implicated in MDD. Our cohort is unique because of the collection of samples at the patients' first presentation with depression, as well as at time points during and after recovery from the episode. Our goal n size will be 100 patients, and as it is a longitudinal study, biomarker changes from illness to recovery may help to develop tests that could help identify the depressed state.

P16 The Development of a Biosensor for Real Time Monitoring of Brain Extracellular Superoxide

Other

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Superoxide anion is the primary species of the reactive oxygen species (ROS) and is generated as a reduced intermediate of molecular oxygen. Superoxide in biological samples lies within the narrow range of 50-200nM. When their production exceeds the body's natural body to deal with these potentially cytotoxic species a variety of pathological conditions may occur including stroke, cancer and neurodegeneration. The objective of this research is the development of a novel biosensor to detect superoxide (O2-) using LIVE. This will allow the real-time in-vivo recording of this ROS. LIVE requires a micro sensor to be implanted into a specific brain region and local changes in the concentration of substances to be monitored with sub-second time resolutions over extended periods. Experiments were performed using a standard three electrode cell consisting of a working reference (Saturated Calomel Electrode (SCE)) and an auxiliary electrode (silver wire) in 5mL of Phosphate Buffer Solution (pH 7.4) containing 0.002U of xanthine oxidase in a glass electrochemical cell. Experiments were performed using CPA at +700mV vs. SCE. The optimum sensor design thus far is Pt/SOD/0.5%GA/2%PEI which has a linear region slope of 1.73 ± 0.17 nA/μM (n = 4) showing that this sensor displays a high sensitivity to superoxide at physiological levels.

P17 Investigating the temporal and phase structure of oscillatory mechanisms in auditory binding.

Cognitive and Behavioural - Human

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Previous research examining the psychophysical mechanisms concerned with combining tonal signals into auditory Gestalten has revealed a rate (33 Hz) and time-specific reaction-time (RT) enhancement for inharmonic tones. The aim of the present study was to investigate an enhancement effect that is dependent on a temporal relationship defined by the frequency of the oscillatory response, thus not confined to oscillations of 33 Hz. Participants responded as rapidly and accurately as possible to the presence or absence

of a target tone in the second of a sequence of two sounds (N = 13). The parameters of these stimuli were designed to be proportionately equivalent to the 33 Hz stimuli in the paradigm which produced the previous RT enhancement. The results revealed an inharmonic enhancement effect that was significant for all frequencies. However, the findings suggest that the phase relationship is more general than hypothesised. By converting ISIs for each level of rate into fractions of the evoked oscillatory cycle and mapping the inharmonic target present (ITP) RT as a function of this cyclic phase, an anti-phase relationship was revealed. The suggestion is that when neurons in the oscillatory activity established by the prime are maximally deactivated (i.e. correspond to a phase angle of 180°), sounds that elicit a slightly different neural response, such as inharmonics, become most salient. This supports the hypothesis that certain frequencies facilitate the feature binding process dependent on the temporal parameters of the oscillatory responses involved.

P18 Training Dependent Changes in Spatial Memory and Zif268 Expression in the Hippocampus and Prefrontal Cortex

Cognitive and Behavioural - Animal

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Immediate early genes (IEGs) are strongly implicated in learning-related plasticity and memory formation. Research has demonstrated that activation of IEGs in the hippocampus correlates highly with spatial memory performance. Our aim is to illustrate training dependent changes in spatial memory retention and IEG expression in the prefrontal cortex and hippocampus. Rats were trained to locate a hidden platform in the Morris water maze for five or ten days using two visual, distal cues. Twenty-four hours post-acquisition animals were divided into 4 groups and retested (n = 8/group). Two groups that had been trained for five and ten days, respectively, were tested in the presence of both cues (as per acquisition). The two remaining groups, also having been trained for five and ten days, respectively, were tested with only one cue present. Ninety minutes post-retention, brains were removed and processed for expression of the well-known IEG Zif268. Behavioural results demonstrated that all animals acquired the task. Further, groups retested in the presence of two cues showed strong retention, irrespective of training length. Of the groups tested with one cue, only the group trained for ten days showed good retention, while the group trained for five days were impaired. Significantly higher Zif268 expression was found in all brain regions for the one cue cue group compared to the control group after five days. This group difference disappeared after 10 days of training. Findings indicate training-related behavioural changes which may correspond to a shift in regional IEG expression over time.

P19 Unc-51-like kinase 4 heterozygous mice display an anxiety-like behaviour profile and alterations in the GABAergic system within the amygdala

Cognitive and Behavioural Neuroscience - Animal

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Gamma-Aminobutyric acid (GABA) transmission within the amygdala is associated with emotional processing in anxiety disorders [1]. Recent evidence has demonstrated that unc-51-like kinase 4 (Ulk4) is expressed on GABAergic neurons and depletion of Ulk4 in vitro and in vivo results in compromised neuronal function [2]. We examined if heterozygous deletion of the Ulk4 gene in mice alters anxiety- or depressive-like behaviour, and GABAergic neuronal density and receptor subunit expression in the amygdala. Female C57Bl/6N wildtype (WT) and Ulk4+/- mice were assessed for anxiety-like behaviour in the elevated plus maze (EPM) and marble burying test, depressive behaviour in the forced swim test (FST) and locomotor activity in the open field test. Animals were sacrificed and brains processed for glutamate decarboxylase (GAD67) immunohistochemical staining or PCR array analysis of GABA-related genes in the amygdala. Ulk4+/- mice spent less time on the open arms of the EPM and buried more marbles in the marble burying test than WT animals. Time spent immobile in the FST and locomotor activity did not differ between groups. The density of GAD67+ neurons in the basolateral amygdala, and expression of GABAA receptor subunits (β1, δ, ε, ρ) and GABA transporter, GAT-3, in the amygdaloid tissue of Ulk4+/- mice were reduced when compared with WT counterparts. These data indicate a possible reduction in GABAergic function within the amygdala of Ulk4+/- mice which may underlie the anxiety-related phenotype observed in these animals. Acknowledgements: Funding received from SFI (RSF1135), NUI Galway (RSU002) and Molecular Medicine Ireland CTRSP.

P20 Sex-dependant alterations in locomotor activity and interferon expression following TLR3 activation

Neurophysiology

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Toll-like receptors (TLRs) are important in mediating innate immune response to bacterial and viral infection. Several lines of evidence indicate the expression and function of TLR2 and 4 differ between males and females. However, it is unknown if sexual dimorphic effects are observed in response to activation of TLR3. This study investigated the effect of systemic administration of the TLR3 agonist polyI:C on behavioural and inflammatory responses in male and female rats. Homecage locomotor activity monitoring revealed that female rats display greater locomotor activity when compared to male counterparts. PolyI:C (3mg/kg) resulted in a pronounced reduction

in homecage locomotor activity of female rats over the 2-8hr period post administration, with a reduction in males only observed in the 4-6hr period. The spleenic expression of interferon (IFN)α was increased 8hrs following polyI:C administration in female rats, while IFNβ was increased at both 4 and 8hr, when compared to saline-treated counterparts. In comparison, polyI:C failed to alter the expression of IFNα in male rats, but enhanced IFNβ expression at the 4hr timepoint. The expression of the NFκB-inducible cytokine TNFα was increased at 4hr while expression of the IRF3/NFκB inducible chemokine IP-10 was increased at 4hr and 8hrs following polyI:C administration, in both male and female rats. Taken together, these data demonstrate sexual dimorphic effects of TLR3 activation on the expression of type1 interferons and locomotor activity. Acknowledgments: This study was supported by the Hardiman Postgraduate Scholarship, the Discipline of Physiology, NUI Galway and Science Foundation Ireland Research Frontiers Project (Grant no. 11/RFP/NES/3175).

P21 Low-tech sensory interventions and computer based assessment of spatial neglect following stroke

Cognitive and Behavioural - Human

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Spatial neglect occurs in approximately one-third of stroke cases and results in a loss of conscious awareness for the contralesional visual field (typically the left). In practical terms this phenomenon can have huge impact on the daily lives of patients; they may fail to shave the left half of their face or leave the left side of a meal uneaten. It also presents hazards as patients bump into things increasing fall risk and the chance of accidental injury. This deficit in spatial attention also has implications for the rehabilitation of other domains following stroke, particularly motor deficits. Furthermore, it can result in unnecessary care placements due to unsatisfactory performance of Activities of Daily Living (ADL) tasks necessary for independent living. Rehabilitation of spatial neglect therefore is highly important. Previous methods have used interventions tied to sensory modalities in an attempt to rehabilitate this deficit and the current and future research will employ low-tech, simple methods tied to visual, auditory and motor domains in pursuit of the same goal. We have also developed a computer based tool for assessment of spatial neglect using the Leap Motion Controller (LMC). The assessment paradigm evaluates presence and severity of neglect and has the potential to give clinicians a more nuanced picture of a patient's neglect, compared to the more binary classification given by current pen and paper methods. We believe these novel methods could represent an effective tool for the assessment and rehabilitation of spatial neglect following stroke.

P22 The Effect of Neurofeedback Training on Attention Networks

Cognitive and Behavioural - Human

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The present study aimed to examine the effect of Z-score LORETA Neurofeedback Training (NFT) on attention. Participants (N=20, 10 males) were quasi-randomly assigned to either the NFT group (n=10, 5 males) or the Control group (n=10, 5 males). In the experimental group, the participants first completed the Attention Network Test (ANT). Following this, they completed five sessions of NFT where 4-8 Hz theta activity in the Anterior Cingulate Cortex (ACC) was trained. It was hypothesised that training theta activity in the ACC would lead to improved attentional executive function as measured by the ANT. Following the five NFT sessions the experimental group completed the ANT again. The control group, who did not perform any NFT, completed the ANT twice with a gap of two weeks. As hypothesised, there was a statistically significant improvement in attentional executive function scores by the NFT group compared to the control group. There was also a significant change in theta activity following EEG analysis. The findings of this study are discussed in relation to the literature.

P23 Antidepressant prescription patterns in Ireland: 2004-2013

Neuropharmacology
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There have been growing concerns about the increasing incidence of antidepressant use in Ireland, which has been particularly played out in the media over the last couple of years. Thus, the purpose of the current study was to investigate antidepressant prescribing patterns over the 10-year period from 2004 to 2013, by requesting such information from the HSE database. This period encompasses the peak of the "Celtic Tiger" economy, as well as covering the subsequent years of economic instability. The population of Ireland has increased by approx. 14% during this period. The total number of antidepressant prescriptions has increased 74% during this 10-year period. However, all tricyclic antidepressants (TCAs), with the exception of amitriptyline, have shown a reduction in prescribing. With selective serotonin reuptake inhibitors (SSRIs), there has been a 61% increase of prescriptions with the most notable increases seen with escitalopram and sertraline, and a reduction in the prescribing of paroxetine. In the "other antidepressants" category, marked increases have been seen with mirtazapine and duloxetine, with an 88% increase of prescriptions for trazodone and 58% increase for venlafaxine; monoamine oxidase inhibitors (MAOIs) have shrunk to negligible levels. The reduction in TCA and MAOI levels reflects a shift to safer alternatives, as seen by the rise in prescriptions for the newer antidepressants. Paroxetine use has declined as a consequence of the concerns raised about the drug's safety in certain patient groups. In conclusion, this study demonstrates a dramatic and sustained increase in antidepressant prescribing in Ireland, with drug-specific patterns that can be explained by prevailing best practice.

P24 Pharmacological inhibition of fatty acid amide hydrolyase attenuates social behavioural deficits in the valproic acid animal model of autism

Diseases and Disorders

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The (endo)cannabinoid system modulates emotionality and social behaviours, and alterations in this system has been demonstrated in several animal models of autism. This study evaluated the effect of inhibiting fatty acid amide hydrolyase (FAAH), the primary enzyme responsible for the catabolism of anandamide, on behavioural responding in the valproic acid (VPA) rat model of autism. Pregnant female Sprague Dawley rats received VPA (600mg/kg s.c.)/saline on gestational day G12.5 and behavioural testing was carried out on offspring during adolescence. On the day of testing animals received the FAAH inhibitor PF3845 (10mg/kg i.p.)/vehicle and behaviour was assessed in the hotplate test (thermal nociception) and 3-chamber sociability test (social preference, repetitive behaviour, locomotor activity and exploratory behaviour). Male rats prenatally exposed to VPA exhibited thermal hyperalgesia, reduced social and exploratory behaviour, and enhanced repetitive behaviour when compared to saline-treated counterparts. Systemic administration of PF3845 attenuated the social impairment observed in VPA exposed male animals without altering nociceptive, repetitive or exploratory behaviour. In comparison, female rats prenatally exposed to VPA rats exhibited enhanced repetitive and reduced exploratory behaviour, effects which just failed to reach statistical significance. PF3845 did not alter social, repetitive or thermal responding, but reduced locomotor activity and exploratory behaviour in VPA, but not saline, exposed females. These data indicate sexual dimorphic effects of FAAH inhibition on behavioural responding in an animal model of autism, and support an important role for FAAH in the regulation of social behaviour in autistic males. Acknowledgements: The Wellcome Trust Biomedical Vacation Scholarship and Physiology/Pharmacology NUI Galway.

P25 Cyclooxygenase-1 dependent prostaglandins mediate susceptibility to systemic inflammation-induced acute cognitive dysfunction

Data Blitz 1: 12:55-13:00 - Cognitive and Behavioural - Animal

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Systemic inflammatory events often precipitate acute cognitive dysfunction in elderly and demented populations. Delirium is a highly prevalent neuropsychiatric syndrome characterised by acute inattention and cognitive dysfunction, for which prior dementia is the major predisposing factor and systemic inflammation is a frequent trigger. Inflammatory mechanisms of delirium remain unclear. We have modelled aspects of delirium during

dementia by exploiting progressive neurodegeneration in the ME7 mouse model of prion disease and superimposing systemic inflammation induced by bacterial endotoxin, lipopolysaccharide (LPS). Here, we have used this model to demonstrate that the progression of underlying disease increases the incidence, severity and duration of acute cognitive dysfunction. This increasing susceptibility is associated with increased CNS expression of cyclooxygenase 1 (COX-1) in microglia and perivascular macrophages. The COX-1 specific inhibitor SC-560 provided significant protection against LPS-induced cognitive deficits and attenuated the disease-induced increase in hippocampal and thalamic PGE2 while the COX-2 specific inhibitor NS-398 was ineffective. SC-560 treatment did not alter levels of the pro-inflammatory cytokines IL-1b, TNF-a, IL-6 or CXCL-1 in blood or brain, but systemic IL-1RA blocked LPS-induced cognitive deficits and systemic IL-1β was sufficient to induce similar deficits in the absence of LPS. Furthermore, the well-tolerated COX inhibitor, ibuprofen was protective against IL-1b-induced deficits. These data demonstrate that progressive microglial COX-1 expression and prostaglandin synthesis can underpin susceptibility to cognitive deficits, which can be triggered by systemic LPS-induced IL-1b. These data contribute to our understanding of how systemic inflammation and ongoing neurodegeneration interact to induce cognitive dysfunction and episodes of delirium.

P26 Iron loading with ferrocene dysregulates iron homeostasis in an organotypic hippocampal brain slice model

Diseases and Disorders

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Background: Iron is known to accumulate in the brain under chronic neurodegenerative conditions such as those seen in individuals with Alzheimer's disease, Parkinson's disease or Multiple Sclerosis. Clarification of how brain iron is regulated could reveal a role for iron in neurodegeneration. Objective: Develop an organotypic hippocampal slice model of iron loading Materials & Methods: Organotypic hippocampal slices derived from postnatal P10/P11 rats were cultured for 10 days before iron exposure. Endogenous iron content was also assessed in non-cultured postnatal hippocampus. Iron levels were quantified using a ferrozine colorimetric assay and viability was assessed using a LDH assay. Results: For the first time in organotypic hippocampal slices, we demonstrated differential uptake of iron after iron loading with ferrous ammonium sulphate, ferric citrate or ferrocene (FAS FC, or Ferr, respectively; 10 uM). Ferr produced a significant 1.3-fold increase in total iron compared with vehicle (8.05±0.98 and 4.97±0.57 nmol/mg, respectively; $p<0.05$). FAS and FC, however, caused only 1.2- and 1-fold increase ($P>0.05$). One uM Ferr produced optimal iron 1.6-fold accumulation ($P<0.05$). This ferrocene-induced increase in iron content was accompanied by minor toxicity, as indicated by a 1.3-fold increase in LDH activity compared with vehicle ($p<0.05$). In adjunct to this in vitro work, iron content throughout the

postnatal brain aged P10-11 and also during hippocampal development (P08-P45; n=3) was characterised. Notably, the levels of iron detected in cultured hippocampal slices were similar to those in the equivalent aged non-cultured P21 hippocampus (i.e. 5.61 ± 0.615 and 6.62 ± 1.06 nmol/mg, respectively; $p>0.05$), which indicates that iron content develops as normal in this model. Conclusions: This slice model of iron loading appears to be a promising platform for the study of iron regulation in the CNS.

P27 Time-dependent effects of the TrkB agonist, 7,8-dihydroxyflavone, on spatial learning in the rat.

Cognitive and Behavioural Neuroscience – Animal

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Our previous studies(REF1) show that one week of exercise or icv injection of Brain-Derived Neurotrophic Factor (BDNF) enhances hippocampal-dependent learning and increases cell proliferation (an early step in neurogenesis) in the rat. Here, we assess the effects of 7,8-dihydroxyflavone (7,8-DHF), an agonist of the BDNF receptor TrkB(REF2), on spatial learning and neurogenesis. Male Han Wistar rats (n=28) were divided into Vehicle (Veh n=14) and 7,8-DHF-treated (n=14), then subdivided into day 9 or day 30 cognitive testing groups. Rats were injected daily with 7,8-DHF (500ul IP; 5mg/kg in 0.9% NaCl) or vehicle (0.9% NaCl) for 7 days. BrdU (500ul IP; 50mg/kg in 0.9% NaCl); a thymidine analogue that labels dividing cells, was injected daily following 7,8-DHF or vehicle. Half of the Veh and 7,8-DHF groups (n=7 per group) were trained in an Object Displacement (OD) Task on day 8, tested on Day 9 and killed following testing. The other half were trained on day 29, tested on day 30 and killed following testing. Brains were hemisected; one hemisphere was processed for analysis of BrdU by immunocytochemistry. Dentate Gyrus, hippocampus, and entorhinal cortex were subdissected free from the other hemisphere, and prepared for Western Blot analysis, ELISA, and PCR. The 7,8-DHF group displayed significantly enhanced memory on Day 30 compared to Vehicle ($p<0.05$; 2-way ANOVA); this enhancement was not observed in 7,8-DHF-treated rats tested on Day 9. The timing of these experiments indicates that the mechanism underlying this cognitive enhancement may involve neurogenesis. Tissue is being analysed to test this hypothesis.

P28 FAAH-mediated modulation of TLR3-induced neuroinflammation in the rat hippocampus.

Neuroimmunology

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Several studies have demonstrated that (endo)cannabinoids regulate toll like receptor (TLR)4 induced neuroinflammation, however, there is a paucity of studies investigating their effects on inflammation associated with the activation of other TLRs. The present study examined the effects of

inhibiting FAAH, both systemically and centrally, on the expression of TLR3-responsive genes in the rat hippocampus. Animals received systemic or central administration of the FAAH inhibitor URB597 or vehicle, 30 minutes prior to systemic administration of the TLR3 agonist polyI:C or saline. Animals were killed 4 hours post polyI: C and the expression of the interferon's and cytokines determined using qRT-PCR. Concentrations of anandamide (AEA), 2-arachidonylglycerol (2-AG) and the N-acylethanolamines, N-palmitoylethanolamide (PEA) and N-oleoylethanolamide OEA, were determined using LC-MS-MS URB597 increased hippocampal levels of PEA and OEA, but not AEA or 2-AG. Systemic administration of URB597 increased expression of IFNα and IFNγ, in the presence of polyI:C. The polyI:C-induced increase in IL-1β and TNFα expression were attenuated, while concurrently IL-6 expression was augmented by systemic URB597.In comparison, central administration of URB597 did not alter the expression of the type 1 interferon's but attenuated the polyI:C-induced increase in IFNγ and IP-10. Furthermore, this treatment regime attenuated the polyI:C-induced increase in TNFα and IL-6 expression, and concurrently increased the IL-10 expression. Taken together, these data demonstrate that increasing FAAH substrates within the brain elicits anti-inflammatory effects which support an important role for FAAH-mediated regulation of TLR3-induced neuroinflammatory responses.
Acknowledgements: Funding provided by Science Foundation Ireland Research Frontiers Project (Grant no. 11/RFP/NES/3175).

P29 Regulation of microRNAs in the Amygdala by the Gut Microbiota: Implications for Brain and Behaviour

Diseases and Disorders

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Background: The ability of the gut microbiota to influence brain and behaviour is a relatively new area of research. One of the most consistent findings is in relation to anxiety-like behaviours and the stress response. However, the molecular mechanisms underpinning this remains poorly understood but may well be due to alterations in gene expression. It is unknown if the gut microbiota also recruits microRNA machinery to wield this influence. The aim of this experiment was to establish if germ-free animals have altered microRNA expression patterns in the amygdala, a key brain region for anxiety and fear. Methods: Using Next Generation Sequencing, we assessed alterations in microRNA expression in the amygdala of conventional, germ-free and colonized germ-free mice. Results: The microbiota-deficient germ-free animals display altered expression of 54 miRNAs in the amygdala compared to conventional animals. However, colonisation of the germ-free animals post weaning normalises the expression of 6 miRNAs, suggesting partial reversibility of the cumulative molecular changes. Within these, miR-182 and mir-183 have been previously linked to amygdala-dependent stress-related outputs in preclinical models Conclusion: This is, to our knowledge, the first

demonstration that the gut microbiota can regulate miRNA expression in the amygdala. Further studies are required to verify the exact contribution of these miRNAs to amygdala-dependent anxiety-related behaviours. The results from this study will be essential in increasing our understanding of the molecular mechanisms underpinning the impact of microbiota-gut-brain axis communication on both brain and behaviour. Further analysis of mRNA targets may reveal important molecular pathways for microbiota-gut-brain axis signalling.

P30 Assessment of the neurotrophic effects exerted by glial cell line-derived neurotrophic factor (GDNF) following delivery of neurotrophin-secreting stem cells to the rat brain in the lipopolysaccharide model of Parkinson's disease

Neuropharmacology
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The delivery method of GDNF has hampered its efficacy as a neuroprotectant in Parkinson's disease(PD). Ex vivo gene therapy, in which suitable cells, such as bone marrow-derived mesenchymal stem cells (MSCs), genetically engineered to overexpress GDNF prior to transplantation may be more beneficial for GDNF delivery than direct brain infusion of the neurotrophin. In this study, we used an inflammatory model of PD (the lipopolysaccharide model) to assess the ability of transplanted GDNF-GFP-MSCs to protect against LPS-induced neuroinflammation, neurodegeneration and behavioural impairment. 30 male Sprague Dawley rats were used in this experiment. Motor performance was assessed daily using Stepping and Whisker tests pre- and post-surgery. Rats were performance matched into 3 groups (LPS, LPS + GFP-MSCs, LPS + GDNF-GFP-MSCs; n=10/group). Both cell groups received a transplant of either 200,000 GFP-MSCs or 200,000 GDNF-GFP-MSCs. One day post-transplantation, all rats received a unilateral infusion of LPS (10µg in 2µl sterile saline) into the substantia nigra. Rats were sacrificed by transcardial perfusion-fixation and their brains preocessed for post-mortem quantitative immunohistochemistry. Injection of LPS into the substantia nigra induced a pronounced inflammatory response which resulted in 20% loss of nigrostriatal dopaminergic neurons and a mild, transient effect on contralateral motor dysfunction. While neither GFP-MSCs nor GDNF-GFP-MSCs transplanted into the striatum protected against motor dysfunction or the nigrostriatal pathway as a whole, dense areas of TH-staining proximal to the transplant site were observed. Importantly, this effect was observed only in the GDNF-GFP-MSC transplanted group. This demonstrates protection and/or sprouting of the dopaminergic terminals induced by trophic effects of secreted GDNF in the LPS-lesioned rats and thus highlights the potential of ex vivo gene therapy using GDNF-GFP-MSCs.

P31 The Effects of Cannabidiol in models of Alzheimer's Disease: A Study of Long Term Potentiation

Diseases and Disorders

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Cannabidiol (CBD), a non-psychoactive constituent of the cannabis plant, has been shown to have anti-inflammatory, antioxidant and neuroprotective properties, and thus has been implicated as a potential therapeutic agent in the treatment of neurological disorders, including Alzheimer's Disease (AD). We examined the effects of CBD on Long term Potentiation (LTP); a cellular form of learning and memory, in both an acute and a chronic treatment model of AD. In both treatment models, LTP was induced via high frequency stimulation of the CA1 Schaffer-collateral pathway (2 trains of 100Hz for 1s with a 30s inter-stimulus interval) and measured 60min following induction. In acute experiments, hippocampal slices from naive 6-12 week c57/Bl6 mice were perfused for 30min prior to LTP induction with amyloid beta (Aβ 1-42) protein (500nM), in the form of amyloid derived diffusible ligands. Aβ perfusion caused attenuation of LTP. Pre-treatment with CBD (10μM) for 30 min prior to application of Aβ reversed this attenuation of LTP. In our second model, LTP was assessed in hippocampal slices from 9 month old APPswe/PS1dE9 mice and their age-matched littermates, treated with vehicle or CBD (10mg/kg) i.p. for 29 days. We found that LTP levels were unaltered in both vehicle and CBD treated wild type mice, however, the level of LTP in vehicle treated APPswe/PS1dE9 mice was depressed compared to control. Chronic CBD treatment significantly enhanced the level of LTP in APPswe/PS1dE9 mice to control levels. Our data support a neuroprotective role for cannabidiol in our models of Alzheimer's Disease.

P32 Altered CB1 receptor signalling in the lateral PAG of Wistar-Kyoto rats is associated with enhanced formalin-evoked nociceptive behaviour compared with Sprague Dawley rats

Neuropharmacology

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Recent evidence suggests that impaired functioning of the endocannabinoid system in the descending inhibitory pathway of Wistar-Kyoto (WKY) rats may contribute to their hyperalgesic phenotype (Rea et al., 2013). The aim of this study was to investigate whether altered expression and/or functionality of CB1 receptors in the PAG underlie hyperalgesia to formalin injection in WKY versus SD rats. Adult male SD and WKY rats were used. Tissue levels of endocannabinoids and cannabinoid CB1 receptor mRNA in the PAG were measured by LC-MS-MS and qRT-PCR, respectively. Another cohort of male SD and WKY rats received bilateral microinjection of vehicle or CB1 receptor agonist, arachidonyl-2-chloroethylamide (ACEA; 0.05pmol), into the lateral PAG (lPAG) and formalin-evoked nociceptive behaviour and

quantitative immunohistochemical analysis of c-Fos staining in the RVM and spinal cord were assessed. WKY rats displayed enhanced formalin-evoked nociceptive behaviour and lower CB1 receptor mRNA and increased levels of the endocannabinoid 2-arachidonoyl glycerol (2-AG) in the lPAG than SD rats. Intra-lPAG administration of ACEA reduced formalin-evoked nociceptive behaviour with a concomitant increase in neuronal activity in the RVM and reduced neuronal activity in the dorsal horn of the spinal cord in SD rats only. In contrast, intra-lPAG administration of ACEA to WKY rats potentiated nociceptive behaviour towards the end of the formalin trial. Enhanced formalin-evoked nociceptive behaviour in WKY rats is associated with increased 2-AG levels and down-regulation of CB1 receptor mRNA expression in the lPAG. CB1 receptor activation in the lPAG of WKY rats did not modulate formalin-evoked nociceptive behaviour or neuronal activation in the RVM or spinal cord. Thus, dysfunction of the endocannabinoid system within the descending inhibitory pain pathway may contribute to the WKY hyperagelsic phenotype.

P33 Cognitive dissonance induction in everyday life: an fMRI study

Cognitive and Behavioural Neuroscience – Animal

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Cognitive dissonance describes the discomfort we feel when we consider psychologically inconsistent notions at the same time. This discomfort motivates us to expend cognitive and behavioural efforts to reduce it and restore cognitive consistency. Although the psychological processes of dissonance are well established, the neural mechanisms have only begun to be explored. This fMRI study explored the neural substrates of cognitive dissonance during dissonance induction. A novel task was developed based on the results of a separate item selection study (n=125). Items were designed to generate dissonance by prompting participants to reflect on everyday personal experiences that were inconsistent with values they had expressed support for. Three control conditions (justification, consonance, non-self related inconsistency) were used for comparison. Items of all four types were presented to each participant (n=14) in a randomized design. Results showed that in comparison with the control conditions the dissonance experience led to higher levels of activation in several brain regions including the anterior cingulate cortex (ACC), anterior insula (AI), inferior frontal gyrus, and precuneus. These brain regions have been implicated in emotional processing, cognitive conflict and control, social cognition, as well as self-referential memory retrieval and attentional motor control. In no case did we find stronger activation during the induction phase for the control conditions. The results support current perspectives which emphasize the role of the ACC and AI in dissonance processing. Less extensive activation in the prefrontal cortex than in some previous studies is consistent with this study's emphasis on dissonance induction, rather than reduction.

P34 Altered resting state functional connectivity of the hippocampus and thalamus in amnestic mild cognitive impairment: an fMRI study

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Data Blitz 2: 14:45-14:50 - Cognitive and Behavioural - Human

Alzheimer's disease (AD) is sometimes preceded by a stage known as amnestic mild cognitive impairment (aMCI), which is characterised by memory deficits abnormal for age in the absence of dementia. In the current study we investigated the resting state functional connectivity (FC) of two important subcortical brain structures, the hippocampus and thalamus using functional magnetic resonance imaging (fMRI) in a group of 15 aMCI subjects and 16 healthy controls (HC). The groups were matched for age, gender and education level. Compared to the HC, the aMCI group showed significantly reduced FC of the hippocampus and thalamus to a number of brain regions ($p < 0.05$ corrected in all cases), particularly in the frontal and parietal cortex. FC was reduced between both right and left thalamus and bilateral supramarginal gyrus and inferior frontal gyrus (IFG) and left cerebellum; and between both right and left hippocampus and areas of frontal, temporal and parietal cortex. This study is being conducted as part of a wider project which incorporates diffusion imaging tractography of limbic white matter pathways. In the same cohort there was found to be almost no difference in white matter indices of the fornix, which directly connects the hippocampus and thalamus, suggesting that FC may be an earlier biomarker for connectivity changes in aMCI. This study is being conducted as part of the NeuroSKILL project, and is funded under the European Regional Development Fund through the Interregional 4A Ireland Wales Programme 2007 - 13.

P35 The course of cognitive deficits in first episode psychosis and clinical correlate.

Cognitive and Behavioural - Human

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Neurocognitive deficits in first-episode psychosis (FEP) are a common feature of the disorder. The course of cognitive deficits in FEP over time is less certain. We examined cognitive deficits in FEP individuals compared to healthy controls (HCs) over 4 years to determine the variation of cognitive function after the onset of a psychotic illness and the relationship with clinical variables. Twenty three FEP patients (8 female, mean age±SD, 33 ±8) and 21 healthy volunteers (8 female, 34±8) underwent neuropsychological testing at first presentation and on average four years later (mean duration±SD, 4±0.8 yrs) using the MATRICS cognitive consensus battery. Variation in cognitive scores over time was examined using ANCOVA and controlling for baseline scores, age and gender. Relationships between clinical variables and cognition were examined using correlation analysis

and regression. The FEP group performed poorer on most cognitive tests compared to healthy controls at follow-up. There was significant group differences in three areas of cognition; trail making test (TMT), verbal fluency and verbal learning with scores improving less in patients compared to controls. The change in other cognitive metrics from baseline to follow-up in the FEP group did not differ statistically from the controls. Duration of untreated psychosis, negative and positive symptoms in the patient group were not associated with cognitive tests where group differences were found. Cognitive deficits in those who experienced a psychotic episode largely remained stable over time however there was evidence for potential vulnerabilities in TMT, fluency and verbal learning which was independent of clinical variables.

P36 LPS-induced locomotor and inflammatory responding in the stress sensitive WKY rat

Other

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Recent data has demonstrated altered immune function, including enhanced expression of toll-like receptors (TLRs), in the stress-hypersensitive Wistar Kyoto (WKY) rat. This study examined the effect of acute administration of the bacterial endotoxin and TLR4 agonist lipopolysaccharide (LPS) on locomotor activity and pro-inflammatory cytokine levels in WKY rats in comparison to the less stress-sensitive Sprague-Dawley (SD) strain. Home-cage locomotor activity monitoring revealed that male WKY rats exhibit reduced locomotor activity when compared to SD counterparts. Systemic administration of LPS (1 or 5mg/kg) or saline increased locomotor activity of all animals in the 30 minute time period post injection, an effect significantly blunted in WKY rats. Locomotor activity of SD LPS-treated rats was significantly reduced in between 90-150 minutes post administration when compared to saline-treated counterparts, an effect not observed in WKY rats. WKY rats exhibits lower liver and spleen to body weight ratio when compared to SD counterparts, an effect not altered by LPS. Assessment of pro-inflammatory cytokine levels revealed the LPS did not alter the levels of TNF-α, IL-6 or IL-1β in serum but significantly increased IL-1β, levels in liver of both SD and WKY when compared with saline-treated counterparts. Taken together, WKY and SD rats exhibit similar peripheral pro-inflammatory, but not locomotor, responses to TLR4 activation. Thus, neuro-immune signalling may underlie the altered behavioural response to TLR4 activation in this stress sensitive model. Acknowledgements: Work supported by College of Medicine, postgraduate fellowship and Discipline of Physiology, NUI Galway.

P37 The Role of Bid in Toll-like Receptor Signalling in Microglia following mutant SOD1-induced neuroinflammation

Data Blitz 2: 14:50-14:55- Neuroimmunology

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Neuroinflammation is a pathological hallmark of neurodegenerative disease, with evidence of increased microgliosis and astrogliosis in Amyotrophic Lateral Sclerosis (ALS). Non-cell autonomous death of motoneurons mediated by activated microglia and astrocytes is proposed to be a key event in ALS aetiology. Toll-like Receptors (TLRs) are the master regulators of immune response and are highly expressed on glial cells, with elevated levels of TLRs -2 and -4 identified in the brain and spinal cord in ALS pathology. The Bcl2 family member, Bid has recently been shown to have a role in inflammatory regulation via interactions with the IKK component of the TLR-NF-κB pathway. This study examined both the role of Bid in the inflammasome and the effects of Superoxide Dismutase 1 (S0D1), mutations of which are associated with ALS, on TLR-induced glial activation in vitro. Transient transfection of microglia (BV-2) with SOD1G93A revealed increased tlr2, tlr4 expression. Interestingly, the expression of the NF-κB target gene, COX-II, is decreased in BV2 cells following Bid siRNA transfection and subsequent treatment with motoneuron SOD1G93A -conditioned media, compared with control siRNA-transfected cells exposed to SOD1G93A -conditioned media. Our data shows a delayed IκBα degradation in bid-/- microglia compared to wt upon LPS stimulation, indicating a differential role of Bid in the activation of NF-κB. This data demonstrates that TLR signalling is activated by overexpressed SOD1G93A, and that Bid may play an important role in mediating TLR-induced pro-inflammatory signalling in glial cells.

P38 A pilot study investigating the neural correlates of social cognition using fMRI

Cognitive and Behavioural - Human

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Social cognition can be defined as mental processes allowing people to perceive and process information about themselves and others, enabling successful navigation of the social world (Van Overwalle, 2009). Social cognitive defects (such as emotion recognition and mental state reasoning, or 'theory of mind') are a core feature of several psychiatric disorders, including schizophrenia (Couture et al., 2006) and strongly predict functional outcome (Fett et al., 2011). For this reason social cognition is a potential target for new pharmacological and/or cognitive treatments. A better understanding of the neurobiological mechanisms involved are a step towards this. The present study aims to elucidate these mechanisms using functional MRI across a sample of psychosis patients (N = 30) and demographically-matched healthy controls(N = 30). Three robust social

cognitive tasks will be used during fMRI, including (1)emotion recognition, where participants observe video clips of angry or neutral facial expressions (Grosbras and Paus, 2006), (2)theory of mind, where participants view cartoons and contemplate the mental states of the characters (Brüne et al., 2008) and (3)social exclusion, where participants experience social exclusion from a computer ball game (Sebastian et al., 2011).This study will also examine effects of putative risk factors for psychosis, including effects of genome-wide associated genetic risk variants (Ripke et al., 2011) and environmental factors. Using a single healthy volunteer, this pilot fMRI study highlighted several brain regions that were activated during each of these social cognitive tasks at a $p<0.05$ level, including corticolimbic and default mode networks, consistent with previous social neuroimaging studies.

P39 Towards real-time decoding of attentional selection in a multi-speaker environment, using single-trial EEG

Cognitive and Behavioural Neuroscience - Human

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Recently it has been shown to be possible to ascertain the target of a subject's attention in a cocktail party environment from single-trial (~60 s) electroencephalography (EEG) data. Specifically, this was shown in the context of a dichotic listening paradigm where subjects were cued to attend to a story in one ear while ignoring a different story in the other and were required to answer questions on both stories. This paradigm resulted in a high decoding accuracy that correlated with task performance across subjects. Here, we extend this finding by showing that the ability to accurately decode attentional selection in a dichotic speech paradigm is robust to the particular attention task at hand. Subjects attended to one of two dichotically presented stories under four task conditions. These conditions required subjects to 1) answer questions on the content of the attended story, 2) detect vibrato targets in the voice of the attended speaker 3) answer questions and detect vibrato targets, and 4) detect target words in the attended stream. All four tasks led to high decoding accuracy (~90%). In addition, we show that the attended vibrato targets evoked a distinctive P300. When incorporating these event related potentials (ERPs) in our classifier, we were able to boost the average decoding accuracy to 99%. These results offer new possibilities for developing user-friendly brain computer interfaces (BCIs).

P40 Hidden dangers of 2,5-dimethoxy -4-bromophenethylamine (2C-B) abuse revealed using Danio rerio as a neurodevelopmental toxicity model

Neuropharmacology

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2,5-dimethoxy -4-bromophenethylamine (2C-B) is a designer drug of abuse. A member of the 2C class of substituted phenethylamines, it has both psychedelic and entactogenic effects and is often consumed in combination with 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy). The effective dose range of 2C-B (8-10mg) is approximately ten times lower than ecstasy (75-125mg) and it has recently been linked with several cases of hospitalisation throughout Ireland and the UK. Several cases of persistent psychosis have also been reported following the consumption of 2C-B alone, thus highlighting the need for urgent research into both its pharmacological and toxicological effects. This study compared the effects of 2C-B with related analogues 2,5-dimethoxy-4-bromoamphetamine (DOB), and MDMA both in-vitro and in-vivo. In vitro work uncovered a profound cytostatic effect on the cell cycle in two distinct human cell lines; the catecholminergic SH-SY5Y neuroblastoma cell line and the HEK293 embryonic kidney cell line. The teratogenic and neurotoxic potential of 2C-B and its related analogues were also investigated using the zebrafish (Danio rerio) as a developmental model. 2C-B induced significant dysmorphological effects in developing larvae and also effected larval movement when assessed using standard behavioural assays, both potential indicators of developmental neurotoxicity. This work highlights the hidden dangers involved when consuming unknown pharmacological entities such as 2C-B, particularly during early pregnancy.

P41 Auditory cortical evoked potentials as a window to cochlear implant performance.

Other

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Cochlear implants can partially restore hearing in deaf individuals by electrically stimulating the auditory nerve. Research has shown that cortical auditory evoked potentials (AEPs) can re-develop close to normal morphology after cochlear implantation (Pantev et al., 2006). Re-cent electrophysiological work suggests that spectral discrimination abilities of experienced cochlear implant users can be derived from electroencephalography (EEG) data recorded via an unattended odd-ball paradigm known as mismatch negativity (MMN; Lopez Valdes et al., 2014). While research suggests that speech perception performance in cochlear implant users is correlated with their spectral discrimination abilities (Won et al., 2007), it is not clear whether spectral discrimination in cochlear

implant users is driven by neural plasticity in the auditory cortex or defined by the implant's fitting parameters. Here we investigate the progression of four cochlear implant user's spectral discrimination ability along their first three months of aural rehabilitation. Subjects underwent four to five sessions in total. Each session consisted of three assessments: 1) Psychoacoustic evaluation of spectral discrimination; 2) EEG recorded to an auditory MMN paradigm; and 3) Speech per-ception test in quiet and competing noise. Preliminary results show that spectral discrimina-tion ability as well as speech perception performance improves over time despite minimal changes to hardware settings. Changes in AEPs are in line with previous literature; however, there is no clear evidence of MMN components at the three month mark.

P42 The effects of Z-score Neurofeedback on procedural learning
Cognitive and Behavioural Neuroscience - Human
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Neurofeedback training (NFT) is becoming increasingly popular as a method of brain training. In the past, it has been shown that single electrode NFT can enhance procedural learning in a serial reaction time task (SRTT). This study uses LORETA Z-score NFT (LZNFT), a new form of NFT, to investigate whether this effect can be replicated . Twenty participants were randomly assigned to either an experimental group who received LZNFT, or to a control group who received 'sham feedback' (SFB) based on a pre-recorded brain activity. 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 (RTs) across trial blocks when compared to task completion without NFT. This study replaced traditional NFT with LZNFT and introduced a separate SFB control group. It was found that 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.

P43 The consequences of pre or postnatal methamphetamine exposure on offspring neonatal development in rats
Neuropharmacology
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There has been an increase in the number of preclinical studies investigating prenatal and postnatal methamphetamine (MA) exposure in recent years due to the increased use of MA during pregnancy and/or lactation in humans. For developmental studies, it is important to represent the human scenario as closely as possible. However, preclinical studies have deviated from this regarding dose, route of administration and exposure durations.

The aim of this study was to determine if prenatal or postnatal MA exposure at a pharmacological dose affects neurodevelopment in the offspring. Pregnant Sprague-Dawley dams (n=8-10 dams/group) received MA (3.75mg/kg) or control (distilled water) daily via oral gavage from gestation day 7-21 or postnatal day 1-21. A range of well-recognised neurodevelopment parameters were examined in the neonatal period. Data were analysed using Repeated-Measures ANOVA and Two-way ANOVA or Friedman's ANOVA and Kruskal-Wallis with relevant post-hoc tests. The level of significance was $p<0.05$. Prenatal and postnatal MA significantly reduced maternal weight gain, which is correlated to reduced food intake in the prenatal and postnatal periods, respectively. A significant increase in pup mortality (stillborn and neonatal) was observed in both MA treatment groups. Significant impairments in neurodevelopmental parameters were also evident in both MA treatment groups including somatic development (e.g. pinna unfolding, fur appearance) and behavioural development (e.g. surface righting, forelimb grip). This study demonstrates that MA, at a pharmacological dose, can have a profound effect on neonatal outcome when administered prenatally or postnatally. If extrapolated to the clinical scenario, this will give cause for concern regarding the risks associated with this drug of abuse on neonatal neurodevelopment.

P44 Double stranded RNAs of different lengths have divergent effects on innate immune activation in the periphery and the brain

Neuroimmunology

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Poly-Inosinic: Poly-Cytidylic Acid (Poly I:C) is a synthetic double stranded analogue of a double stranded RNA (dsRNA). This viral mimetic is used to study Maternal Immune Activation (MIA) in schizophrenia, type I interferon effects on neurophysiology, and the impact of anti-viral acute phase responses during neurodegeneration. We observed divergent outcomes in an MIA model using preparations of poly I:C from 2 different suppliers and it is clear that preparations from different suppliers differ fundamentally. Here we examined the peripheral and central responses to poly I:C (20 mg/kg) from different sources (Amersham, Sigma, Invivogen). We found significantly different responses at 3 hours post poly I:C stimulation, with Sigma producing undetectable IL-1b, TNF-a and IFNb responses and a much reduced IL-6 response compared to the very robust response with Amersham. Even at a higher dose of Sigma, which induces a similar IL-6 response to Amersham, very low IFNβ and TNFα induction was observed. These data suggested fundamentally different pathways and we thus compared their molecular weights and innate immune responses to those of invivogen poly I:C high molecular weight (HMW, 800-10000 bp) and low MW (200-1000 bp). DNA gels confirm that Amersham and Sigma provide HMW and LMW poly I:C respectively. This demonstrates that length of poly I:C is a key determinant in activating alternate pathways in the periphery. This has a very significant impact on current studies in neuroscience since

similar studies are apparently unknowingly examining different pathways of innate immune activation using poly I:C.

P45 FTY720 attenuates infection-induced pathology in a mouse model of Alzheimer's disease

Neuroimmunology

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Recent studies suggest that exposure to infection can trigger inflammatory changes in the brain and may be a risk factor for Alzheimer's disease (AD) progression. The objective of this study was to assess the effect of infection on neuroinflammation in mice which overexpress amyloid precursor protein (APP) and presenilin 1 (PS1; APP/PS1 mice), a commonly-used animal model of AD. Wildtype and APP/PS1 mice (4 and 10 months old) were infected with the respiratory pathogen Bordetella pertussis. There was a significant infection-induced increase in the absolute number of CD3+ T cells in the brains of 12 month-old APP/PS1 mice when assessed 56 days post infection, which was associated with enhanced glial activation and amyloid-β deposition. We next determined whether the infection-induced pathology could be reversed by treatment with FTY720, an agonist of the sphingosine-1-phosphate receptor 1 on lymphocytes which prevents T cell migration from lymph nodes. Wildtype and APP/PS1 mice (10 months old) were infected with B. pertussis and a group of mice were chronically treated with FTY720 orally (0.3 mg/kg). Treatment of APP/PS1 mice with FTY720 significantly attenuated the enhanced plaque deposition observed in the brain of B. pertussis-infected APP/PS1 mice when assessed 70 days post infection; this was accompanied by a significant decrease in GFAP and IL-6 expression. This study demonstrates that respiratory infection can enhance T cell migration and amyloid-β plaque burden in the brain of aged APP/PS1 mice. Chronic treatment with FTY720 protects the APP/PS1 brain from infection-induced pathology, and may be a suitable therapy in AD.

P46 Paired associative transcranial alternating current stimulation increases the excitability of corticospinal projections in humans.

Cognitive and Behavioural Neuroscience - Human

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Many types of non-invasive brain stimulation alter corticospinal excitability (CSE). Paired associative stimulation (PAS) attracts particular attention as its effects ostensibly adhere to Hebbian principles of neural plasticity. In prototypical form, a single electrical stimulus is directed to a peripheral nerve in close temporal contiguity with transcranial magnetic stimulation (TMS) delivered to the contralateral primary motor cortex (M1). Repeated pairing of the two discrete stimulus events (i.e. association) over an extended period either increases or decreases the excitability of corticospinal projections from M1, contingent on the interstimulus interval

(ISI). We studied a novel form of associative stimulation, consisting of short trains of peripheral afferent stimulation paired with short bursts of high frequency (≥ 80 Hz) transcranial alternating current stimulation (tACS) over contralateral M1. Elevations in the excitability of corticospinal projections to the forearm were observed for a range of tACS frequency (80Hz, 140Hz and 250Hz) and current (1mA, 2mA and 3mA) parameters. Paired stimulation bursts of 1000ms duration generated larger increases in CSE than 250ms or 500ms bursts. The effects were more reliable than those brought about by PAS or transcranial direct current stimulation (tDCS). When paired with tACS, muscle tendon vibration induced greater elevations of CSE than electrical nerve stimulation. In demonstrating that associative effects are expressed when the timing of the peripheral and cortical events is not precisely circumscribed, these findings suggest that multiple cellular pathways may contribute to a LTP-type response. Their relative contributions will differ depending on the nature of the induction protocol that is used.

P47 Semaphorin-Plexin signalling influences early ventral telencephalic development and thalamocortical axon guidance

Molecular biology and genetics

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Brain functions are critically dependent on specific neural connections between distant areas being established during development. In particular, the formation of projections from thalamus to cortex is fundamental for sensory inputs processing. Information from different sensory modalities is segregated at thalamic level into discrete, specialised nuclei, the neurons of which extend their axons following topographically organised pathways to connect with cognate cortical areas. Interactions between Semaphorin-6A and its binding partners, Plexin-A2 and Plexin-A4, have been implicated in several neurodevelopmental processes, including axon guidance and neuronal migration. In our studies, we have shown that Sema6A–PlxnA2/PlxnA4 signalling disruption affects thalamocortical wiring. During normal brain development, thalamocortical axons (TCAs) extend first through the ventral telencephalon before making a dorsal turn towards their cortical targets. Axonal navigation in these stages relies on the presence of intermediate targets and guiding cell populations, such as corridor and guidepost cells found at the internal capsule (IC). In Sema6A and PlxnA2;PlxnA4 null mice, however, TCAs exhibit a selective guidance defect characterised by the abnormal extension of caudally projecting axons into superficial regions of the ventral telencephalon, instead of through the IC. We have found that these proteins are differentially expressed in the developing ventral telencephalon, and that their loss of function results in cytoarchitectural disorganisation of intermediate TCA guidance structures. More generally, these findings illustrate how even subtle defects in early neurodevelopmental events can have substantial effects on contingent processes, such as guidance of major axonal tracts.

P48 Dynamic functional connectivity patterns in the resting state.

Cognitive and Behavioural - Human

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The aim of this study was to investigate the dynamic functional connectivity (dFNC) between neural networks in the resting state. 18 young healthy adults underwent 4 sessions of resting state fMRI scanning. A memory encoding task was performed between resting state sessions 1 and 2, and sessions 3 and 4. The GIFT toolbox was implemented to run group independent component analysis (ICA) on all 4 sessions. The dFNC toolbox was used to estimate dFNC between resting state networks. ICA analysis revealed 18 networks comprising of motor, auditory, visual, default mode (DMN), attention, fronto-parietal, subcortical, cerebellum and cingulo-opercular. The 18 networks were organised into 6 different states of functional connectivity (FNC). State 5 was most frequent accounting for 34% of all time windows. States 1-4 and 6 each accounted for between 11-15%. Across every state there was positive FNC between two posterior DMNs, one including the posterior cingulate and one the precuneus. There was negative FNC between one standard DMN, including posterior cingulate and frontal regions, and a cingulo-opercular network. In state 5 visual networks were positively correlated with each other, as were motor networks. In state 3 two attention networks were positively correlated with motor, auditory and one visual network. Two DMNs, the standard and posterior cingulate, were positively correlated with motor and auditory. In state 2, one attention network was positively correlated with visual, motor and auditory networks. The standard DMN was negatively correlated with visual networks. In conclusion, during rest there is a dynamic interaction among neural networks. Grant support from SFI and Centre for Advanced Medical Imaging is acknowledged.

P49 The role of Type-I interferons in Poly I:C induced sickness behaviour

Cognitive and Behavioural Neuroscience – Animal

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Polyinosinic:polycytidylic acid (poly I:C), an agonist for TLR3, induces type-I interferons and other inflammatory mediators such as TNFα, IL-6 and to a lesser extent IL- 1β. Poly I:C induces sickness behaviour in mice and it is known that type-I interferons impact on behaviour and CNS function. Here we assess the role of type-I interferons in pI:C-induced sickness behaviour. Type-I interferon receptor 1 knockout (IFNAR1-/-) and WT C57BL/6 mice were challenged with pI:C (12 mg/kg i.p). IFNAR1-/- animals displayed reduced sickness behaviour compared to WT mice and only WT animals displayed a significant hypothermic response. All mice showed a reduction in weight 28 hours post-challenge but full recovery was more rapid in

IFNAR1-/- mice. In addition to this, 3 hours post-challenge, WT mice showed decreased activity in the open field with respect to IFNAR1-/-. As expected, the interferon responsive genes PKR and IRF7 were not induced by pI:C in IFNAR1-/- mice. While IL-1β and TNFα responses to pI:C were equivalent in KO and WT in blood, hippocampus and hypothalamus, there was no synthesis of IL-6 in IFNAR1-/- in either blood or brain. These results demonstrate a role for type-I interferons in the sickness behaviour response to pI:C and in the induction of IL-6 responses. Further investigations will examine whether the IL-6 deficiency seen in IFNAR1-/- mice is responsible for the reduced pI:C-induced sickness behaviour.

P50 Processing of directional information of a motor task in brain, revealed by EEG pattern classification

Neurophysiology
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Event-related potentials (ERPs) and event-related spectral perturbations (ERSPs) of electroencephalogram (EEG) during human movements show cosine-tuning by movement direction as in invasive recordings. It is, however, not clear what sensorimotor processes contribute most to this modulation or the directional information in EEG, in general. We, therefore, investigated EEG during isometric tasks, where there is no change in extrinsic limb coordinates, using an instruction-delay experiment. Subjects (n=8) prepared, planned for and executed center-out directional arm isometric exertions in the horizontal plane to 4 directions according to the visual cues, while multi-channel surface EEG was recorded. The results show no statistical difference between ERPs or ERSPs for different directions in any electrode, across subjects. However, the single-trial classification rates of exertion direction of EEG, tested with a repertoire of classification techniques, show presence of significant directional information both in planning and execution stages. The directional information is maximal in the early stage of planning and above parietal regions. The results suggest that changes in extrinsic limb coordinates, is a major contributor to cosine-tuning of EEG features, but not the only source of directional information in EEG. The results are of interest for studying sensorimotor information processing using non-invasive recordings, and for neuro-rehabilitation applications. This study was supported by Scottish Funding Council (GRPE).

P51 Comparative assessment of the motor dysfunction induced by neurotoxic, inflammatory and environmental Parkinson's disease-related neurotoxins in rats

Cognitive and Behavioural Neuroscience – Animal

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Parkinson's disease has been modelled in preclinical animals using selective catecholaminergic neurotoxins such as 6-hydroxydopamine and MPTP. However, as these models bear little etiological resemblance to the human condition, there has been a requirement to develop and characterise models with improved validity. Two such models are those induced by the bacterial inflammagen, lipopolysaccharide (LPS), and the organic pesticide, rotenone. However, these models have been poorly characterised with respect to more established models. Thus, the aim of this project was to characterise the motor impairments induced by LPS and rotenone and compare with those induced by 6-hydroxydopamine. Twenty four male Sprague Dawley rats underwent baseline testing on a variety of tests of lateralised motor function (Stepping Test, Whisker Test, Corridor Test and Cylinder Test). They were performance-matched into groups for unilateral infusion of 6-hydroxydopamine (28 mg, n=8), LPS (20 mg, n=8) or rotenone (3.6 mg, n=8). Motor testing resumed one day post lesion and continued for ten weeks. Three weeks post lesion, rats were tested for amphetamine-induced rotational asymmetry. Immunohistochemistry for neurodegeneration, microgliosis and astrocytosis was also performed. All neurotoxins induced significant contralateral motor dysfunction. The impairment induced by 6-hydroxydopamine was significantly more pronounced and stable than that induced by the other neurotoxins. For amphetamine induced rotations, the 6-hydroxydopamine and rotenone-lesioned rats rotated significantly in the ipsilateral direction, while LPS-lesioned rats did not rotate. There was also significant neurodegeneration, microgliosis and astrocytosis in all groups on the side ipsilateral to the lesion. This study demonstrates the key differences in the patterns of motor dysfunction induced by different Parkinsonian neurotoxins and their associated neurodegenerative effects which should be taken into consideration when selecting the most appropriate model for Parkinson's disease preclinical studies.

P52 Activation of the Unfolded Protein Response in myelinating rat cerebellar tracts

Other

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The development of white matter tracts requires a dramatic increase of lipid and protein synthesis in oligodendrocytes to produce myelin. The endoplasmic reticulum (ER) is the primary site of synthesis for membranous proteins and lipids. We hypothesise that the Unfolded Protein Response

(UPR) is activated in oligodendrocytes in order to expand ER capacity and facilitate myelination. Chromogenic immunohistochemistry was used to characterise myelin development in the rat cerebellum. ER stress signalling was detected using antibodies for activated UPR transducers (pIRE1, ATF6 and pPERK) and associated downstream molecules (peIF2a, XBP1, PDI, GRP78, GRP94, CHOP and calreticulin). The density of positive cells in developing white matter tracts was blindly assessed and normalised to the mean cell density of each age to account for white matter expansion. Nuclear staining for ATF6 (indicative of the active transcription factor) peaked at P10 ($p<0.01$), concurrent with early myelination. This was matched by an increase in non-nuclear (inactive) stained cells at later timepoints ($p<0.05$). Positive cells for activated IRE1 were widespread at P14 and P17 vs P7 and adult ($p<0.05$, $p<0.01$). Downstream targets of the UPR were all significantly upregulated at P17 (vs P7 $p<0.01$, $p<0.001$, $p<0.01$ for GRP78, GRP94 and PDI respectively), and remained significantly elevated in adult tissue. Expression levels of pPERK and associated molecules were negligible. Expression of ER-associated molecules was observed in dual-labelled olig2-positive cells in developing white matter tracts. To our knowledge, this is the first demonstration of the activated UPR in developing white matter. This data may have implications for mechanisms underlying remyelination for disorders such as multiple sclerosis.

P53 Examining the relationship between impulsivity and the BOLD response in risky and safe drivers.

Cognitive and Behavioural - Human

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Theory has linked certain stages of brain development to the increase in impulsive and risk-taking behaviours commonly associated with adolescence and young adulthood. Previous research has also demonstrated a link between impulsivity and risky driving, with young 'risky' drivers displaying higher psychometric and cognitive impulsivity than young 'safe' drivers. However, these studies do not explain why some individuals have a greater propensity towards driving risk, nor do they address why impulsivity and risky driving can persist into later adulthood in some individuals, but not in others. This project utilised fMRI to examine the relationship between cognitive impulsivity, risky driving behaviours and the BOLD response in older adults. The current study compared the impulsivity of 20 'risky' (penalty points and/or collision culpable) and 20 'safe' older male drivers (N = 40, age range = 29-56, M = 37.59, SD = 7.58). Participants completed psychometric measures of impulsivity and driving behaviour prior to scanning. Scanning lasted one hour, during which time participants completed three tasks (the Iowa Gambling Task, Monetary Incentive Delay task and the Go/No Go task), each designed to assess different facets of cognitive impulsivity. Analyses of the data are on going. Detectable differences in the impulsivity of the groups may be explained by differences in the BOLD response during the cognitive tasks. This may give insight into

the origin of risky driving behaviours. The study would like to acknowledge the Road Safety Authority for their support in funding the project.

P54 Persistence of the effects of voluntary exercise on spatial learning in the rat: assessment of underlying mechanisms.

Cognitive and Behavioural Neuroscience - Animal
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We have previously shown that the enhancing effect of wheel running on spatial learning in rats persists for 3 weeks after exercise cessation, but expression and phosphorylation of plasticity-related proteins is not enhanced by exercise at this timepoint. We hypothesise that neurogenesis may mediate the persistence of the exercise-induced improvement in cognitive function. Male Han Wistar rats (n=16) were divided into voluntary wheel running (n=8) or sedentary control (n=8) groups. Exercising rats had access to a running wheel for 1 hr/day for 1 week; all rats received daily injections of the thymidine analogue bromodeoxyuridine (BrdU; 50mg/kg ip). Rats were trained in an object displacement (OD) task and tested and killed 2 weeks after training. Brains were hemisected; sections were prepared from left hemispheres for immunohistochemical analysis. Dentate gyrus and hippocampus were subdissected from right hemispheres and prepared for RNA isolation and qPCR. We show that mRNA expression of Ki67, a cell proliferation marker, does not differ significantly between groups. Neither were there significant differences in mRNA expression of the exercise and plasticity-related proteins brain-derived neurotrophic factor, nerve growth factor, vascular endothelial growth factor or TrkA and TrkB between groups, suggesting a return to baseline expression levels at this time point. Cognitive testing occurred during a critical period in neuronal development during which the immature cells are known to exhibit enhanced plasticity. Immunohistochemical analysis of BrdU labelled cells in the dentate gyrus samples is currently underway to test whether the cognitive enhancement we observed in exercised rats is due to increased neurogenesis. Funding support from Department of Physiology, School of Medicine, Trinity College Dublin.

P55 An investigation of global network structure in bipolar disorder

Cognitive and Behavioural - Human
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Network analysis is a novel technique used to identify brain connectivity patterns. Metrics of centrality, integration and segregation allow for brain networks to be quantified into neurobiologically meaningful measures. This analysis aims to elucidate disrupted anatomical wiring as an attribute of psychiatric illness. Participants were recruited as part of the Galway Bipolar Study (43 Healthy Controls & 42 subjects with Euthymic Bipolar Disorder).

Diffusion MRI data was acquired on a 1.5 Tesla Scanner. Connectivity matrices were produced using ExploreDTI. Network metrics were generated using the Brain Connectivity Toolbox in MATLAB. The Network Based Statistic toolbox is a method to identify an experimental effect at the cluster level. FWER corrected p-values are calculated for each component using permutation testing. Properties of integration and segregation revealed between group differences in metrics of Characteristic Path Length [p=0.017], Global Efficiency [p=0.015] and Clustering Coefficient [p=0.047]; with greater brain network disorganization in patients relative to controls. Network analysis was carried out through the NBS with M= 5000 permutations at $p< 0.05$, revealing a contrast in patients relative to controls across varying (t-statistic) thresholds, in which a single disconnected sub-network comprising multiple dysconnections was identified for each threshold. Metrics that characterize brain communication revealed greater disorganization in patients relative to controls. The NBS findings demonstrated consistency across t-statistic thresholds among occipital and default mode network regions. This study, applying novel network based statistics to MRI and DTI data, indicates that disrupted neuroanatomical connectivity is a trait based feature of bipolar disorder.

P56 Advanced imaging of hippocampal white matter in adolescents with psychotic symptoms

Other

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The hippocampus has been identified as a key structure in the in the pathophysiology of schizophrenia (1) and implicated in the cognitive deficits observed in schizophrenia and psychosis (2,3). Neuroimaging studies have captured structural changes in patients with schizophrenia and more recently in those individuals deemed as “ultra high risk” for the development of the illness. Technological advances in neuroimaging have provided researchers with an opportunity to examine the neuroanatomy for evidence of the these disease related morphologies and structural anomalies, yet it remains unclear if these changes occur before the onset of the disease. This pilot study employs a multimodal MR imaging (MRI) strategy to investigate the white matter tissue of the brain in 28 adolescents aged (11-16), and 28 matched controls. High resolution 3T MRI was used to acquire structural and diffusion images of each individual. Advanced image anaylsis techniques are employed to perform a detailed quantitative volumetric analysis of the the hippocampus including it’s subdivisions. The hippocampus is then used as a mask region for the purpose of advanced white matter tractography to interrogate the white matter fibre tracts in proximity to the region. Detailed diffusion metrics are used to probe the white matter tissue for subtle changes. Results pending 1. Wood S.J., et al. Neuroimage. 2010. 52: 62-68. doi: 10.1016/j.neuroimage.2010.04.012 2. 2. Hannan K.L. et al., Psychiatry Research:Neuroimaging. 2010. 182: 233-230. doi:10.1061/J.pscychresns

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P57 Lack of evidence for a role of the NF-kappaB pathway in the suprachiasmatic circadian clock.

Neuroimmunology

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Circadian rhythms are recurring patterns in behavioural and physiological that display periods of approximately every twenty four hours. The master circadian pacemaker is the suprachiasmatic nuclei (SCN) in the anterior hypothalamus. Alterations in circadian rhythms by inflammation, aging and neurodegenration have being described. The transcription factor nuclear factor- k B (NF-kappaB) is one pathway which has not been systemically investigated in terms of regulation of the SCN function. We hypothesised that the NF-kappaB pathway plays a role in rhythm generation and phase-resetting in the SCN clock. Circadian regulation of NF-kappaB signalling components was assessed in animals in constant darkness, sampled every 4 hours across the 24 hour cycle. There was no significant temporal regulation of p65, phosphorylated(P)-IKK, or p-IkB in the SCN. Light pulses at CT15 and CT22 did not alter expression of p65. The NF-kappaB inhibitor pyrrolidinedithiocarbamate(PDTC) was administered in drinking water over 4 weeks; this did not attenuate behavioural rhythms, nor did it alter expression of p65, c-fos and PER1 in the SCN at ZT6 and ZT12. PER2::LUC SCN slice explants were treated in vitro with PDTC to examine whether alterations might be present in molecular oscillations in the SCN following manipulation of the NF-kappaB signalling pathway, but no significant alterations in rhythm period or amplitude was noted compared to control. Likewise, LPS treatment of slices, which should activate NF-kappaB, did not alter PER2::LUC expression. From these data we conclude that this pathway does not play a significant role in the normal running or resetting of the clock.

P58 Role of the nuclear receptor TLX in cognition during adolescence and adulthood

Cognitive and Behavioural Neuroscience - Animal

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The nuclear receptor Nr2e1 (TLX) is a key regulator of embryonic and adult hippocampal neurogenesis. Adult hippocampal neurogenesis plays a role in spatial learning and memory, a function which is impaired in TLX-deficient mice. However, the role of TLX in a variety of cognitive tasks remains largely unexplored. Moreover, it is not yet clear whether there are critical periods during postnatal life when TLX plays a more predominant role in cognition,

and whether such effects are sex-dependent. The aim of this study was to determine the role of TLX in hippocampal neurogenesis-dependent cognition as well as in hippocampus-independent cognition during adolescence and adulthood. To this end, a variety of cognitive processes were examined in adolescent (P28) and adult (P56) male and female wildtype (WT), Nr2e1+/- and Nr2e1-/- mice. Motor learning, a cortico-cerebellar and cortico-striatal based learning process, was assessed utilizing the rota-rod latency to fall paradigm. Adult hippocampal neurogenesis-associated cognition was assessed using spontaneous alternation in the y-maze. Locomotor activity was measured in an open field. Results indicate that adolescent male and female Nr2e1-/- mice were hyperactive compared to Nr2e1+/- and WT mice ($p<0.05$) and that this effect persists in adulthood. Motor learning was unaffected by genotype and sex. Female Nr2e1-/- mice showed impaired spontaneous alternation during adolescence compared to Nr2e1+/- and WT mice ($p<0.05$). Whether this phenotype persists into adulthood is still under investigation. Together, these findings suggest a role for TLX in hippocampal neurogenesis-associated cognition but not in cortico-cerebellar /striatal cognitive processes. Supported by Science Foundation Ireland (SFI/IA/1537).

P59 Electrophysiological correlates of relational learning in a derivation task

Cognitive and Behavioural Neuroscience – Human

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This research aimed to explore the neural correlates of relational learning by recording high-density EEG during a behavioural task involving directly-trained and derived relations within two three-member equivalence classes. A total of 15 participants (5 male; age range 18-23 years; mean age = 20.0 years) completed contextual cue training, relational learning and derivation test blocks while 128-channel event-related potentials (ERPs) were recorded from the scalp. Differences in response latencies were predicted between the two derived (combinatorially- and mutually-entailed) and directly-trained relations, with longest latencies hypothesised for the combinatorially-entailed and shortest for the directly-entailed relations. This pattern was observed but was non-significant. ERPs revealed a P3a positivity, from 230-350ms, at three right posterior scalp sites (P6, E115 and E121). Significantly larger mean amplitudes were found at these three channels for the combinatorially-entailed relations compared to the two other types. We believe this may constitute a first demonstration of differences in brain electrophysiology between equivalence relations of hierarchical levels of complexity.

P60 Auditory object formation via temporal coherence

Cognitive and Behavioural Neuroscience - Human
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The brain has evolved to operate effectively in highly complex auditory environments, segregating multiple continuous sound sources into perceptually distinct auditory objects. One theory which seeks to explain such a percept argues that stream segregation depends primarily on the temporal coherence between the neural responses that encode various features of a sound source. Studying this phenomenon using non-invasive techniques such as magneto- and electroencephalography (MEG/EEG) has traditionally been constrained by time-locked averaging approaches, which make it difficult to disentangle the temporally overlapping responses to each of the many stimuli which compose a complex auditory scene. Recently, the application of linear regression methods has allowed for the extraction of localized neural correlates of individual features of interest. Using these methods in a stream segregation paradigm, we show that it is possible to extract a neural response that is likely indicative of the neural processing of temporal coherence in relative isolation. Furthermore, we show the effects of attention on this response. Our findings show an early effect of coherence, lasting from ~75 to 200ms post-stimulus, with no significant difference between attended and unattended responses. Subsequently, attended and unattended neural responses show significantly different results, with the attended response persisting until ~650ms post-stimulus. This is followed by a third component, in the attended only condition, lasting from between ~775 and 975ms. These findings suggest early and automatic neural computations of temporal coherence, followed by a later response enhanced by attentional engagement.

P61 The Omega-3 Polyunsaturated Fatty Acid Docosahexaenoic acid (DHA) as a Novel Strategy for Stress-related Psychiatric Disorders: Reversal of Corticosterone-induced Changes in Cortical Neurons

Other
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Growing evidence suggests that omega-3 polyunsaturated fatty acids (PUFAs) may have a beneficial effect on health including mental health. However, the ability of PUFAs to abrogate the stress-induced toxic effects on neurons has not been well investigated. To this end, we studied the protective effect of the omega-3 PUFA docosahexaenoic acid (DHA), against corticosterone (CORT)-induced cellular changes in a mixed cortical primary culture. We first characterized the effect of CORT (75, 100, 150, 200uM) at different time points (24, 48, 72 hours) in a mixed cortical primary culture over 10 days in vitro (DIV), prepared from rats at postnatal day 1-2. Cells were then pretreated with DHA (3, 6uM) at 1DIV. CORT (72 hours) induced a dose-dependent reduction in cellular viability as assessed by MTT. Moreover, we demonstrated that CORT (200uM - 72 hours) decreased the

percentage composition of neurons whilst increasing the percentage of astrocytes as assessed by B-III tubulin and GFAP immunostaining, respectively. In contrast, DHA (6uM but not 3uM) attenuated CORT (200uM)-induced cell death (72 hours). This translated into a capacity for DHA to prevent neuronal death as well as astrocytes overgrowth following chronic exposure to CORT. Furthermore, DHA (6uM) reversed CORT-induced neuronal apoptosis as assessed by TUNEL, and attenuated CORT-induced reductions in BDNF and CREB mRNA expression. Finally, DHA inhibited CORT-induced down-regulation of GR expression on b-III tubulin-positive neurons. In conclusion, this work supports the view that DHA may be beneficial to ameliorate stress-related cellular changes in the brain and may be a beneficial strategy for stress-related psychiatric disorders. Research was funded by Food Institutional Research Measure (FIRM) under Grant No. 4600 R14358, the Alimentary Pharmabiotic Centre (APC) under Grant No. 07/CE/B1368 and 12/RC/2273, and Science Foundation Ireland under Grant No. 12/IA/1537.

P62 Using the Oculus Rift for recording head turns

Cognitive and Behavioural Neuroscience - Human
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Cervical dystonia is an autosomal dominant disorder with reduced penetrance. Recent experiments have shown that patients with dystonia have abnormal temporal discrimination of asynchronous punctuate visual stimuli. This would suggest that the superior colliculus plays an important role in the disorder. Furthermore, the superior colliculus is part of the network that controls head turns which have also been shown to be abnormal in patients with dystonia. This project aims to measure head turns in a controlled environment which can then be deployed in any setting. In order to do this, participants will wear a lightweight head mounted display (Oculus Rift). The Occulus Rift has a built-in 3 axis gyroscope, accelerometer and magnetometers which we used to monitor head rotations. The experiment entails participants making different sized head turns to the left and right in a cue target paradigm, where the cue can be either valid or invalid. Here, we will present pilot data from healthy adults to illustrate the feasibility of acquiring head movement data with the Oculus Rift, and the extraction of head turn biomarkers. These results show the feasibility of recording precise head movement data outside of a lab environment, which is essential when dealing with a clinical population with limited mobility. In future studies, we intend to investigate the link between head turning and the abnormal temporal discrimination of visual stimuli of patients with dystonia. This will strengthen the role of the mid-brain in the disorder.

P63 An examination of the effectiveness of a Cognitive Group intervention for people with Acquired Brain Injury

Cognitive and Behavioural - Human

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Objective: This study investigated, in a sample of people with Acquired Brain Injury (ABI), whether participating in a twelve-week Cognitive Group intervention brings about significant change in areas of cognition, distress, satisfaction with life, community integration and knowledge of brain injury. Method: A matched control design was used. Twenty-two participants (n=22) with an ABI completed a series of neuropsychologcal tests and questionnaires at two time-points over a twelve week period. Result: Preliminary results showed significant change in the intervention group on two neuropsychologcal tests, namely the California Verbal Learning Test and the Digit-Span Task, indicating an improvement in learning and memory functioning. Conclusion: This study provides support for the effectiveness of a group-based cognitive intervention using a holistic approach. These findings have important implications for neurorehabilitation service providers, as well as being of interest to individuals with an ABI and their families. The study provides an opportunity for investigating further the potential for group-based cognitive interventions using a holistic approach.

P64 Analysis of the electroconvulsive stimulation hippocampal miRNome using a deep sequencing approach

Molecular biology and genetics

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Electroconvulsive stimulation (ECS), the animal model equivalent of electroconvulsive therapy (ECT), induces molecular and cellular changes in the brain that are believed to be important for its antidepressant effect. However, the precise means by which these changes occur and how they contribute to the antidepressant effects of ECS is unknown. One possibility is that such effects are mediated by microRNAs (miRNAs). MiRNAs control about half of all protein-coding genes in mammals and are found in abundance in the brain where they carry out a variety of functions. It is therefore likely that miRNAs contribute significantly to the development of complex brain disorders, such as depression, and their treatment. We used the hypothesis neutral approach of next-generation deep sequencing here to examine the effects of chronic ECS on miRNAs in rat hippocampus. Rats (n=8 per group) were randomised to receive either “sham” or “real” ECS. ECS (100pulses/s; 0.5ms; 0.7s; 75mA) was administered daily for 10 days. Hippocampal total RNA samples were run on a SOLiD sequencing platform. The results show that nine miRNAs were significantly differentially expressed ($p<0.001$) following ECS after correcting for multiple comparisons. These include rno-miR-212, which we previously reported to

be altered following ECS, and three novel 'predicted' miRNAs. Alterations in miRNA expression may be informative about the mechanism of action of ECS/ECT and in turn may give insight into the neurobiology of depression. A better understanding of the role of miRNAs in depression and its treatments may lead to novel therapeutic targets.

P65 Semantic associations in a memory recognition task: an ERP-study
Other
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It is well-known that a word is processed faster and more accurately, if a semantically associated word is presented before (Priming effect, e.g. Neely, 1976). One explanation for this phenomenon is that semantically associated words are strongly connected in our memory structure, because of their frequent common occurrence. The Associative Read-Out Model (AROM) of Hofmann et al. (2011) is the first interactive model with an implemented semantic layer and includes the idea of associative activation spreading. We conducted a memory recognition task, in which 80 words were presented in a study phase and 160 words in a test phase to 33 participants. To investigate different neuronal correlates of the processing of high and low co-occurrence words, 32-channel EEG was measured. In regard to the behavioral results high co-occurrence words increased the "yes" response in learned and non-learned words. A significant interaction of the factors Oldness and Co-occurrence was observed in terms of the reaction times, showing the longest reaction times for high co-occurrence new words and the shortest reaction times for high co-occurrence old words. The ERPs recorded during the test phase showed a significant Oldness effect ($F(1) = 42.58$, $p < .000$) and a significant Co-occurrence effect ($F(1) = 11,78$ $p = .01$) for the N400 amplitude, which was characterized by smaller amplitudes for high co-occurrence words and larger amplitudes for low co-occurrence words. Since the highest "yes" responses and the smallest N400-amplitudes were produced by high co-occurrence words, the behavioral and neurophysiological results support the AROM-Model and the idea of associative activation spreading.

P66 A natural solution for Obesity - Devil´s Claw attenuates food intake via ghrelin receptor modulation
Diseases and Disorders
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Ghrelin is an orexigenic hormone that stimulates food intake in the hypothalamus through the growth hormone secretagogue receptor (GHS-R1a). A dysregulated ghrelin signalling may contribute to the development of metabolic disorders such as obesity. On the other hand, current pharmacologic anti-obesity treatments are lacking efficacy and have shown severe side effects, highlighting the urgent need for novel strategies to the

maintenance of a healthy weight. Natural products are receiving special consideration as source of bioactives with beneficial health effects due to they seem safer and more attractive for consumers than synthetic therapeutics. This study aims to investigate the effect of a root extract from the traditional medicinal plant Harpagophytum procumbens on GHS-R1a receptor modulation in vitro and analyse its effects on food intake in vivo. GHS-R1a receptor activating potential of H. procumbens extract was analysed by calcium mobilization and receptor internalization assays in human embryonic kidney cells (Hek) stably expressing the GHS-R1a receptor. Furthermore, cumulative food intake was investigated in male C57Bl/6 mice following intraperitoneal (IP) administration of the H. procumbens extract. Exposure to this extract demonstrated a significant increased cellular calcium influx but did not induce subsequent GHS-R1a receptor internalization, which is a characteristic for full receptor activation. A significant anorexigenic effect was observed in male C57BL/6 mice following peripheral administration of H. procumbens extract. We conclude that H. procumbens is a potential novel source for anti-obesity bioactives. These results reinforce the promising potential of natural bioactives to be developed into functional foods with weight-loss and weight maintenance benefits.

P67 Impact of a FKBP5 polymorhism on brain activity during cognitive suppression of emotional content

Diseases and Disorders

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Recent research suggests a role of FKBP5, a glucocorticoid receptor (GR) regulating co-chaperone, in the development of stress-related diseases such as depression and anxiety disorders. In particular, the allele T of FKBP5:rs1360780 appears to be linked to stress hormone dysregulation. This variant was found to be overrepresented in depressed patients and has also been investigated as a candidate for treatment response prediction. However, its relevance on brain function is unknown. Our study aims to assess the impact of the FKBP5:rs1360780 C/T polymorphism on brain function during an emotional attention bias task using functional magnetic resonance imaging (fMRI) in 33 patients suffering from major depressive disorder and 43 healthy controls. During cognitive inhibition of positive emotional responses, we found a significantly higher reduction of activity in healthy controls compared to depressed patients in posterior Default Mode Network regions ($p<0.05$, FDR corrected). In the inhibition of negative stimuli, on the other hand, patients have shown an increased activity in the hippocampus and temporal lobe ($p<0.05$, FDR corrected). Moreover, we report a significant interaction between diagnosis and the FKBP5 polymorphism, with depressed homozygous C patients compared to T-allele carriers showing significantly greater BOLD responses during non-emotional processing of negative pictures in the insular cortex and caudate nucleus ($p<0.05$, FDR corrected). Our results indicate that the T allele of the

FKBP5:rs1360780 polymorphism might be associated with less successful cognitive inhibition of negative emotional content in a subset of patients, maybe due to the genetic regulation of GR function in the insula and striatum.

P68 Investigation of neurophysiological changes during olfactory habituation in Drosophila melanogaster

Neurophysiology

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Brain systems filter irrelevant sensory information. Habituation to inconsequential stimuli allows salient stimuli to be selectively broadcasted to attentional, emotional, and learning systems. Individuals diagnosed with autism spectrum disorder are impaired in habituation processes. This defect could contribute causally to stimulus hypersensitivity and altered salience mapping. Despite its importance, habituation mechanisms are poorly understood. Both, humans and fruit flies show habituation to odour stimuli. As their olfactory systems are remarkably conserved, Drosophila melanogaster with its genetic tools and well-defined olfactory circuitry is ideal to reveal conserved mechanisms of olfactory habituation (Twick et al., 2014) . Genetic and behavioral experiments in the Ramaswami lab suggest that continuous exposure to an odorant results in enhanced inhibitory transmission onto projection neurons activated by the odorant (Ramaswami, 2014). However, this simple model for habituation still needs to be tested on the basis of neurophysiological observations and further experiments will be required to elucidate potential mechanisms. My aim is to test and elaborate this enhanced inhibition model through experiments, which directly assess neurophysiological changes that occur during olfactory habituation. I have established a calcium imaging protocol that allows me to study changes in neuronal activity in a living preparation. Using this protocol I have shown alterations in the spatio-temporal activation patterns of a range of olfactory neuronal types after continuous odour exposure. I will continue to address whether and how the neuromodulator dopamine suppresses neurophysiological changes associated with olfactory habituation as indicated by behavioral experiments.

P69 The classic P300 component indexes an accumulation-to-bound decision signal

Cognitive and Behavioural - Human

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The P300 component of the human event-related potential has been the subject of intensive experimental investigation across a five-decade period, drawing enduring interest for its apparent role in a range of cognitive operations and its sensitivity to brain disorders. Yet, its exact contribution to

cognition remains unresolved in the absence of conclusive empirical data linking the P300 to a specific neural mechanism. Here, a new analysis of ERPs elicited by auditory and visual targets, combined with computational simulations, reveals that, rather than being the culmination of a unitary neural event, the P300 is a dynamically evolving process that triggers action upon reaching a stereotyped level and whose rate-of-rise determines reaction time at the single-trial level. Thus, the P300 exhibits the critical properties of the theoretical 'decision variable' signals predicted by sequential sampling models and directly observed in monkey neurophysiology. In identifying the P300 as a decision variable signal we place it at the heart of a well-established, explanatory framework that should facilitate more mechanistically principled investigations of sensorimotor transformations in both the typical and atypical human brain.

P70 The role of cognitive load on freezing of gait in Parkinson's disease: an approach based on EEG and gait analysis using a virtual reality environment

Diseases and Disorders

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Background: Freezing of gait (FOG) is a highly disabling gait disorder in Parkinson's disease (PD) with a prevalence of approximately 60%, incidence increasing with the stage of PD. Despite its prevalence, the underlying pathology of FOG is still widely unknown and no treatment has proven to be effective. B. Methods: Subjects with PD were recruited from the Mater Misericordiae University Hospital, nine with clinically determined FOG symptoms (freezers) and seven non-freezers. All participants navigated through a customised virtual reality (VR) corridor by stepping in place (SIP) on a force plate. Simultaneously, brain activity was recorded. Subjects performed a dual cognitive visual go/no-go response task, recorded during SIP and while seated. C. Results: All but one freezer displayed FOG episodes during testing. The percentage of time spent frozen was significantly longer during the dual task while SIP compared to the SIP task alone. The EEG analysis time locked to the participant's response show a P3b component preceded by a negative component in non-freezers in both stepping and seated conditions. However, for freezers this negative component was only elicited when seated. D. Conclusion: The VR environment proves to be a reliable method for inducing FOG. Freezers showed decreased gait and behavioural performance when the SIP condition was combined with a secondary cognitive task. Furthermore, the absence of a negative ERP peak preceding the P3b component for freezers during the SIP condition despite robust visual responses, suggests pathological interference of the motor response preparation for PD subjects with FOG.

P71 Towards an understanding of Semaphorin-6A function in cortical lamination.

Molecular biology and genetics

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The cell surface guidance molecule, Semaphorin-6A (Sema6A), is known to interact with Plexin-A2 and Plexin-A4 to direct lamination and organisation of various layered structures in the brain, including the retina, hippocampus and cerebellum. Through analyses of Sema-6A mutant animals we are characterising a novel role for this molecule in organising cortical layers 1, and 2/3 and directing lamination of the layer 2 layer 1 border. In Sema-6A mutant animals, cell bodies that are normally confined to the borders of layer II are seen to stray into the marginal zone and the normally dense, uniform assembly of cell bodies juxtaposed against dense neuropil at the interface layer 2 and marginal zone is perturbed. The ectopic cells consist largely of Cux-1 positive layer II/III pyramidal neurons and are obviously ectopic by postnatal day 2. Apical dendrites normally densely packed in the neuropil are loosened and appear to either branch early or invade the outer layer 2 border. In situ hybridisation confirms that the most severely affected cells express Plexin-A2 but not Plexin-A4, while cells that co-express these molecules are less severely affected, though still visibly perturbed. Interestingly, preliminary immunohistochemical analyses of Plexin-A2 knockouts show no ectopic layerII/III phenotype while PlxA4 -/-, PlxA2-/- double knockout results in ectopic layer II cells and similarly disorganised neuropil. We hypothesise an interaction between Sema6A, Plexin-A2 and Plexin-A4 normally keeps these layers separate and aids in the orchestration of the final stages of radial migration for cortical neurons.

P72 Plasma from APP-PS1 mice upregulates the expression of CXCL1 in J774.2 cells

Neuroimmunology

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Monocytes are rapidly recruited to the site of tissue damage or inflammation where they differentiate into macrophages of varying phenotypes. Classical activation (M1) can be induced by inflammatory stimuli such as lipopolysaccharide (LPS) or interferon-γ (IFNγ), and alternative activation (M2) is induced by anti-inflammatory cytokines like interleukin (IL)-4/IL-13. Our objective was to first assess if the M1 phenotype can be induced by IFNγ in a mouse monocyte/macrophage cell line, J774.2, and to investigate if amyloid-β (Aβ) has a similar effect. Secondly, we sought to determine if the plasma from an animal model of Alzheimer's disease, APP-PS1, exerts a greater pro-inflammatory effect than its wild-type counterparts on J774.2 cells. We incubated J774.2 cells in the presence of IFNγ (20ng/ml), Aβ (10μM), or plasma from wild-type (WT) and APP-PS1 mice (15-17 months old) for 4 hours. IFNγ and Aβ significantly increased mRNA expression of

archetypal markers of M1 activation tumour necrosis factor (TNF)a, IL-6 and inducible nitric oxide synthase (iNOS). Aβ, but not IFNγ, significantly increased the expression of CXCL1. CXCL1 mRNA was also increased in J774.2 cells that were incubated with plasma from APP mice but not WT mice. The evidence indicates that Aβ induces J774.2 cells to adopt the M1 activation state, mimicking the effect of IFNg. Significantly, Aβ increased expression of CXCL1, and a similar effect was induced when cells were incubated with plasma from APP-PS1 mice. Further investigation will determine whether this is due to the presence of Aβ or some other component present in the plasma.

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