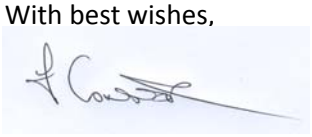
3rd Annual Neuroscience Ireland Conference

The Local Organising Committee are delighted to welcome you to the 3rd annual conference of Neuroscience Ireland.

This year's programme brings together national and international researchers spanning all areas of neuroscience, with a particular emphasis on Neurodegeneration & Neurorepair; Psychiatric Disorders; Neuropharmacology; and Learning, Memory & Cognition. We are also delighted to host a satellite symposium entitled "MRI applications in experimental neuroscience" which will highlight developments in small animal imaging in the Neurosciences in Ireland.

We very much hope you enjoy the conference as well as your stay in Dublin.

With best wishes,

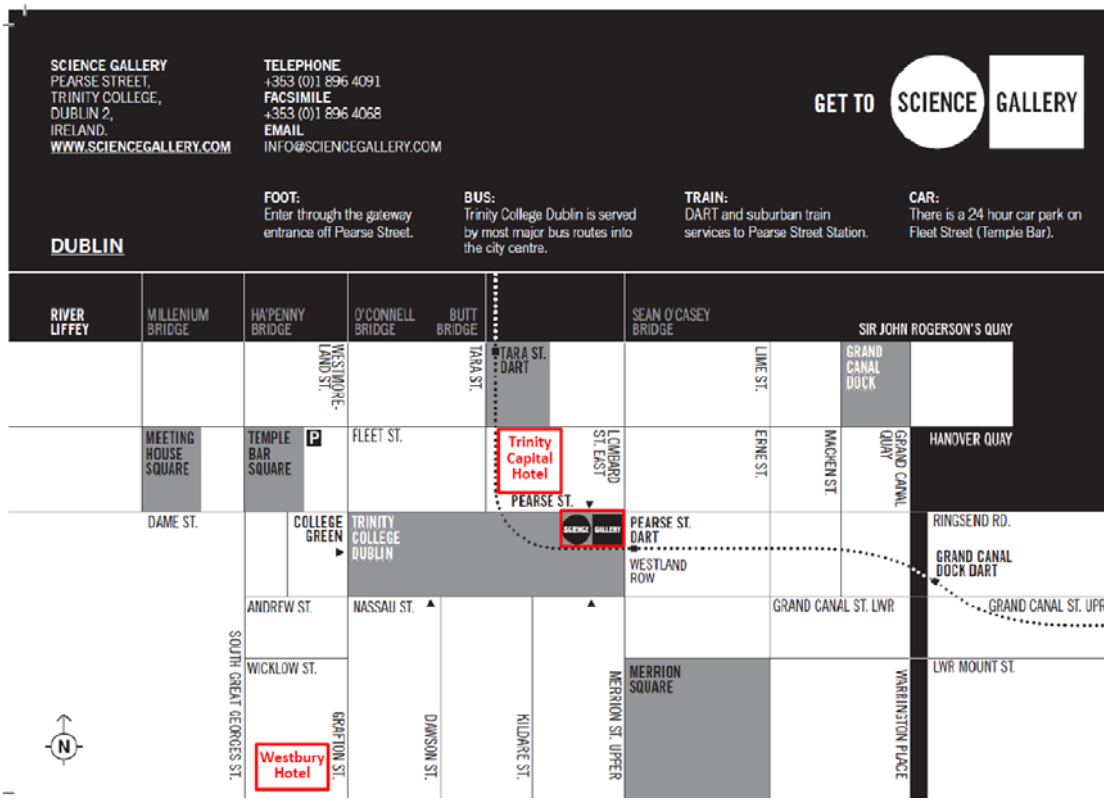


Dr. Thomas Connor
Chair, Local Organising Committee

Coffee & Lunch: Coffee and lunch will be provided on the upper level of the Science Gallery.

Prizes: Prizes will be awarded for the best oral communication and best poster presented by a postgraduate student or post-doctoral reseacher. Runner-up prizes in each category will also be awarded.

Conference Dinner: The conference dinner will be held on Thursday 10th September at 8 pm in the Westbury Hotel on Grafton Street.



Sponsors

The Local Organising Committee wish to thank the following organisations and companies for their generous support of Neuroscience Ireland 2009:

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Trinity College Institute of Neuroscience

Science Gallery

European Brain and Behaviour Society (EBBS)

Bio-Sciences

Scientific Programme, Thursday 10th September 2009

9.15-10:15		**Registration, Tea & Coffee**
10.15-10:30		**Opening of the conference/Welcome address** Prof. Patrick Prendergast, Vice-Provost, Trinity College Dublin Dr. Kieran McDermott, President, Neuroscience Ireland.
SESSION I ***Chairpersons:***		**NEURODEGENERATION & NEUROREPAIR** Prof. Veronica Campbell & Dr. David Henshall
10:30-11:15	IS-1	**Invited speaker (sponsored by SFI)** ***Prof. Scott Small,*** Columbia Univeristy, New York, USA *Zooming in on Alzheimer's disease: MRI maps to molecular mechanisms*
11:15-11:30	OP-1	***Megan Coakley,*** Department of Biochemistry, University College Cork *Hyperactivation of Akt associates with the accumulation of Aβ in the 3 x Tg-AD model of Alzheimer's disease with associated defects in insulin receptor status*
11:30-11:45	OP-2	***Malgorzata Dytko,*** School of Medicine and Medical Science, Conway Institute, University College Dublin *Further insights into the function of the troyer syndrome protein, Spartin*
11:45-12:00	OP-3	***Dr. Colm Cunningham,*** School of Biochemistry and Immunology & Trinity College Institute of Neuroscience, Trinity College Dublin *Mimetic of viral systemic infection exacerbates neurodegenerative disease: Microglial priming and amplified CNS IL-1β and type I interferon responses*
12:00-12:15	OP-4	***Dr. Hans-Georg König,*** Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland *Excitotoxicity and p65/NF-κB: Characterization of differentially regulated signalling cascades in neurons*
12:15-1:00	IS-2	**Invited speaker (sponsored by SFI)** ***Prof. Christopher Linington,*** Univeristy of Glasgow, Scotland *From adaptive immunity to neuronal degeneration*
1:00-2:00		**LUNCH, POSTERS & TRADE EXHIBITION** **Neuroscience Ireland Council meeting, TCIN boardroom**

Scientific Programme, Thursday 10th September 2009

SESSION II		**PSYCHIATRIC DISORDERS**
Chairpersons:		Prof. Declan McLoughlin & Prof. Ciaran Regan
2:00-2:45	IS-3	**Invited speaker (sponsored by SFI)** ***Dr. Trevor Sharp,*** University of Oxford, UK *Neurobiological effects of altered 5-HT transporter expression: Implications for depression and anxiety*
2:45-3:00	OP-5	***Prof. Thomas Frodl,*** Department of Psychiatry & Trinity College Institute of Neuroscience, Trinity College Dublin *Effects of stress and genetic vulnerability of endophenotypes in major depression?*
3:00-3:15	OP-6	***Dr. Andrew Coogan,*** Department of Psychology, National University of Ireland, Maynooth *Disruption of behavioural, endocrine and molecular circadian rhythms in adult attention deficit/hyperactivity disorder*
3:15-3:30	OP-7	***Bartlomiej Lukasz,*** Applied Neurotherapeutics Reseach Group, UCD School of Biomolecular and Biomedical Science, Conway Institute, University College Dublin *Aberrant immune signalling in rodent models of schizophrenia*
3:30-3:45	OP-8	***Prof. Declan McLoughlin,*** Department of Psychiatry & Trinity College Institute of Neuroscience, Trinity College Dublin *Cognitive effects of electroconvulsive therapy for depression: A systematic review and meta-analysis*
3:45-4:30	IS-4	**Invited speaker (sponsored by SFI)** ***Prof. Nick Craddock,*** University of Cardiff, UK *Rethinking psychosis*
4:30-5:30		**Poster Session I (P1-1 to P1-55 to present), Tea & Coffee**

Scientific Programme, Thursday 10th September 2009

SATELLITE SYMPOSIUM: MRI Applications in Experimental Neuroscience

***Chairpersons*:** Dr. Andrew Fagan & Dr. Andrew Harkin

5:30-5:40		***Joseph Gallagher*,** Trinity College Institute of Neuroscience *Introduction to MRI*
5:40-5:50	MRI-1	***Ronan Kelly,*** Trinity College Institute of Neuroscience *Optimized voxel-based morphometry and T2 relaxometry reveal significant age-related decreases in areas of the rat brain*
5:50-6:00	MRI-2	***Christoph Blau,*** Trinity College Institute of Neuroscience *Age-related magnetic resonance relaxometry changes in rat brain cannot be accounted for by changes in grey matter volume as measured by voxel-based morphometry (VBM)*
6:00-6:10	MRI-3	***Joseph Gallagher,*** Trinity College Institute of Neuroscience *The age-related decrease in T2 relaxation time is not exacerbated in male APP/PS1 at 8-9 months of age*
6:10-6:20	MRI-4	***Michael Kelly,*** Trinity College Institute of Neuroscience *Quantitative functional magnetic resonance imaging with bolus-tracking arterial spin labelling*
6:20-6:30	MRI-5	***Dr. Oliviero Gobbo,*** School of Pharmacy and Pharmaceutical Sciences & Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2. *RNAi-mediated reversible opening of the blood-brain barrier and blood-retina barrier*
6:20-6:30	MRI-6	***Jennifer Rouine,*** School of Pharmacy and Pharmaceutical Sciences & Trinity College Institute of Neuroscience, Trinity College Dublin *Perfusion magnetic resonance imaging using spin labelling of arterial water shows increased cortical blood flow following methylenedioxymethamphetamine (MDMA; "Ecstasy") administration to rats*
6:40-7:00		Discussion

8:00 **CONFERENCE DINNER, Westbury hotel**

Scientific Programme, Friday 11th September 2009

SESSION IV		**NEUROPHARMACOLOGY**
Chairpersons:		Dr. Caroline Herron & Dr. Daniel Ulrich
9:00-9:45	IS-5	**Invited speaker (sponsored by SFI)** ***Prof. Bernhard Bettler,*** University of Basel *Molecular basis for functional and pharmacological heterogeneity of native GABA-B responses*
9:45-10:00	OP-9	***Laura Batti,*** UCD School of Biomolecular and Biomedical Science, Conway Institute, University College Dublin. *A role for the prolyl hydroxylase inhibitor, DMOG, on synaptic transmission and neuroprotection in an ex vivo model of stroke*
10:00-10:15	OP-10	***Dr. Eric Downer,*** Institute of Immunology, Department of Biology, National University of Ireland Maynooth *An investigation of the anti-inflammatory properties of the cannabinoid compound R(+)WIN 55,212-2 in primary glia and U373 astrocytoma cells*
10:15-10:30	OP-11	***Dr. Sarah Harney,*** Department of Physiology, Trinity College Dublin *Synaptic NMDA receptor subunit composition and plasticity in principal cells and interneurons in the dentate gyrus*
10:30-10:45	OP-12	***Dr. Olivia O'Leary,*** Neuroscience Center, University of Helsinki, Finland & School of Pharmacy, University College Cork *The antidepressant fluoxetine increases expression of synaptic proteins in the hippocampus of a model of reduced hippocampal synapse density*
10:45-11:15		**TEA & COFFEE, POSTERS and TRADE EXHIBITION**
11:15-12:00	IS-6	**Invited speaker (sponsored by GlaxoSmithKline)** ***Prof. Paul Matthews,*** Imperial College, London, and Glaxo SmithKline Clinical Imaging Centre, Hammersmith Hospital, UK. *Imaging for translational pharmacology*

Scientific Programme, Friday 11th September 2009

12:00-1:00 **POSTER DATA BLITZ (10 x 3min talks + 2min of questions)**
Chairperson: Prof. Marina Lynch

P1-16
MIDKINE IS A LEARNING-ASSOCIATED PEPTIDE WITH POTENT EFFECTS ON HIPPOCAMPAL NEURITE OUTGROWTH AND HIPPOCAMPAL-DEPENDENT MEMORY CONSOLIDATION.
L. M. Connole, N. C. O'Sullivan, J. Connellan, C. Regan, M. N. Pangalos, D. von Schack, M. Beyna, R. H. Ring, K. J. Murphy.

P1-33
THE ROLE OF GSK-3B IN INFLAMMATION INDUCED CHANGES IN EMBRYONIC RAT HIPPOCAMPAL CELL FATE.
H.F. Green, Y. Nolan.

P1-34
BRIEF SACRAL NERVE ROOT STIMULATION INCREASES CORTICAL SOMATOSENSORY POTENTIAL EVOKED BY ELECTRICAL STIMULATION OF THE ANAL CANAL IN AN EXPERIMENTAL MODEL.
K. M. Griffin, C. O'Herlihy, P. R. O'Connell, J. F.X. Jones

P1-42
A METHOD FOR THE RAPID ASSESSMENT OF VISUAL PROCESSING LATENCIES IN MULTIPLE SCLEROSIS
E.C. Lalor, R. Lonergan, H. Kiiski, K. Kinsella, R.B. Reilly, M. Hutchinson, N. Tubridy, R. Whelan**.**

P1-49
GLOBAL DOWNRELULATION OF MIRNAS IN TEMPORAL LOBE EPILEPSY
R.C. Mc Kiernan, E.M. Jimenez-Mateos, I. Bray, R. Stallings, N. Delanty, D. Henshall.

P1-55
UNCOVERING THE NEURAL SIGNATURE OF LAPSING ATTENTION: ELECTROPHYSIOLOGICAL PREDICTORS OF HUMAN ERROR ARE APPARENT UP TO 20s IN ADVANCE
R. G. O'Connell, P. M. Dockree, I. H. Robertson, M. A. Bellgrove, J. J. Foxe, S. P. Kelly.

P2-11
ENDOCANNABINOIDS PREVENT LYSOSOMAL MEMBRANE DESTABILISATION EVOKED BY TREATMENT WITH β-AMYLOID IN RAT CULTURED CORTICAL NEURONES
J.J. Noonan, R. Tanveer, S. Cunningham, V.A. Campbell

P2-13
THE ROLE OF THE ENDOCANNABINOID SYSTEM IN THE RAT DORSOLATERAL PERIAQUEDUCTAL GREY IN FEAR-CONDITIONED ANALGESIA
W.M.Olango, M.Roche, D.P. Finn.

P2-22
THE TRANSCRIPTION COFACTOR MKL REGULATES HIPPOCAMPAL MEMORY-ASSOCIATED NEURONAL STRUCTURAL REORGANISATION
N.C. O'Sullivan, M. Pickering, F. Carr, D. Di Giacomo, J.S. Loscher, K.J. Murphy.

P2-47
ELUCIDATING THE CORTICAL CORRELATES OF THE PERCEPTION OF NATURALNESS
T. A. Whitaker, C. Simões-Franklin, F. N. Newell.

Scientific Programme, Friday 11th September 2009

1:00-2:00		**LUNCH** **& NEUROSCIENCE IRELAND AGM (1.30 – 2pm)**
SESSION IV ***Chairpersons*:**		**LEARNING, MEMORY AND COGNITION** Prof. John O'Doherty & Dr. Aine Kelly
2:00-2:45	IS-7	**Invited speaker (sponsored by EBBS and SFI)** ***Prof. Wolfram Schultz,*** University of Cambridge, UK *Neurophysiology of reward and risk*
2:45-3:00	OP-13	***Amy Birch,*** Department of Physiology & Trinity College Institute of Neuroscience, Trinity College Dublin. *Environmental enrichment in the absence of exercise enhances cognitive function in the male Wistar rat.*
3:00-3:15	OP-14	***Sabina Brennan,*** School of Psychology & Trinity College Institute of Neuroscience, Trinity College Dublin. *Contribution of alpha to memory failures in healthy elderly*
3:15-3:30	OP-15	***Dr. Graham Sheridan,*** Applied Neurotherapeutics Research Group, UCD School of Biomolecular and Biomedical Science, Conway Institute, University College Dublin *The chemokine, fractalkine (CX3CL1), modulates synaptic plasticity and is upregulated in the rat hippocampus following a spatial learning task.*
3:30-3:45	OP-16	***Dr. Robert Whelan,*** Department of Neurology, St. Vincent's University Hospital/University College Dublin & Trinity Centre for Bioengineering, Trinity College Dublin. *ERP abnormalities in Multiple Sclerosis patients: A high density EEG study.*
3:45-4:45		**Poster Session II (P2-1 to P2-50 to present), Tea & Coffee**
4:45-5:30	IS-8	**Invited speaker (sponsored by SFI)** ***Prof. Adrian Owen,*** University of Cambridge, UK *When thoughts become actions: Detecting awareness in the vegetative state*
5:30-5:45		**FAREWELL AND PRIZEGIVING**

***POSTER SESSION I:* P1-1 to P1-55**
Presenting author to be present during ***Poster Session I: 4.30-5.30 on Thursday 10th September***

P1-1
BEHAVIOURAL DISTURBANCES OBSERVED IN EXPERIMENTAL COLITIS ARE ASSOCIATED WITH ACTIVATION OF THE KYNURENINE PATHWAY AND EXPRESSION OF HEPATIC TRYPTOPHAN 2,3 DIOXYGNEASE
A. Abautret-Daly, C. Medina, T.J. Connor, A. Harkin

P1-2
MODULATION OF CLAUDIN-5 AND P-GLYCOPROTEIN EXPRESSION IN THE AGED RAT BRAIN
H.J. Abuhusain, A.M. Lynch

P1-3
GREY MATTER VOLUME REDUCTIONS IN THE HIPPOCAMUS AND INSULAR CORTEX AS BIOMARKERS OF VULNERABILITY TO DEPRESSION
F. Amico, N. Koutsouleris, E. Meisenzahl, M. Reiser, T. Frodl

P1-4
EFFECT OF QUANTUM DOTS ON DIFFERENTIATED PHEOCHROMOCYTOMA CELLS
B.R. Prasad Bodi, A. Tonery, N. Nikolskaya, D. Connolly, T.J. Smith, S.J. Byrne, Y.K. Gun'ko, Y. Rochev.

P1-5
CIRCADIAN REGULATION OF NF-κB P65 IN SERUM SHOCKED FIBROBLASTS
A.L. Beynon, K. Baer, J. Davies, A.N. Coogan

P1-6
THE EFFICACY OF EXERCISE AS A COGNITIVE ENHANCER IN MALE WISTAR RATS: ANALYSIS OF UNDERLYING MECHANISMS.
R. G. Bechara, Á. M. Kelly

P1-7
THE EFFECT OF CHRONIC INGESTION OF ETHANOL ON THE ANXIETY AND SPATIAL MEMORY OF RATS
V. Bortolani, G.M. Miquelin, M.S. Graça, R.M. Álvares, M.M. Iyomasa, M.L.N.M. Rosa.

P1-8
ISOFORMS OF B-AMYLOID PRECURSOR PROTEINS ARE DECREASED IN HIPPOCAMPUS OF RATS REARED IN ISOLATION FROM WEANING.
R.G. de Souza, L.N. Kerbauy, R.S. Sestito, L.B. Tridade, M.M. Iyomasa, M.L.N.M. Rosa.

P1-9
RATS REARED UNDER ISOLATION SHOW A REDUCTION IN THE EXPRESSION OF β-AMYLOID IN HIPPOCAMPUS AND AMYGDALA.
L.N. Kerbauy, R.G. de Souza, R.S. Sestito, L.B. Tridade, M.M. Iyomasa, M.L.N.M. Rosa.

P1-10
THE EFFECT OF MATERNAL SEPARATION ON FEAR AND ANXIETY BEHAVIORS AND ON SPATIAL MEMORY.
F.H. Limonte, M.T.R. Pereira, M.M. Iyomasa, M.L.N.M. Rosa.

P1-11
BEHAVIOURAL EFFECTS OF DIETARY TRYPOTPHAN MANIPULATIONS ON C57BL/6J AND BALB/C MICE
C.A. Browne, G. Clarke, T.G. Dinan, J.F. Cryan.

P1-12
MITOCHONDRIAL LOCALIZATION OF THE FOXO3A TRANSCRIPTION FACTOR.
A. Caballero-Caballero, T. Engel, M. Dunleavy, E.M. Jimenez-Mateos, P.Weizova, P. Chang, D.C. Henshall.

P1-13
5HT6 RECEPTOR ANTAGONIST SB742457 RECOVERS AN AGE RELATED DEFICIT IN WORKING MEMORY BUT NOT IN SPATIAL MEMORY IN THE RAT
C.K. Callaghan, B. Wan Wang, H. Milton, M. Maloney, A. Della Chiesa, V. Hok, D.J. Virley, N. Upton, S.M. O'Mara.

P1-14
TEST-RETEST RELIABILITY ANALYSIS OF EVENT RELATED POTENTIALS.
S.M. Cassidy, R.G. O'Connell, I.H. Robertson

P1-15
AUDIO-VISUAL SEARCH IN DEPTH USING 'REAL' AND 'VIRTUAL' ENVIRONMENTS
J. S. Chan, C.T. Maguinness, S. Dobbyn, P. McDonald, H. J. Rice, C. O'Sullivan, F. N. Newell

P1-16
MIDKINE IS A LEARNING-ASSOCIATED PEPTIDE WITH POTENT EFFECTS ON HIPPOCAMPAL NEURITE OUTGROWTH AND HIPPOCAMPAL-DEPENDENT MEMORY CONSOLIDATION.
L. M. Connole, N. C. O'Sullivan, J. Connellan, C. Regan, M. N. Pangalos, D. von Schack, M. Beyna, R. H. Ring, K. J. Murphy.

P1-17
DEFICIENCY IN SIGIRR LEADS TO IMPAIRMENT OF SYNAPTIC PLASTICITY AND HIPPOCAMPAL-DEPENDENT MEMORY
D.A. Costello, M.B. Watson, M.A. Lynch.

P1-18
A CD200 FUSION PROTEIN EXERTS ANTI-INFLAMMATORY EFFECTS *IN VITRO* AND *IN VIVO*
F. Cox, A.M. Miller, A. Lyons, M.A. Lynch.

P1-19
A NOVEL PROTEIN COMPLEX PICK1-PARKIN-CDC4A LINKING MITOCHONDRIAL DYSFUNCTION TO PARKINSON'S DISEASE
D. Deb, K.K. Dev

P1-20
CD200 RECEPTOR-LIGAND INTERACTIONS IN THE SPINAL CORD IN EAE DISEASE PROGRESSION.
B.F. Deighan, A.C. Murphy, M.A. Lynch.

P1-21
SOCIAL STRESS IN ADOLESCENT NRG1 HETEROZYGOUS KNOCKOUT MICE – A PUTATIVE MODEL OF GENE × ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA.
L. Desbonnet, C. O'Leary, N. Clarke, C. O'Tuathaigh, D. Lai, R. Harvey, J.L.Waddington.

P1-22
EFFECT OF DISTAL CUE CONFIGURATION LOCATION ON MORRIS WATER MAZE PERFORMANCE: AN IN-DEPTH BEHAVIOURAL AND MOLECULAR ANALYSIS.
M. Diviney, S. Commins

P1-23
IDENTIFICATION OF NOVEL PROTEINS REGULATING S1P-R AND PAEL-R RECEPTOR TRAFFICKING
P. Dutta, L.M. Healy, K.K. Dev.

P1-24
WHITE MATTER TRACTS IN EUTHYMIC BIPOLAR 1 DISORDER: A DTI STUDY OF THE CINGULUM BUNDLE AND UNCINATE FASCICULUS
L. Emsell[1], L. Holleran[1], A. Leemans[2], C. Langan[1], G. Barker[3], W. van der Putten[1], P. McCarthy[1], R. Skinner[1], C. McDonald[1], D. M. Cannon[1]

P1-25
THE INFLUENCE OF FACIAL EXPRESSION ON ASSOCIATIVE MEMORY PERFORMANCE AND THE RELATIONSHIP TO CORTISOL LEVELS.
J. Feeney, S.M. O'Mara.

P1-26
DELINEATING THE ROLE OF THE BASAL FOREBRAIN CHOLINERGIC SYSTEM IN DELIRIUM DURING DEMENTIA USING THE MURINE-p75-SAPORIN IMMUNOTOXIN
R. Field, A. Gossen, A. O'Connor, C. Cunningham.

P1-27
ELECTROPHYSIOLOGICAL INDICES OF ATTENTIONAL DECREMENTS IN MILD COGNITIVE IMPAIRMENT
S.P. Finnigan, R.G. O'Connell, R. Reilly, I.H. Robertson.

P1-28
IDENTIFICATION OF CAPTODIAMINE AS A PUTATIVE ANTIDEPRESSANT
S. Gannon, R. Ring, M. Pickering, A. Coyle, L. Conboy, N. O'Boyle, D. Scully, C. M. Regan.

P1-29
THE GEOMETRY AND INFORMATION CARRYING CAPACITY OF SPIKE TRAINS
J.B. Gillespie , C.J. Houghton.

P1-30
THE β_2-ADRENOCEPTOR AGONIST CLENBUTEROL ATTENUATES KAINIC ACID-INDUCED NEUROINFLAMMATION AND APOPTOSIS IN THE HIPPOCAMPUS: A ROLE FOR BDNF
L.C. Gleeson, T.J. Connor, A. Harkin

P1-31
AGE-RELATED BEHAVIOURAL DEFICITS IN RATS CHRONICALLY TREATED WITH AMYLOID-β PEPTIDE
R. Gonzalez-Reyes, T. Cowley, M.A. Lynch.

P1-32
THE EFFECT OF Δ^9-TETRAHYDROCANNABINOL ON POST TRANSLATIONAL MODIFIERS OF THE PRO-APOPTOTIC TUMOUR SUPPRESSOR PROTEIN p53.
A. Gowran, C.E. Murphy, V.A. Campbell.

P1-33
THE ROLE OF GSK-3β IN INFLAMMATION INDUCED CHANGES IN EMBRYONIC RAT HIPPOCAMPAL CELL FATE.
H.F. Green, Y. Nolan.

P1-34
BRIEF SACRAL NERVE ROOT STIMULATION INCREASES CORTICAL SOMATOSENSORY POTENTIAL EVOKED BY ELECTRICAL STIMULATION OF THE ANAL CANAL IN AN EXPERIMENTAL MODEL.
K. M. Griffin, C. O'Herlihy, P. R. O'Connell, J. F.X. Jones

P1-35
DEVELOPMENTAL EXPOSURE TO 17β-ESTRADIOL DOES NOT ALTER NEURAL CELL FATE IN WISTAR RATS.
K.A. Harris, L.J. Mulryan, K.J. Murphy, C.M. Regan.

P1-36
WHAT IS A NEURON'S FIRING RATE?
C. Houghton.

P1-37
WORDS IN THE BRAINS LANGUAGE: A MISMATCH NEGATIVITY STUDY
W. Hutch, R. Fourie, C.M. Pettigrew.

P1-38
AUTOBIOGRAPHICAL MEMORY IN AMNESTIC MILD COGNITIVE IMPAIRMENT: EXPLORATION OF AUTONOETIC CONSCIOUSNESS AND CONTEXT-DEPENDENT MEMORY
M. Irish, B.A. Lawlor, S.M. O'Mara, R.F. Coen.

P1-39
STIMULATION OF THE TRANSSULFURATION PATHWAY BY GLIOTOXINS IN C6 GLIOMA CELLS
S. Kandil, L. Brennan, G. McBean.

P1-40
PINK1: MUTATIONS IN WHICH CAUSE PARKINSONISM, IS ALSO DEFECTIVE IN ALZHEIMER' DISEASE
A.P. Kiely, A.M. Moloney, M.F. Coakley, and C. O' Neill

P1-41
P3 ABNORMALITIES IN MULTIPLE SCLEROSIS AS A FUNCTION OF OLIGOADENYLATE SYNTHETASE GENOTYPE
H. Kiiski, R. Lonergan, R. Whelan, H. Nolan, K. Kinsella, M O'Brien, R.B. Reilly, M. Hutchinson, N. Tubridy.

P1-42
A METHOD FOR THE RAPID ASSESSMENT OF VISUAL PROCESSING LATENCIES IN MULTIPLE SCLEROSIS
E.C. Lalor, R. Lonergan, H. Kiiski, K. Kinsella, R.B. Reilly, M. Hutchinson, N. Tubridy, R. Whelan**.**

P1-43
INDUCTION OF BURST-FIRING MEDIATED LONG-TERM DEPRESSION IS INDEPENDENT OF IONOTROPIC EPSPs.
F. Lanté, D. Ulrich.

P1-44
THE IMPACT OF FUNCTIONAL BRAIN CONNECTIVITY ON PREDICTION AND THERAPY EVALUATION IN MAJOR DEPRESSION
D. Lisiecka, J. Scheuerecker, N. Koutsouleris, E. Meisenzahl, M. Reiser, T. Frodl.

P1-45
AUDIO-VISUAL SPEECH PROCESSING IN OLDER ADULTS
K.E. Burke, C. T. Maguinness, A. Setti, R.A. Kenny, F.N. Newell

P1-46
THE EFFECTS OF ALERTNESS ON SELECTIVE ATTENTION
L.P. McAvinue, S. Vangkilde, K.A. Johnson, S. Kyllingsbaek, T. Habekost, C. Bundesen, I.H. Robertson.

P1-47
MIXED EMOTIONS: AUDITION CAN MODULATE THE VISUAL PERCEPTION OF THE EMOTION OF A CROWD.
J.E. McHugh, F.N. Newell

P1-48
Bifidobacterium infantis 35624 REDUCES VISCERAL HYPERACTIVITY IN A RAT MODEL OF CHRONIC STRESS
D. P McKernan, C. Bongiovanni, P. Fitzgerald, T. G Dinan, J.F Cryan

P1-49
GLOBAL DOWNRELULATION OF MIRNAS IN TEMPORAL LOBE EPILEPSY
R.C. Mc Kiernan, E.M. Jimenez-Mateos, I. Bray, R. Stallings, N. Delanty, D. Henshall.

P1-50
THE ROLE OF AGEING ON EFFICIENT AUDIO-VISUAL INTEGRATION IN THE BRAIN: AN EEG STUDY
L. McLaren, R. Sobolewski, A. Setti, S. Finnigan, R. B. Reilly, I. H. Robertson, F. N. Newell.

P1-51
SIMVASTATIN MODULATES HIPPOCAMPAL NEURONAL EXCITABILITY AND SYNAPTIC PLASTICITY IN C57/BLACK6J MICE.
C. Metais, C.E. Herron.

P1-52
MESENCHYMAL STEM CELLS FROM THE GREEN FLUORESCENT PROTEIN TRANSGENIC RAT ARE HYPOIMMUNOGENIC FOLLOWING TRANSPLANTATION TO THE INTACT ADULT RAT STRIATUM
T.C. Moloney, P. Dockery, F.P. Barry, A.J. Windebank, L. Howard, E. Dowd.

P1-53
THE ENDURING EFFECT OF COGNITION ENHANCING DRUGS ON GENE EXPRESSION IN THE RODENT HIPPOCAMPUS
S. Moyna, K.J. Murphy

P1-54
INTRACEREBRAL INFUSION OF ROTENONE INTO THE STRIATUM OR SUBSTANTIA NIGRA CAUSES BEHAVIOURAL DEFICITS AND NIGROSTRIATAL DEGENERATION ASSOCIATED WITH PARKINSON'S DISEASE.
P.J. Mulcahy, A. Paucard, S. Walsh, E. Dowd

P1-55
UNCOVERING THE NEURAL SIGNATURE OF LAPSING ATTENTION: ELECTROPHYSIOLOGICAL PREDICTORS OF HUMAN ERROR ARE APPARENT UP TO 20s IN ADVANCE
R. G. O'Connell, P. M. Dockree, I. H. Robertson, M. A. Bellgrove, J. J. Foxe, S. P. Kelly.

POSTER SESSION II: **P2-1 to P2-51**

Presenting author to be present during ***Poster Session II: 3.45-4.45pm on Friday 11th September***

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IS-1: ZOOMING IN ON ALZHEIMER'S DISEASE: MRI MAPS TO MOLECULAR MECHANISMS

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Although assumed to be mechanistically distinct, both late-onset Alzheimer's disease and normal aging cause hippocampal dysfunction. Based on the molecular anatomy of the hippocampal formation we have hypothesized that AD and aging should target separate subregions that make up the hippocampal formation. Pinpointing hippocampal subregions differentially affected by AD and aging is potentially important, for diagnostic purposes but also for identifying underlying mechanisms. In order to achieve this goal, we first optimized a high-resolution variant of fMRI so that the functional integrity of hippocampal subregions could be assessed in humans and animal models. By imaging AD patients, aging rhesus monkeys, and mouse models of disease, we have identified hippocampal subregions differentially affected by AD and aging. Next, relying on this imaging information as a guide, we used gene-expression technology to identify molecular correlates underlying AD and aging. In the case of AD, deficiencies in retromer, a trafficking and sorting complex, was identified as the top hit. Finally, to confirm the pathophysiological relevance of this finding we developed and characterized genetically-modified retromer-deficient mice and flies, and show that they recapitulate many key features of AD and provide mechanistic insight into the pathogenesis of this devastating and intractable illness.

IS-2: FROM ADAPTIVE IMMUNITY TO NEURONAL DEGENERATION

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Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterised by formation of persistently demyelinated plaques of astroglial scar tissue in white matter tracts. For many years loss of myelin was considered the major cause of neurological dysfunction in MS, but this "myelinocentric" view of the disease was revised following recognition that axonal pathology provides a better correlate to clinical symptoms. There is however a complex relationship between inflammatory demyelination and axonal pathology in the CNS. Inflammation will induce acute axonal injury and conduction block, but does not necessarily lead to the extensive irreversible axonal loss as seen in patients with MS. However, axonal damage is exacerbated by demyelination which not only increases axonal susceptibility to inflammatory mediators such as nitric oxide, but also disrupts axo-glial interactions important for long-term axonal survival. These observations led to speculation that axonal injury in MS is simply a result of "bystander damage secondary to inflammatory demyelination, but can such collateral damage account for the extensive loss of axons seen in patients with chronic disease? An increasing number of clinical and pathological studies suggest not, raising the possibility that additional pathomechanisms are involved in the development of this axonal pathology in MS. The presence of immunoglobulins and complement activation products in MS lesions is often stated as evidence for the involvement of antibodies in disease pathogenesis; a concept supported by the efficacy of therapeutic plasma exchange and B cell depleting therapies in some patients. Yet the specificity, mode of action and clinical relevance of autoantibodies in MS remains controversial. The majority of studies have focused on the role of myelin-specific antigens such as myelin oligodendrocyte glycoprotein (MOG), galactosyl ceramide or sulphogalactosyl ceramide that can act as targets for autoantibody-mediated demyelination in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. In contrast, the possible significance of autoantibody responses to neuronal and axonal antigens in MS has gone largely unrecognised. We have now identified neurofascin as a target for antibody-mediated axonal injury in a subset of patients with MS and will discuss the significance of antibody-dependent mechanisms in the development of axonal pathology and neurodegeneration in MS and other diseases.

IS-3: NEUROBIOLOGICAL EFFECTS OF ALTERED 5-HT TRANSPORTER EXPRESSION: IMPLICATIONS FOR DEPRESSION AND ANXIETY

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Brain 5-hydroxytryptamine (5-HT) neurones are implicated in common and complex behavioural traits, and variation in 5-HT neurotransmission is widely considered to be a major psychiatric disorder risk factor. The 5-HTT gene plays a critical role in the regulation of synaptic 5-HT, and is one of the most intensively investigated human gene in terms of its association with neuropsychiatric phenotypes. However, it is often uncertain if reported genotype-phenotype associations are due to variation in 5-HTT expression or some other linked neurobiological mechanism. As an example, one common polymorphism in the promoter region of the human 5-HTT gene that increases 5-HTT expression, is linked with low anxiety and reduced risk of depression in human populations. However it is unproven whether, as predicted, this link is due to increased 5-HTT expression and resulting changes in 5-HT transmission. We tested this hypothesis by studying the neurochemistry and behaviour of mice genetically engineered to overexpress the 5-HTT (Jennings et al, J Neuroscience (2006) 26:8955-64). The mice showed a 2-3 fold increase in 5-HTT mRNA and protein. In both *in vivo* microdialysis and *in vitro* voltammetry studies, the mice had decreased 5-HT release which was reversed (in part) by 5-HTT blockade. The mice exhibited a low anxiety phenotype in a range of tests including elevated plus maze and fear conditioning, and this phenotype was also reversed by 5-HTT blockade. In comparison, the mice lacked a clear phenotype in a range of other behavioural tests. These findings suggest that increased 5-HTT expression is associated with reduced anxiety, and mediated by decreased 5-HT transmission. Interestingly, the neurochemical and behavioural phenotypes of 5-HTT overexpressing mice are in many ways opposite to those reported in 5-HTT knock-out mice (Murphy & Lesch, Nature Rev. Neuroscience 9:85-96). Collectively, these studies provide a neurobiological basis for human 5-HTT genotype-phenotype associations.

IS-4: RETHINKING PSYCHOSIS

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It has been conventional for psychiatric research, including the search for predisposing genes, to proceed under the assumption that schizophrenia and bipolar disorder are separate disease entities with different underlying etiologies. These represent the traditional dichotomous classification of the so-called "functional" psychoses and form the basis of modern psychiatric diagnostic practice. Recently positive findings have been emerging in molecular genetic studies of psychoses. However, the pattern of findings shows increasing evidence for an overlap in genetic susceptibility across the traditional classification categories - including association findings at DISC1 and NRG1. Genome-wide association studies (GWAS) now provide greater power to explore the relationship between mood and psychotic illness. Within the context of the Wellcome Trust Case Control Consortium (WTCCC) we have studied 2700 mood-psychosis cases and 3000 controls and several other large-scale studies have been undertaken, including studies of structural genomic variation. The emerging evidence suggests the existence of both relatively specific as well as more general relationships between genotype and psychopathology. For example, in our dataset variation at $GABA_A$ receptor genes is associated with susceptibility to a form of illness with mixed features of schizophrenia and bipolar disorder. Genome-wide significant associations at CACNA1C in bipolar disorder and ZNF804A in schizophrenia show evidence for a contribution to susceptibility across the traditional diagnostic boundaries. The elucidation of genotype-phenotype relationships is at an early stage, but current findings highlight the need to consider alternative approaches to classification and conceptualization for psychiatric research rather than continuing to rely heavily on the traditional dichotomy. As psychosis susceptibility genes are identified and characterized over the next few years, this will have a major impact on our understanding of disease pathophysiology and will lead to changes in classification and the clinical practice of psychiatry.

IS-5: MOLECULAR BASIS FOR FUNCTIONAL AND PHARMACOLOGICAL HETEROGENEITY OF NATIVE GABA-B RESPONSES

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$GABA_B$ receptors are the G-protein-coupled receptors for γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain. $GABA_B$ receptors are promising drug targets for a wide spectrum of psychiatric and neurological disorders. Receptor subtypes exhibit no pharmacological differences *in vitro* and are based on the subunit isoforms $GABA_{B1a}$ and $GABA_{B1b}$, which associate with $GABA_{B2}$ subunits to form heteromeric $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors. $GABA_{B1a}$ differs from $GABA_{B1b}$ in its ectodomain by the presence of a pair of conserved protein-binding motifs, the sushi domains. We started to address individual functions of the two receptor subtypes by generating 1a-/- and 1b-/- mice, which express either one or the other $GABA_{B1}$ subunit isoform. Studies with 1a-/- and 1b-/- mice revealed that the subunit composition of $GABA_B$ receptors determines their spatial distribution within neurons. A highly conserved feature in the central nervous system is that $GABA_{B(1a,2)}$ receptors are more abundant than $GABA_{B(1b,2)}$ receptors at glutamatergic terminals. However, it remained unclear whether $GABA_{B(1a,2)}$ are more efficient than $GABA_{B(1b,2)}$ receptors in inhibiting glutamate release in response to physiological activation. We now have analyzed this question at hippocampal mossy fiber terminals. In addition, we recently identified an abundant secreted $GABA_{B1}$ isoform comprising the two sushi domains. I present data suggesting that secreted $GABA_{B1}$ isoforms are of regulatory significance.

While $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors have indistinguishable properties *in vitro,* it has been shown that $GABA_B$ receptors exhibit differences in agonist potency, desensitization rate and tonic activity *in vivo*. The reasons for these native differences are unclear. We have used a combined genetic and electrophysiological approach to analyze how phosphorylation of a serine residue that alters $GABA_B$ receptor desensitization *in vitro* influences $GABA_B$ responses *in vivo*. Our data provide a molecular explanation for pharmacological and functional differences between native $GABA_B$ responses.

IS-6: IMAGING FOR TRANSLATIONAL PHARMACOLOGY

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Translational pharmacology refers to biologically driven therapeutics development involving hypothesis-led research that is performed across levels of biological complexity (e.g., cells to tissue preparations) across species (e.g., mouse to man). It involves moving from bench to bedside- and back again. Imaging provides a powerful enabling tool for translational pharmacology, as it allows quantitative measures of pharmacology and physiology to be performed non-invasively in the living animal or human. In this way, imaging for translational pharmacology can be contrasted with diagnostic imaging as technically used in a clinic. Clinical diagnostic imaging is testing a general null hypothesis: is the image 'normal'? It is typically qualitative and categorical. Imaging for translational pharmacology, however, tests specific pharmacological hypotheses and is quantitative. A broad range of imaging tools can be used- covering a range of spatial and temporal dimensions- depending on the question that needs to be answered. In neurosciences, common types of questions that are approached using particular positron emission tomography (PET) or magnetic resonance imaging approaches include problems of biodistribution, receptor occupancy and pharmacodynamics. In specific applications, the latter may allow differentiation of mechanisms between pharmacologically active molecules. There remains hope that imaging may provide a tool, either in clinical trials (or later, in clinical applicatios) to stratification of patients. A first goal with use of imaging tools is to provide more confident and more efficient development of new therapeutics by answering key questions early, particularly early after transition to human studies. Ultimately, we want to develop more targeted therapeutics, delivering them to the *right* patient with greater confidence.

IS-7: NEUROPHYSIOLOGY OF REWARD AND RISK

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The functions of rewards are based primarily on their effects on behaviour and are less directly governed by the physics and chemistry of input events as in sensory systems. Therefore the investigation of neural mechanisms underlying reward functions requires behavioral theories that can conceptualize the different effects of rewards on behavior. Animal learning theory and economic utility theory have produced a theoretical framework which can help to elucidate the neural correlates for reward functions in learning, goal-directed approach behavior and decision-making under uncertainty. The reward system of the brain is comprised of specific structures which include the midbrain dopamine neurons, orbitofrontal cortex, striatum and amygdala. The neural activity can be related to basic theoretical terms of reward and uncertainty, such as magnitude, probability, expected value and variance (risk).

IS-8: WHEN THOUGHTS BECOME ACTIONS: DETECTING AWARENESS IN THE VEGETATIVE STATE

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How can we ever know, unequivocally, that another person is aware?
Leaving deeper philosophical considerations aside about the nature of consciousness itself, the only reliable method we have for detecting awareness in others is by eliciting a predicted response to an external prompt or command. Logically therefore, our ability to detect awareness in others is determined, not by whether they are aware or not, but by their ability to communicate that fact through a recognised behavioural response. This problem exposes a central conundrum in the study of awareness in general, and in particular, how it relates to so-called 'disorders of consciousness' such as the vegetative state. From this perspective, I discuss various solutions to this problem using functional neuroimaging. In particular, I will contrast those circumstances in which fMRI data can be used to infer awareness in the absence of a reliable behavioural response, with those circumstances in which it cannot.

OP-1

HYPERACTIVATION OF AKT ASSOCIATES WITH THE ACCUMULATION OF Aβ IN THE 3 X TG-AD MODEL OF ALZHEIMER'S DISEASE WITH ASSOCIATED DEFECTS IN INSULIN RECEPTOR STATUS

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Insulin receptor (IR) and IGF-1 receptor (IGF-1R) mediate many of their essential metabolic, growth and survival functions *via* activation of the serine threonine kinase Akt. Defects in this signalling pathway are emerging to be an integral part of Alzheimer's disease (AD) pathogenesis, where pathological increases in neuronal Akt activation are associated with loss of Akt signalling neurons [1] linked to defects indicative of reduced IR and IGF-1R responsiveness [2].

We hypothesise that this aberrant signalling results from Aβ accumulation in AD. To determine whether this is the case, the present study investigated whether the progressive accumulation of Aβ and tau pathology in the 3xTg-AD mouse associates with alterations in Akt and IR status. 3xTg-AD and non-transgenic (non-Tg) littermates (*Mus musculus,* strain 129SVxC57) were employed using isoflurane as an anaesthetic prior to cervical dislocation. Brains were formalin-fixed, paraffin embedded, and sectioned for immunofluorescent microscopy.

Results from immunofluorescent microscopy with antibodies to activated phospho^{Ser473}-Akt, Akt, IR, Aβ and pathological hyperphosphorylated tau (PHF-1) detected a strong relationship between Akt activation, IR loss and developing AD pathology in 3xTg-AD mice. Significantly increased levels of phospho^{Ser473}-Akt and decreased levels of IR were evident from 6, 12, and 18 months of age in 3xTg-AD mice. Double immunofluorescent microscopy detected a clear relationship between the accumulation of intracellular neuronal Aβ, increased Akt activation and decreased IR levels, with IR colocalising with extracellular plaques at 18 months. The spatiotemporal relationship between phospho^{Ser473}-Akt, IR, Aβ and PHF1 is more difficult to delineate. However, increased phospho^{Ser473}-Akt and decreased IR levels correlate with increased PHF-1 levels. Age-matched non-Tg mice did not show the aforementioned signalling defects. We conclude that Aβ may drive hyperactivation of Akt in AD neurons, thereby blocking IR (IGF-1R) induced activation of Akt, causing defects in neuronal survival, metabolism and function.

Breeding pairs of 3xTg-AD mice and 129SV x C57 littermates were very kindly provided by Professor Frank LaFerla, University of California, Irvine, CA, USA. We gratefully acknowledge financial support from Science Foundation Ireland (Research Frontiers Programme)

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OP-2

FURTHER INSIGHTS INTO THE FUNCTION OF THE TROYER SYNDROME PROTEIN, SPARTIN

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Hereditary spastic paraplegia describes a group of neurodegenerative diseases characterized by lower limb progressive weakness and spasticity. Troyer syndrome is an autosomal recessive form of hereditary spastic paraplegia caused by a frameshift mutation (1110delA) in the *SPG20* gene encoding spartin protein, the cellular function of which remains unknown. Knowledge about spartin interactors is also very limited. In this study we apply a broad spectrum of proteomics techniques to identify novel spartin binding proteins. We used a Tandem Affinity Purification technique followed by HPLC-mass spectrometry to characterize potential spartin binding partners. Selected putative interactions were confirmed by co-immunoprecipitation experiments. We identified 94 potential spartin-binding proteins which were grouped into functional categories. We performed co-immunoprecipitation experiments to confirm that spartin interacts with GRP78, GRP75 and nucleolin proteins. Additionally our mass spectrometry results confirmed previously published information about spartin interaction with ubiquitin and the E3 ubiquitin-protein ligases, AIP4/Itch and AIP5/WWP1. Our studies suggest that spartin is a multifunctional protein and for the first time we suggest a role for spartin in protein folding and turnover both in mitochondria and endoplasmic reticulum. We also show for the first time interaction between spartin and a nucleolar protein, nucleolin.

OP-3

MIMETIC OF VIRAL SYSTEMIC INFECTION EXACERBATE NEURODEGENERATIVE DISEASE: MICROGLIAL PRIMING AND AMPLIFIED CNS IL-1β AND TYPE I INTERFERON RESPONSES

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Chronic neurodegeneration provokes a local inflammatory response, but the role of inflammation in the progression of neurodegenerative disease remains unclear. We have previously shown that the resident brain macrophages, the microglia, are primed by chronic neurodegeneration, making them susceptible to exaggerated cytokine responses to systemic challenges with bacterial lipopolysaccharide (LPS) with consequent acute cognitive impairments and accelerated progression of disease. Poly inosine:polycytidine (poly I:C) is an agonist of toll-like receptor 3 (TLR3) and induces type I interferons (IFNα/β), thus mimicking anti-viral acute phase responses. In the current study we hypothesized that systemic challenge of mice with poly I:C during chronic neurodegenerative disease would exacerbate CNS inflammation, produce acute neurological impairments and accelerate progression of disease. Using the murine ME7 model of prion disease and systemic challenge with poly I:C (12 mg/kg) we have shown that prior disease primes these animals to suffer heightened hypothermic responses with respect to normal controls treated with poly I:C. Poly I:C induced the pro-inflammatory genes IL-1β, IL-6 and TNF-α in normal animals but resulted in higher levels of IL-1β and IL-6 and depressed expression of TNF-α in ME7 animals. ME7+poly I:C animals also showed exaggerated IFNβ expression and amplified expression of several IFN-dependent genes confirmed its expression and action in the brain. Among these IFN-dependent genes, increased protein kinase R (PKR) and oligoadenylate synthetase (OAS) transcription suggested activation of pro-apoptotic pathways in the brain of ME7+poly I:C animals and this was associated with acute neurological changes and acceleration of disease. The finding that systemic poly I:C accelerates neurodegeneration has implications for the control of systemic viral infection during chronic neurodegenerative disease and indicates that type I interferon responses in the brain are not necessarily benign.

This work was supported by the Wellcome Trust.

OP-4

EXCITOTOXICITY AND P65/NF-κB: CHARACTERIZATION OF DIFFERENTIALLY-REGULATED SIGNALLING CASCADES IN NEURONS.

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Neuronal development, plasticity and survival depend on constitutive activity of the transcription factor nuclear factor-kappaB (NF-κB). In addition, excitotoxic injury as incurred during ischemia, epilepsy or neurodegenerative diseases has repeatedly been linked to elevated nuclear NF-κB. Synaptic NF-κB activation was characterized previously, and we recently found a constitutive clustering of activated NF-κB in the axon-initial segment (AIS) of neurons. However, the upstream regulators of neural NF-κB are largely unkown and the impact of the transcription factor on cell survival remains controversial.

To clarify the role of NF-κB in excitotoxic injury we treated neurons with the glutamate agonist NMDA (100 μM). Nuclear translocation of p65-eGFP, IκBα-Cerulean and cell death was monitored in real-time. Fifteen or thirty minutes of NMDA-excitation resulted in increased p65 translocation. However, when applied for thirty minutes the majority of neurons did not recover from mitochondrial membrane potential ($\Delta\Psi_m$) loss and died within a four hour period. While these neurons retained p65-eGFP in the nucleus, recovery of $\Delta\Psi_m$ correlated with fast nuclear export of p65-eGFP. Surprisingly, p65-eGFP translocation was preceded by IκBα-Cerulean nuclear translocation rather than its degradation. Prolonged excitotoxicity also released sequestered p65 from the AIS, independent of proteasomal or calpain-mediated degradation of the NF-κB inhibitor. Furthermore, shRNA-mediated knock-down of the AIS-specific cytoskeletal anchor AnkyrinG ablated the constitutive NF-κB cascade in the AIS and resulted in increased κB-reporter-gene activity.

Our results suggest compartment-specific, differentially-regulated NF-κB activation in our models. In addition, our experiments suggest that excitotoxic stimli activate NF-κB pathways that differ from the canonical pathways which require proteolysis of IκBα. Further analysing the impact of these differential pathways on neuronal survival or death will deepen our understanding of classical and non-classical NF-κB signaling cascades in neurons.

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OP-5

DISRUPTION OF BEHAVIOURAL, ENDOCRINE AND MOLECULAR CIRCADIAN RHYTHMS IN ADULT ATTENTION DEFICIT/ HYPERACTIVITY DISORDER

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Circadian rhythms are patterns in various parameters with periods of approximately twenty four hours. The circadian clock is a key determinant of the sleep-wake cycle, and sleep disturbance is a hallmark of a number of psychiatric conditions. We examined circadian rhythmicity in a common psychiatric condition, adult attention-deficit/hyperactivity disorder (ADHD; [1]). ADHD in adults manifests itself through behavioural and attentional problems, and is strongly associated with social maladaptation. Previous work has indicated that sleep regulation is compromised in adult ADHD, and a previous genetic study has associated the circadian system with this condition [2].

Adult ADHD (n=12) and age and sex-matched controls (n=24) were recruited from an outpatients clinic. Subjects wore an ActiWatch to gather behavioural data over a period of at least 1 week. Subjects were then asked to take buccal swabs and saliva samples every 4 hours for a 24 hour period in the home setting. Quantitative real time PCR was carried out for the expression of the clock genes *PER2* and *BMAL1* in oral mucosa and ELISA was used to determine salivary cortisol and melatonin levels. Circadian rhythmicity was assessed by the single cosinor method.

Actigraphic data revealed significant differences between the groups in a number of parameters, most strikingly in the deviation of the circadian period in the patient group away from 24h ($p<0.05$). The control groups displayed significantly ($p<0.05$) rhythmic expression of *PER2* and *BMAL1* with peaks of expression in the early to mid morning for both groups. The ADHD group did not display rhythmic expression of either *PER2 or BMAL*. Likewise in the control group both cortisol and melatonin displayed their expected rhythmic profiles (peaking at 8am and 4am respectively), whilst the ADHD group did not display rhythmic expression of either melatonin or cortisol. These results indicate a marked circadian dysfunction in adult ADHD which may be significant in the aetiology and/or symptommology of the condition.

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OP-6

EFFECTS OF STRESS AND GENETIC VULNERABILITY OF ENDOPHENOTYPES IN MAJOR DEPRESSION?

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Experimental studies found that stress results in neuroplastic changes and suggest that these processes may also occur during depressive episodes. The aim of the studies were to translate these findings into research in patients with major depression.

We investigated patients with major depression and healthy controls during the illness course over 3 years using structural MRI and over 4 weeks during a treatment trial using functional und structural MRI as well as with genetic analysis.

Our investigations in patients with major depression support the findings from experimental studies that neuroplastic stress-related processes occur in hippocampus, amygdala, DMPFC, DLPFC and ACC during depressive episodes. In turn, those patients with more structural abnormalities had a more severe illness course. Moreover, stress and genetics interact and have effects on structural integrity of the brain. Structural alterations also influence the function of brain networks implemented in regulation of emotions as shown with combined structural MRI and functional MRI investigations. Antidepressant treatment can normalize these functional abnormalities in ACC, DMPFC and DLPFC, whereby antidepressants with different mechanisms of action have different effects on the functional brain networks.

In conclusion, depressive episodes can result in structural abnormalities particular in patients with a more severe disease course and, in turn, these structural abnormalities predict a bad clinical outcome as well as functional alterations in the network of emotion regulation. Antidepressant therapy results in normalization of altered functional brain circuits. Whether antidepressant therapy also affects the brain structures remains unknown and needs further investigations.

OP-7

ABERRANT IMMUNE SIGNALLING IN RODENT MODELS OF SCHIZOPHRENIA

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Schizophrenia is unusual among neurodevelopmental disorders in that the positive, negative and cognitive symptoms that characterise the disorder are not evident in the early years of life but rather emerge in the late teenage period. Studies of the aetiology of schizophrenia suggest genetic risk interacts with environmental insults, such as second trimester influenza infection or traumatic childhood events, to impinge on cortical development in particular in the prefrontal cortex and hippocampus.

Here, we have investigated the consequences of combining two environmental models of schizophrenia-like behavioural deficits, isolation rearing from postnatal day 25 and immune challenge with viral dsRNA analogue, poly(I:C), in male Wistar rats across the critical postnatal day 36 to 44 period of prefrontal cortical maturation.

Our results confirmed isolated animals to have a deficit in sensorimotor gating as revealed by decreased pre-pulse inhibition (PPI). Interestingly, animals treated with polyI:C appeared normal at postnatal day 60 with a PPI deficit only emerging at postnatal day 80. Combination of the insults did not exacerbate the deficits seen with either insult alone suggestive of a convergence on a common mechanism of disruption. To further investigate this possibility, using qPCR, we assayed the hippocampal dentate gyrus of isolated animals for alterations viral response genes, namely, Irf7, Mx2, Pkr and Ifit2. These analyses revealed a profound decrement (6.5 – 46.9%) in expression of these genes across the postnatal day 30-40 period. Moreover, western blot analysis showed an associated decrease (18.7%) of Irf7 protein in P40 isolated animals. In summary, our findings suggest that disruption of specific immune response systems may be an important common component of several environmental insults known to increase risk of developing schizophrenia.

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OP-8

COGNITIVE EFFECTSPF ELECTROCONVULSIVE THERAPY FOR DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Electroconvulsive therapy (ECT) is the most acutely effective treatment for depression but use may be limited by cognitive effects. However, research regarding persistence, severity and precise pattern of these effects is inconsistent.

To quantify ECT-induced cognitive changes as measured by standardised tests, specify their configuration and determine progression over time. MEDLINE, EMBASE, PsycARTICLES, PsychINFO and PsychLIT were systematically searched through December 2008. Reference lists from relevant reviews were also searched.

All independent, within-subjects design studies (either randomised, cohort or case control) of depressed patients receiving ECT where cognition was assessed using standardised tests.

Cognitive effects on intellectual and global functioning, attention, episodic memory, spatial, and executive functioning were summarised using standardised pooled means of pre-post treatment differences by a fixed-effect model with respect to delay between end of ECT course and cognitive testing. Information was also extracted on potential moderators, e.g. electrode placement, stimulus waveform, ECT frequency.

Twenty-four cognitive variables from 84 studies (2981 patients) were meta-analysed. Significant decreases in cognitive performance were observed 0-3 days after ECT in 72% of variables with effect sizes ranging from -1.10 (95% confidence interval [CI], -1.53 to -0.67) for executive functioning to -0.21 (95% CI, -0.40 to -0.01) for visual memory. Four to 15 days after ECT, all but one CI included zero or showed positive effect sizes, from 0.28 (95% CI, 0.07 to 0.49) for visual memory to 0.51 (95% CI, 0.30 to 0.62) for verbal memory. No negative effect sizes were observed after 15 days with 57% of variables showing positive effect sizes, ranging from 0.35 (95% CI, 0.07 to 0.63) for verbal memory to 0.75 (95% CI, 0.43 to 1.08) for executive functioning. Moderators did not influence cognitive outcomes after three days post-ECT.

As detected by standardised tests, these cognitive abnormalities associated with ECT, are mainly limited to the first three days post-treatment. Pre-treatment levels of functioning are subsequently recovered. After 15 days, processing speed, working memory, anterograde memory and some aspects of executive function improve beyond baseline levels.

OP-9

A ROLE FOR THE PROLYL HYDROXYLASE INHIBITOR, DMOG, ON SYNAPTIC TRANSMISSION AND NEUROPROTECTION IN AN *EX VIVO* MODEL OF STROKE

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A reduction in oxygen availability in neurones triggers a broad spectrum of transcriptional and non-transcriptional responses inducing adaptation to insufficient oxygen supply. One of the main mechanisms leading to these adaptations is the activation of hypoxia-inducible transcription factor-1α (HIF-1α) which regulates the expression of numerous genes including vascular endothelial growth factor (VEGF) and adrenomedullin [1]. Hypoxic regulation of gene expression can be mimicked by dimethyloxalylglycine (DMOG), a cell permeable competitive inhibitor of HIF1-α prolyl hydroxylase, which leads to the stabilization of HIF. Although DMOG application appears as a highly attractive target for therapeutic intervention in ischaemic disease [2, 3], its effect on synaptic activity is unknown. We have investigated the action of DMOG on transcriptional and non-transcriptional changes in rat hippocampal slices and compared the changes in synaptic transmission to those occurring in brain slices exposed to low oxygen. We also investigated the therapeutic effects of DMOG pre-conditioning on neuronal viability in an *ex vivo* model of stroke. External field recording and staining experiments were carried out in the rat CA1 hippocampus a region found to be very vulnerable to hypoxic injury. We report here for the first time similarities between DMOG treatment and hypoxic exposure in brain slices, both in terms of transcriptional changes and in relation to the synaptic response. Both treatments resulted in HIF-1α and P-IKKα/β accumulation in hippocampal tissue ($p<0.05$), reversible depression of synaptic transmission (at 0.1 and 1 mM DMOG) ($p<0.01$), increased paired pulse facilitation and reduced NMDA receptor activation ($p<0.05$). In addition, pre-conditioning with DMOG in organotypic hippocampal slices showed a neuroprotective effect in an ex vivo model of stroke. These results indicate a key role for PHD inhibitors in synaptic transmission and a putative strategy to pharmacologically induce neuro-protection in the hippocampus.

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OP-10

AN INVESTIGATION OF THE ANTI-INFLAMMATORY PROPERTIES OF THE CANNABINOID COMPOUND *R*(+)WIN 55,212-2 IN PRIMARY GLIA AND U373 ASTROCYTOMA CELLS

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One of the most intriguing actions of cannabinoids is their ability to regulate inflammation. Cannabinoids have potential medicinal value for the treatment of a variety of inflammatory conditions and are currently under investigation for the management of symptoms of multiple sclerosis (MS) and arthritis. In support of this, previous data from our laboratory has demonstrated that the synthetic cannabinoid *R*(+)WIN 55,212-2 exerts anti-inflammatory properties by abrogating pro-inflammatory cytokine-induced signalling in human astrocytes[1]. In the current study we investigated the proclivity of *R*(+)WIN 55,212-2 to impact pro-inflammatory signalling events induced by Toll-like receptor 3 (TLR3) in response to the double-stranded RNA mimic poly(IC) and by TLR4 in response to lipopolysaccharide (LPS). We report that *R*(+)WIN 55,212-2 abrogates both TLR3 and TLR4 induction of the chemokine, RANTES (regulated upon activation, normal T cell expressed and secreted) and the pro-inflammatory cytokine, tumour necrosis factor-alpha (TNF-α) in human U373 astrocytoma cells stably transfected with CD14. In addition, pre-exposure of U373 cells to *R*(+)WIN 55,212-2 prevented TLR4 induction of nuclear factor-kappa B (NF-κB)-regulated reporter gene, further highlighting the anti-inflammatory potential of *R*(+)WIN 55,212-2. The ability of *R*(+)WIN 55,212-2 to impact TLR4 pro-inflammatory signalling was CB_1 receptor-independent, since pre-exposure of U373 cells to both SR141716 and AM251 failed to reverse the *R*(+)WIN 55,212-2-induced attenuation of LPS-induced NF-κB reporter gene, RANTES and TNF-α. Theses findings were also assessed in parallel in primary murine glial cells. Overall these data demonstrate that future experiments into the pharmacology and molecular mechanisms underlying the anti-inflammatory properties of cannabinoids will provide the insight necessary to develop effective treatments for a range of neuroinflammatory disorders.

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OP-11

SYNAPTIC NMDA RECEPTOR SUBUNIT COMPOSITION AND PLASTICITY IN PRINCIPAL CELLS AND INTERNEURONS IN DENTATE GYRUS

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Diverse populations of inhibitory interneurons with distinct anatomical distributions and characteristic firing properties regulate the activity of principal cells. The dentate gyrus receives cortical input from the perforant path which forms excitatory synapses on the principal granule cells (GCs) and on inhibitory interneurons (INs). Perforant path excitation of interneurons activates feed-forward inhibition which strongly regulates the induction of synaptic plasticity in GC dendrites and, in other brain regions there is evidence for different synaptic properties depending on the postsynaptic target cell type. We have previously described NMDAR-mediated synaptic transmission and plasticity at the medial perforant path-granule cell synapse and here we investigate if NMDARs make a similar contribution to synaptic input in INs and if INs express plasticity of NMDAR-EPSCs that is comparable to that in principal cells. NMDAR-EPSCs recorded from hilar INs had significantly slower decay kinetics compared to those recorded in GCs (weighted decay time constant $\tau = 31 \pm 1$ ms and 62 ± 5 ms for GCs and INs, respectively, $n = 21$ and 27, $P < 0.001$). Inhibition of NMDAR-EPSCs by ifenprodil (3 μM) was similar with depression of 28 ± 6 % of control in GCs ($n = 5$) and 36 ± 8 % of control in INs ($n = 7$), suggesting a similar contribution of NR2B-containing NMDARs. Expression of the NR2D NMDAR subunit in hippocampal interneurons has been reported and, in this study, the NR2D-preferring antagonist UBP141 (3 μM), inhibited NMDAR-EPSCs in INs by 27 ± 4 % of control amplitude ($n = 7$), but had no effect on currents recorded in GCs (99 ± 3 % of control, $n = 4$). High frequency stimulation (HFS) induced LTP of NMDAR-EPSCs in GCs under conditions of low Ca^{2+} buffering and, by contrast, resulted in LTD of NMDAR-EPSCs in INs. Postsynaptic intracellular BAPTA (10 mM) prevented plasticity in GCs, but did not inhibit LTD in INs (72 ± 3 % in control, $n = 13$,and 67 ± 2 % of control with BAPTA, $n = 6$). In addition, coefficient of variation analysis is consistent with a presynaptic change in LTD in INs, suggesting that different mechanisms mediate plasticity of NMDAR-EPSCs at the same afferent inputs to GCs and INs. Further studies will investigate how differences in NMDAR subtypes and plasticity correlate with specific interneuron populations and how NMDAR plasticity in INs influences EPSP-spike coupling and the efficacy of inhibition onto GCs.

OP-12

THE ANTIDEPRESSANT FLUOXETINE INCREASES EXPRESSION OF SYNAPTIC PROTEINS IN THE HIPPOCAMPUS OF A MODEL OF REDUCED HIPPOCAMPAL SYNAPSE DENSITY

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We have previously hypothesized that antidepressants exert their effects by increasing synapse turnover, which in turn may improve information processing in neural networks which are disrupted in depression, such as the hippocampus (Castren, 2005). However, synapses are highly dynamic and increases in synapse turnover may induce significant reorganization of neuronal connections without producing any net change in synapse number. Increases in synapse turnover might become more apparent if a model of reduced synapse density is employed. Therefore, we used ovariectomy (OVX) of the rat as a tool to reduce hippocampal spine synapse density and we subsequently treated sham and OVX rats with the antidepressant, fluoxetine for 21 days. Using Western blotting, we measured changes in the expression of proteins associated with synapse structure, strength and activity namely, PSD-95, the AMPA-receptor subunit GluR1 and phosphosynapsin (Ser9), respectively. Fluoxetine treatment increased expression of phosphosynapsin, PSD-95 and synaptic GluR1 (but not total GluR1) in the hippocampus of OVX but not sham rats. Since BDNF and signalling at its receptor, TrkB, can mediate behavioural responses to antidepressants and can induce neuronal plasticity, we also investigated the contribution of TrkB signalling to fluoxetine-induced changes in synaptic protein expression. To this end, the same experiment was conducted in transgenic mice overexpressing a truncated form of the TrkB receptor (TrkB.T1) which inhibits the activation of the full-length TrkB receptor. Fluoxetine treatment produced a small but significant increase in hippocampal PSD-95 in OVX wildtype mice but not in OVX TrkB.T1 mice or sham mice. In contrast to the rat study, fluoxetine treatment did not alter expression of synaptic GluR1 in OVX mice of either genotype, and did not reverse OVX-induced decreases in hippocampal phosphosynapsin in either genotype. Taken together, these results suggest that chronic fluoxetine treatment might induce changes in neuronal connectivity though alterations in synaptic protein expression and at least some of these effects require TrkB signalling. Furthermore, these effects were only observed in ovariectomised animals, thus suggesting that fluoxetine might only induce such effects when hippocampal synaptic connectivity is perturbed.

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OP-13

ENVIRONMENTAL ENRICHMENT IN THE ABSENCE OF EXERCISE ENHANCES COGNITIVE FUNCTION IN THE MALE WISTAR RAT

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Environmental enrichment has been demonstrated to improve cognitive function in rats, with evidence indicating a role for the neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neuronal proliferation in this process(1). Here we have investigated the effect of different periods of environmental enrichment on object recognition (OR) learning. In parallel, we assessed neurogenesis and expression of NGF protein in the dentate gyrus (DG), a brain region reported to play a role in OR learning.

Male Wistar rats were divided into control (n=6), 2 week (n=6), 3 week (n=8) and 6 week enriched (n=6) groups. Rats were housed 3 per cage: a variety of toys (changed weekly), but not exercise equipment, was placed in the cages of the enriched groups. To measure neurogenesis, rats were injected with 5-bromo-2'-deoxyuridine (BrdU; 50mg.kg^{-1} i.p.) 3 times weekly in the last 2 weeks of their enrichment; control rats were injected in weeks 5 and 6. Rats were tested on the OR task in a circular open field post-enrichment. This task tests the ability of rats to discriminate between a novel and a familiar object 24h following exposure to 2 novel objects.

All groups explored the novel object more than the familiar object ($p<0.001$, two-way ANOVA). In addition, both 3 week and 6 week enriched rats explored the novel object more than the control rats suggesting a cognitive improvement ($p<0.001$, two-way ANOVA).The enriched groups show a temporal increase in NGF protein concentration in the DG, that is significant after 6 weeks ($p<0.05$, one-way ANOVA). There is also a significant increase in BrdU+ labeled nuclei in the DG of the 6 week enriched rats ($p<0.001$, one-way ANOVA).

These data indicate a time-dependent cognitive-enhancing effect of environmental enrichment that is independent of physical activity. These data also support a role for increased expression of NGF in DG, and possibly neurogenesis, in mediating this effect.

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OP-14

CONTRIBUTION OF ALPHA TO MEMORY FAILURES IN HEALTHY ELDERLY.

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A large percentage of older adults do not demonstrate decline in cognitive performance (1). This could mean that cognitive decline is not inevitable with age but may be indicative of early pathology. The objective was to identify novel markers sensitive to age-related and disease-induced cognitive decline.

Twenty-one young (18-28) and 43 older (65-78) adults underwent electrophysiological and neuropsychological investigation. Memory function was assessed by the WMS-III and a novel memory task (cued-encoding/delayed-recognition). Relative Alpha (~10Hz) was measured under two resting EEG conditions (Eyes-Closed/Eyes-Open). Older participants were characterised as cognitively intact (n=25) or compromised (n=18) based on the relationship between their Logical-Memory-II score and their NART-estimated pre-morbid IQ. Whilst IQ for compromised and intact adults were not significantly different, compromised adults had significantly lower memory scores than intact (p<.0005) and young (p<.0005) adults. There was no significant difference in memory between the intact and young groups.

Analysis of variance showed statistical differences (p<.0005) in cognitive function (MMSE) for the three groups. Post-hoc tests (Tukey-HSD) indicated that compromised adults had significantly poorer scores than intact (p<.003) and young (p<.0005). Young and intact groups did not differ significantly. D-prime measures of accuracy on the novel memory task showed that all three groups benefitted from cued encoding (p <0.0005); however, overall recognition performance was significantly reduced in the compromised adults compared to the intact (p<.031) and young (p<.0005). Relative Alpha showed a systematic reduction in power across groups. Compromised adults showed lowest alpha compared to intact (p<.047) and young (p<.0005). Young adults exhibited highest power compared to intact old (p<.011). Whilst frontal measures (Fluency & Stroop) distinguished between young and older groups there was no significant difference between compromised and intact groups.

Resting Alpha may represent a simple easy-to-obtain measure that can distinguish between normal age-related memory change and early pathological decline.

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OP-15

THE CHEMOKINE, FRACTALKINE (CX3CL1), MODULATES SYNAPTIC PLASTICITY AND IS UPREGULATED IN THE RAT HIPPOCAMPUS FOLLOWING A SPATIAL LEARNING TASK

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Hippocampal-dependent memory formation is thought to require modifications to the strengths and efficacies of functional synaptic connections between neuronal ensembles. A group of molecules known to act as modulators of neuronal activity are the cytokine and chemokine families of proteins. Fractalkine (CX3CL1) is a unique member of chemokine ligands, displaying both chemoattractant properties through the actions of its N-terminal chemokine domain and cell adhesion properties exhibited by its membrane-bound mucin stalk C-terminal region. Cleavage of its chemokine domain by matrix metalloproteases releases fractalkine from the surface membrane of neuronal cells. Its receptor, the G protein-coupled CX3CR1, is located mainly on microglial cell-types; though there is evidence to suggest that hippocampal neurons also express the CX3CR1 receptor. In this study we trained rats in the water maze spatial learning task and measured changes in fractalkine protein expression 1, 2 and 3 h post-training in the CA1, CA3 and dentate gyrus (DG) neuronal cell populations. This was achieved by a combination of immunofluorescence, confocal microscopy and an automated image analysis programme. We found increased fractalkine expression in all 3 neuronal subpopulations 2 h post-training (CA1: K-S test, $p<0.001$, D-statistic = 0.085; CA3: K-S test, $p<0.001$, D-statistic = 0.156; DG: K-S test, $p<0.001$, D-statistic = 0.104). Western blot data suggests that the full-length fractalkine molecule is also cleaved and the chemokine domain released in the dentate gyrus at this time-point. The functional significance of this increase in hippocampal fractalkine expression 2 h following spatial learning is unknown. In order to address this question we investigated the effects of the chemokine domain of fractalkine on glutamate-induced calcium influx in mixed neuronal-glial primary cultures and found that an acute exposure to fractalkine (10 min) decreased calcium influx in neuronal (Student's t-test, $p<0.01$) but not glial cell types. We also found that fractalkine decreases neurotransmitter release *in vitro* as assessed by high potassium-induced release on FM-143 dye from synaptic vescicles (Student's t-test, $p<0.01$). This suggests that fractalkine may act *in vivo* to modulate neuronal activity in the hippocampus 2 h post-spatial learning.

OP-16

ERP ABNORMALITIES IN MULTIPLE SCLEROSIS PATIENTS: A HIGH-DENSITY EEG STUDY.

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Cognitive impairment (CI) may occur in up to 65% of multiple sclerosis (MS) patients. Cognitive event-related potentials (time-locked EEG; ERPs), provide an excellent tool for measuring the time-course of processing in the cortex. Early ERP components (P1, N1, and P2) are principally a reflection of sensory processing, whereas later ERP components (N2 and P3) reflect cognitive processing. Increased P3 latency and/or decreased P3 amplitude – a reflection of CI – has previously been described in MS. The question of whether or not P3 impairment in MS is a consequence of delayed early components caused by demyelinating lesions in primary afferent pathways that consequently prolong the N2 and P3, remains to be answered.

Thirty-nine multiple sclerosis patients (20 relapsing remitting MS, 19 secondary progressive MS) and 19 controls were recruited. The mean MS age was 42 yrs (SD: 12, range 19-61), mean illness duration was 14 yrs (SD 13, range 1.5-44 yrs), and the mean EDSS was 3 (SD 2.5, range 0-8). The mean control age was 38.95 yrs (SD 10, range 28-60 yrs). Participants completed visual and auditory oddball tasks. Data were recorded from a 136-channel EEG array. Participants also completed the Paced Auditory Serial Addition Test (PASAT).

In the visual modality, P2, P3 Central and P3 Parietal amplitudes and N2 latency were significantly different across groups. In the auditory modality, P2, N2, and P3 latencies and N1 amplitude were significantly different across groups. Post-hoc tests indicated no significant differences between RR MS and SP MS patients on any ERP component. Auditory latency correlated significantly with PASAT score over parietal scalp areas (Spearman's Rho at Pz = .49, $p < .004$).

In conclusion, the present study found significantly impaired early and late ERP components (N2 and P3) in MS patients when compared to control subjects.

MRI-1

AGE-RELATED MAGNETIC RESONANCE RELAXOMETRY CHANGES IN RAT BRAIN CANNOT BE ACCOUNTED FOR BY CHANGES IN GREY MATTER VOLUME AS MEASURED BY VOXEL-BASED MORPHOMETRY (VBM).

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An age-related decrease in grey matter volume has been documented in both humans and rats. We have also shown that age-related neuroinflammation correlates with transverse relaxation time (T2) decreases in rat grey matter structures such as cortex and hippocampus. The relationship between grey matter loss and T2 in the aged rat was investigated, to determine if the T2 decrease could be accounted for by the loss in grey matter volume.

Young (3 month old) and older (18-22 month old) male Wistar rats were anaesthetised with isoflurane and scanned in a 7-Tesla Bruker MR scanner. Data were acquired using ParaVision software (Bruker Biospin) and analysed using scripts written in IDL language (ITTVIS; relaxometry results) and FSL (FMRIB; volumetric results).

An age-related decrease in global grey matter volume in the rat as measured by MRI was found, as has been previously described in animals and humans. An age-related decrease in T2 in rat grey matter ($p<0.01$; versus young rats; ANOVA) was also identified and these changes correlated with an increase in markers of neuroinflammation.

By adapting voxel-based morphometric methods developed for human volumetric studies to the rat brain, a grey matter template was generated and age-dependent differences in grey matter distribution were investigated. An age-related decrease in global grey matter volume was evident. T2 maps were co-registered to these templates, to determine if areas of decreased T2 coincided with areas of grey matter loss.

It was concluded that the extent of age-related decrease in grey matter volume was not sufficient to account for the all the regions showing decreases in T2. This suggests that T2 changes are due to local differences at a tissue level, and cannot be explained simply by a loss of grey matter. This result provides evidence that T2 may be useful as an *in vivo* biomarker of neuroinflammation.

MRI-2

THE AGE-RELATED DECREASE IN T2 RELAXATION TIME IS NOT EXACERBATED IN MALE APP/PS1 AT 8-9 MONTHS OF AGE.

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Magnetic resonance imaging relaxation time constants, T1 and T2, have been used as potential markers of disease progression in conditions such as multiple sclerosis where neuroinflammatory changes have been described, and the possibility exists that these measures may be useful in early detection of Alzheimer's Disease (AD)[1]. Animal models of AD which overexpress amyloid precursor protein (APP) and presenilin 1(PS1) develop extracellular amyloid-bearing plaque deposition with increasing age. The presence of iron, copper and zinc in these plaques has been confirmed[2] and these metals, in addition to a dense core-restricting fluid presence in plaques, may potentially modulate T2 relaxation times.

We assessed T2 relaxation times in the brains of male wildtype mice (n=6) and male APP/PS1 transgenic mice (n=6) at 3-4 months and 8-9 months of age. Plaque deposition was investigated using immunofluorescence and congo red staining. A significant age-related T2 decrease was observed in the primary somatosensory cortex, CA1 field, CA2/CA3 fields of the hippocampus and the dentate gyrus of wildtype and APP/PS1 transgenic mice (Two-way ANOVA, $p<0.01$). Staining confirmed cortical and hippocampal plaque deposition in the transgenic group. However, hippocampal amyloid deposition displayed distinct spatial pattering with the dentate gyrus remaining free from amyloid deposition.

The results demonstrate age-related changes in T2 relaxation time are not exacerbated by the presence of amyloid plaques in 8-9 month old male APP/PS1 mice although analysis of spatial learning in the Morris water maze in mice at 8-9 months of age revealed that the performance of 8-9 month old APP/PS1 mice was impaired compared with wildtype mice.

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MRI-3

RNAi-MEDIATED REVERSIBLE OPENING OF THE BLOOD-BRAIN AND BLOOD-RETINA BARRIER

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The Blood-Brain barrier (BBB) and Blood-Retina barrier (BRB) remain key elements in retarding the development of novel therapeutics for the treatment of many neurodegenerative and neuromalignant disorders. These barriers contain tight-junctions (TJ's) which reduce the space between adjacent endothelial cells lining the fine capillaries of the brain and retinal microvasculature to form a selective and highly regulatable barrier. We have recently shown that in mice, the BBB and BRB can be transiently and size-selectively opened to molecules with molecular weights of up to approximately 800 Daltons using an RNAi-mediated approach involving suppression of the tight junction protein, claudin-5. We have systemically delivered siRNA targeting claudin-5 to brain microvessel endothelial cells in mice and through a series of tracer experiments and magnetic-resonance-imaging (MRI), we have shown a transient and size-selective increase in permeability at the BBB to molecules below approximately 800 Daltons.

The potential to exploit this specific compromise in BBB and BRB integrity has far reaching implications for the development of experimental animal models of neurodegenerative disorders, and for enhanced delivery of therapeutic molecules which would normally not traverse the BBB or BRB. Moreover, systemic delivery of siRNA targeting a range of other TJ-associated proteins including claudin-1, claudin-12 and occludin may yield important information into the function of these proteins in adult mice, while also potentially opening the paracellular pathway to larger molecules. Results demonstrated here in mouse models, should lead to a 'humanized' adeno-associated virus (AAV) or lentivirus form of systemic or stereotaxic delivery of siRNA/shRNA as opposed to the hydrodynamic approach used in our work to date.

MRI-4

QUANTITATIVE FUNCTIONAL MAGNETIC RESONANCE IMAGING WITH BOLUS-TRACKING ARTERIAL SPIN LABELLING

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The alterations in the BOLD signal when cerebral blood flow, volume and vascular structure change (e.g. due to aging and or neurovascular disease) are relatively unknown (1). The purpose of this study is to develop a new quantitative fMRI technique, bolus-tracking arterial spin labelling (ASL) fMRI, which provides a quantitative assessment of the blood perfusion of an activated brain region.

The theoretical and experimental approach described in (2) was applied to a rat forepaw stimulation experiment. Wistar rats (n=5) were sedated with medetomidine and electrical stimulation of the right forepaw resulted in neuronal activation in the S1FL region. Mean transit time (MTT), capillary transit time (CTT) and cerebral blood flow and volume (CBV and CBF) and the perfusion coefficient, P, were quantified by fitting theoretical curves to ASL concentration-time curves.

Both the MTT and CTT decreased significantly in the activated S1FL region compared to the same region during rest ($P = 0.0012$ and $P = 0.0082$ respectively). CBV increased significantly ($P = 0.0026$). From these results it was calculated that CBF increased by a factor of 1.353 ± 0.78 and P increased by a factor of 1.479 ± 0.148 in the activated S1FL region.

We have developed a new fMRI technique that quantifies the change in cerebral perfusion during neuronal activation. The measured increase in CBF and CBV were expected. However, the ability to quantify MTT, CTT and P are unique to this technique. We hypothesize that the increase in the novel parameter, P, represents an increase in the exchange of water between the capillary bed and tissue. The technique offers the potential to longitudinally monitor changes in these parameters during neuronal activation due to increasing age or disease progression.

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MRI-5

OPTIMIZED VOXEL-BASED MORPHOMETRY AND T2 RELAXOMETRY REVEAL SIGNIFICNT AGE-RELATED DECREASES IN AREAS OF THE RAT BRAIN

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Voxel-based-morphometry (VBM) is commonly used for analysing differences in human brain volumes [1], but similar methodology has not been developed for use in the rat brain. In this study, an optimized VBM protocol was developed for the rat brain and using this, we have undertaken an analysis of age-related changes in brain volume in rats. T2 relaxometry measurements, a biological parameter to distinguish between tissue types, were also taken in specific brain areas in young and aged rats.

High resolution structural MRI images were obtained from groups of young (N = 7) and aged (N = 7) rats using a Bruker 7 Tesla animal scanner (Bruker BioSpin, Ettlingen, Germany) and compared using FSL (FMRIB Software Library, 4.0) tools [2]. Images were skull-stripped using the brain extraction tool (within MIPAV 4.0.2 software,) and the grey matter partitions were registered to the same stereotaxic space using an in-house generic grey matter template image. The resulting images were averaged to create a study-specific template, to which the individual images were compared. Permutation-based non-parametric statistical analysis was undertaken. T2-weighted images were obtained for the relaxometry measurements.

The data indicate that there was a significant ($p=0.05$) reduction in hippocampal and cortical volume in aged, compared with young, rats. Specifically, volume reduction was observed in area CA1 of the hippocampus, as well as in the motor areas M1 and M2 of the cortex. Significant age-related T2 decreases were observed in the motor and entorhinal cortices and corpus callosum.

These findings indicate that this optimized VBM methodology can be used to analyse volumetric changes in the rodent brain.

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[2] FMRIB Software Library tools freely available at http://www.fmrib.ox.ac.uk/fsl

MRI-6

PERFUSION MAGNETIC RESONANCE IMAGING USING SPIN LABELLING OF ARTERIAL WATER SHOWS INCREASED CORTICAL BLOOD FLOW FOLLOWING METHYLENEDIOXYMETHAMPHETAMINE (MDMA; "ECSTASY") ADMINISTRATION TO RATS.

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3,4 Methylenedioxymethamphetamine (MDMA) is a popular recreational drug of abuse. It acts to increase extracellular serotonin (5-HT) by inducing its release from neuronal stores and this action is thought to underlie its psychotropic properties. In addition however, MDMA carries a risk of adverse cerebrovascular events as 5-HT plays an important role in the regulation of cerebrovascular tone. Recent advances in magnetic resonance (MR) imaging have enabled measurement of cerebral blood flow using both exogenous paramagnetic contrast agents and arterial spin labelling, which uses arterial water as an endogenous contrast agent. The aim of the current study was to determine regional changes in blood flow following acute administration of MDMA to rats using arterial spin labelling to determine cerebral blood perfusion.

Male Wistar rats (300 g approx.) were administered MDMA (20 mg/kg i.p.) and 3 hours later anaesthetised with 0.1 ml ketamine (100 mg/ml) and 0.1 ml xylazine (20 mg/ml) and the right femoral vein was catheterised to provide a blood portal for blood gas determinations. Animals were placed into 7-Tesla MRI scanner (Bruker BioSpec 70/30 magnet system). Respiratory rate was monitored continuously. A high resolution MR anatomical scan (T_2-weighted Rapid Acquisition with Relaxation Enhancement (RARE)) was acquired followed by a continuous arterial spin labelling (cASL) sequence. The sequence consisted of the preparation interval which contained the inversion pulse followed by snapshot Fast Low Angle Shot (FLASH) acquisition. Perfusion-weighted images were generated by the subtraction of labelled and control images. A recently developed model of cerebral perfusion was fitted to the experimental data using a least-squares fit. IDL 7.0, ImageJ and Mathematica software were used in the analysis of the MR scans and mean transit time (MTT), a measure that represents the time for labelled spins to traverse the vasculature, and capillary transit time (CTT), a measure of the dispersion of the labelled bolus at the region of interest, values were generated.

Both MTT and CTT are inversely proportional to blood flow. MDMA-induced a reduction in MTT and CTT values in cortical fields in both left and right hemispheres when compared to vehicle treated controls ($P < 0.05$; 2-tailed Student's T-test).

In conclusion MDMA provoked an increase in cortical blood flow in rats. cASL has sufficient temporal and spatial resolution to determine MDMA-induced changes in cerebral blood flow. Further studies will determine the dose dependency, time course and mechanisms mediating increased cortical blood flow associated with MDMA.

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P1-1

BEHAVIOURAL DISTURBANCES OBSERVED IN EXPERIMENTAL COLITIS ARE ASSOCIATED WITH ACTIVATION OF THE KYNURENINE PATHWAY AND EXPRESSION OF HEPATIC TRYPTOPHAN 2,3 DIOXYGNEASE

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Inflammatory bowel diseases (IBD) are chronic conditions characterised by uncontrolled inflammation of the intestinal mucosa. Clinical symptoms include weight loss, diarrhoea, rectal bleeding and abdominal pain. In addition to physical symptoms, patients with IBD are at increased risk of depression and anxiety. Whether these psychological disturbances occur due to stress associated with the unpleasant symptoms of IBD, or as a result of biological mediators of inflammation is unknown. It has been suggested that inflammatory cytokines (particularly IFN-γ and TNF-α) can induce depression and anxiety by degrading tryptophan to kynurenine via induction of indolamine 2,3 dioxygenase (IDO); a tryptophan degrading enzyme that is localised in immune cells. In addition, tryptophan can be metabolised to kynurenine via tryptophan 2,3 dioxygenase (TDO); a liver enzyme that is induced by glucocorticoids. Thus, mechanisms exist whereby both inflammatory mediators, and stress mediators such as glucocorticoids can promote metabolism of tryptophan to kynurenine, and thereby result in depressive symptoms by reducing tryptophan availability for serotonin synthesis.

Here we examined the ability of experimental colitis to induce symptoms of anxiety and depression, and to activate the kynurenine pathway. Colitis was induced in rats by enema containing 60mg of trinitrobenzenesulphonic acid (TNBS). Rats were euthanized 3, 8 or 21 days later (n=4-5) and prior to sacrifice anxiety behaviour was assessed using the open field test, and anhedonia was assessed using the saccharin preference test as an indicator of depressive behaviour. Colonic inflammation was assessed by measuring inflammatory cytokine expression using real time-PCR, and circulating tryptophan and kynurenine concentrations were measured by high performance liquid chromatography. Expression of IDO, TDO and inflammatory cytokines were also assessed in the liver. TNBS-induced colitis lead to weight loss, diarrhoea and macroscopic ulceration of the colon, and increased expression of inflammatory cytokines IL-1β, IL-6, TNF-α and IFN-γ. When tested in the open field rats displayed increased thigmotaxis and spent significantly less time in the centre of the open field 3 and 8 days following TNBS treatment. Similarly, at day 3 and 8 post-TNBS, rats had decreased preference for a palatable sweet solution (0.01% saccharin). These behavioural changes were accompanied by decreased serum tryptophan and increased serum kynurenine 3 days post-TNBS, which is indicative of kynurenine pathway activation. Interestingly, kynurenine pathway activation was associated with increased TDO expression in the liver, whereas IDO expression was not altered in liver, spleen or colon. In summary, TNBS-induced colitis results in signs of anxiety and depression, coupled with activation of the kynurenine pathway. Kynurenine pathway activation could not be accounted for by induction IDO, but was closely paralleled by induction of hepatic TDO expression. Based on these findings we suggest that kynurenine pathway activation in this colitis model most likely occurs secondary to stress associated with the condition, as opposed to via the action of inflammatory mediators on IDO expression.

P1-2

MODULATION OF CLAUDIN-5 AND P-GLYCOPROTEIN EXPRESSION IN THE AGED RAT BRAIN

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The integrity of the blood-brain barrier (BBB) is maintained by structural and enzymatic barriers formed by endothelial cells within the neurovascular unit[1]. The structural nature of the BBB comprises tight junction proteins, such as claudin-5, which are located between adjacent endothelial cells and prevent the paracellular movement of potentially neurotoxic compounds from the peripheral circulation into the brain parenchyma. Endothelial cell efflux transporters, such as p-glycoprotein, assist by excreting toxic metabolites from the parenchyma. There is evidence that BBB permeability is modulated in the aged brain[2]. As claudin-5 and p-glycoprotein are integral components safeguarding the BBB, any alteration in their expression might compromise the brain. The aim of this study was to determine if the expression levels of claudin-5 and p-glycoprotein are modulated in the aged brain and if so, to elucidate the underlying mechanisms.

Hippocampal and cortical tissue from eight young (2-3months) and six aged (22-24 months) male Wistar rats was assessed. Claudin-5 and p-glycoprotein expression levels were determined by immunostaining, PCR and western immunoblotting. Semi-quantitative analysis of immunostained tissue sections from young and aged rats revealed a decrease in claudin-5 expression. Moreover, an age-related decrease in claudin-5 expression in the rat cortex was determined by western immunoblotting. P-glycoprotein expression was also modulated in the aged cortex. In a separate set of experiments, claudin-5 and p-glycoprotein expression levels were altered in the endothelial cell line bEnd3 following treatment with IL-1β (10ng/ml) and LPS (100ng/ml). Because these inflammatory mediators alter claudin-5 and p-glycoprotein *in vitro*, it may be that neuroinflammation, which is a feature of the aged brain underlies the increased BBB permeability *in vivo*.

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P1-3

GREY MATTER VOLUME REDUCTIONS IN THE HIPPOCAMUS AND INSULAR CORTEX AS BIOMARKERS OF VULNERABILITY TO DEPRESSION

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There is evidence that major depression may have a genetic basis and that subjects with family history of depression are more likely to exhibit symptoms of the disorder at some stage in their life (e.g., Duggan et al., 1998). Further, several studies have revealed structural abnormalities in the brain of individuals diagnosed with depression, with particular regard to the hippocampus, orbito-frontal cortex, prefrontal cortex, anterior cingulate cortex and insular cortex (Frodl et al., 2008).

The aim of the present study was to investigate whether subjects with a family history of depression are more likely to exhibit grey matter (GM) volume reductions in the brain than subjects with no psychiatric family history. A cohort of 33 healthy volunteers with family history of depression (Family History Positive, FHP), 66 healthy volunteers with no psychiatric family history (Family History Negative, FHN) and 33 patients with major depression were recruited from the Department of Psychiatry of the Ludwig-Maximilians University, Munich. Clinical variables were documented using the 21-item Hamilton Depression Rating Scale. Magnetic resonance images were obtained with a Magnetom Vision scanner (Siemens, Erlangen, Germany) operating at 1.5 T. A voxel-based morphometry analysis including DARTEL processing was performed on acquired data.

A whole brain analysis ($p < 0.05$, FDR corrected) revealed no significant difference between groups FHP and FHN or between healthy subjects and subjects with major depression. Significant GM volume reductions were found in the hippocampus and insular cortex of the FHP group when compared to the FHN group ($p < 0.001$, uncorrected).

Our results suggest that changes in GM volume in the hippocampus and insular cortex might contribute to increase the risk for depression in healthy individuals, also suggesting that anomalies in these two cortical areas could be linked to the inheritance of specific familial alleles.

P1-4

EFFECT OF QUANTUM DOTS ON DIFFERENTIATED PHEOCHROMOCYTOMA CELLS

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Quantum Dots (QDs) have the potential to use as simultaneous multiple colour labels due to its unique optical characteristics. In view of developing new neuro-therapeutic and neuro-prosthetic strategies, QDs have been modified to create active cellular interfaces with nerve cells [1] and for imaging of neuronal and glial interactions called synaptic clefts, or between an astrocyte process and a neuron [2]. Little work has been undertaken in observing the neuron cell response over long time scales upon exposure to QDs. So we focussed on the analysis of Pheochromocytoma 12 (PC12) cells exposed to QDs which have the ability to be differentiated into neurons upon treatment with nerve growth factors (NGF). We used water soluble Cadmium Telluride Thio-Glycolic Acid capped QDs of ~2-5 nm size. Using Confocal Microscopy, we observed the localisation of QDs distributed heterogeneously. There is no inhibition of neurites growth due to QDs. No evidence of degradation of neurites until 12 days. After that there is sharp increase in degradation of neurites and the cells started to die with QDs still be seen in the dead cells. In another experiment, neurites were destroyed when PC12 cells are exposed to higher concentrations of QDs due to toxicity.

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P1-5

CIRCADIAN REGULATION OF NF-κB P65 IN SERUM SHOCKED FIBROBLASTS

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In mammals circadian rhythms have been shown to be generated in a cell autonomous manner by the vast majority of cell types. The mammalian circadian system is highly distributed, with many tissue and cell types displaying circadian rhythms. The study of the molecular basis of circadian rhythmicity has been facilitated by the use of serum shocked fibroblasts as a cellular model which displays synchronised rhythmic expression of clock genes in a manner similar to brain clocks. It is known that circadian rhythms are affected by immune status, but the mechanisms of these effects are unknown. The current study examined whether NF-κB, a transcription factor implicated in the signalling pathways of many immune mediators, displays a circadian rhythm in its expression in oscillating serum shocked fibroblasts.

NIH3T3 cells were synchronised by a 2 hour shock with 50% horse serum, and nuclear and cytoplasmic extractions were performed every 4hrs for 24hrs. Western blots were used to measure for total p65 subunit of NF-κB in order to determine a profile of protein expression across the circadian cycle.

Serum shock induced a temporal regulation of nuclear p65 in the first 24 hours following shock treatment, with a significant effect of time on p65 expression revealed by the Kruskal-Wallis test ($p<0.05$). Pairwise comparisons by Mann-Whitney U test revealed a significant difference between p65 nuclear expression 8 and 16 hours following the serum shock ($p<0.05$). There was no main effect of time on level of p65 in cytoplasmic extracts across the circadian cycle ($p=0.9$). Efficacy of the serum shock in synchronising rhythms was confirmed by rhythmic expression of the clock gene product Per2. This is the first study to show a variation NF-κB activity level across the circadian cycle in serum shocked fibroblasts, and suggests a role for NF-κB in the regulation of the circadian cycle.

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P1-6

THE EFFICACY OF EXERCISE AS A COGNITIVE ENHANCER IN MALE WISTAR RATS: ANALYSIS OF UNDERLYING MECHANISMS.

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Exercise has been shown to improve learning and increase neurogenesis in rodents[1], possibly via mechanisms mediated by brain-derived neurotrophic factor (BDNF), a neurotrophin that plays a pivotal role in synaptic plasticity[2]. Here we have investigated the effect of a short-term forced exercise protocol on object recognition (OR) and object displacement (OD) learning in the rat. In parallel, we assessed the expression of BDNF in the hippocampus and related areas. We also looked for evidence of neurogenesis in the dentate gyrus of the hippocampus of the rats using BrdU staining.

Male Wistar rats were randomly divided into sedentary (n=6) and exercising (n=6) groups. The exercised group ran on a rodent treadmill for 1 hour/day at 1km/hr for 7 days while controls were placed on the stationary treadmill for the same duration. All rats were injected with BrdU (50 mg/kg i.p.) for the seven consecutive days of the exercise program. On day 8, rats were tested in a cognitive task, and the brains were removed for analysis. All procedures were conducted under National and European Union directives on animal experiments.

Significant enhancements in performance were observed both the OR task (one-way ANOVA; $p<0.001$), and in the OD task (one-way ANOVA, $p<0.05$) with exercise. The neurochemical analysis showed that exercise induced a significant increase in expression of BDNF mRNA, as assessed by real-time PCR, in the dentate gyrus (unpaired Student's *t*-test; $p<0.05$). The assessment of BrdU staining using immunohistochemistry showed a significant increase (unpaired Student's *t*-test; $p<0.0053$) in proliferating cells dentate gyrus with exercise.

We conclude that one week of forced treadmill exercise is sufficient to confer an advantage in both spatial learning and object recognition learning in adult rats. These enhancements may be mediated by changes in the expression of BDNF in the dentate gyrus. The exercise protocol is also associated with an increase in cellular proliferation in the dentate gyrus.

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P1-7

THE EFFECT OF CHRONIC INGESTION OF ETHANOL ON THE ANXIETY AND SPATIAL MEMORY OF RATS

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The aim of this work was to investigate if chronic ingestion of ethanol affects the spatial memory in rats. Male Wistar Rats (150g, n=11-12) were treated with water (control) or 5%-20% of ethanol, increasing 5% per week (habituation), and 20% maintained for 90 days (chronic ingestion) before testing. Spatial memory (elevated plus-maze, EPM): Behavioral responses were scored for 5min: number of entries and time on the open or closed arms and number of stretched attend postures (SAPs). They were retested after 24 hours. Groups were compared by Student *t*-tests ($p<0.05$).

Ethanol chronic ingestion induced a dramatic increase in both number of entries (127%) and time (150%) in the open arms on the first test ($p<0.05$). A significant reduction was seem in both scores in the open and closed arms (36-74%, $p<0.05$) when the controls animals were re-exposed to EPM 24 hours later. However, the chronic ingestion of ethanol induced a significant reduction only in the number of entries (39%) and time (54%) in the open arms ($p<0.05$) when the animals were re-exposed to EPM. An increase was induced in the time in the closed arms (32,5%, $p<0.05$). No change was induced by ethanol chronic ingestion in the number of entries in the closed arms. Also, no changes were found in the number of SAPs when the controls and alcoholic animals were re-tested.

Long period of ethanol chronic ingestion has an anxiolytic-like effect and also, may affect the spatial memory.

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P1-8

ISOFORMS OF β-AMYLOID PRECURSOR PROTEINS ARE DECREASED IN HIPPOCAMPUS OF RATS REARED IN ISOLATION FROM WEANING.

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Isoforms of amyloid precursor protein (APP) play a range of role in several physiological and pathological processes in the brain. However, the functions of APP isoforms are still not clear. Isolation rearing of rats from weaning has been used as experimental model of affective disorders like schizophrenia. This study aimed at evaluating the changes induced by isolation rearing in the expression of APP_{695} and $APP_{751/770}$ in the hippocampal formation of rats.

In two groups of Wistar rats (n=6/each) the pups remained with their mothers (6/mother) until weaning (21 days) when they were allocated randomly to one of two conditions: 1) grouped, housed 3/cage and handled 3 times/week; 2) isolated, housed individually and handled once/week. After 10 weeks all animals were deeply anaesthetized (50ml/kg of Urethane 25%), perfused and their brains removed. 40-μm sections were used for immunohistochemistry. The immunopositive cells (IC) were counted bilaterally, in 3 sections/rat, in hippocampus, amygdala and entorhinal cortex. Student *t*-test ($p<0.05$).

Isolation rearing induced a significant decrease in APP_{695} - IC (43%) only in the hillus of dentate gyrus ($p=0.001$). No difference was seen in any other hippocampal area, amygdaloid nuclei or entorhinal cortex in isolated compared to grouped rats. $APP_{751/770}$ - IC were noted only in CA2 area of the hippocampus, where a high reduction (38%) was induced by isolation rearing ($p>0.001$). No change was induced by isolation rearing in $APP_{751/770}$ in amygdala and entorhinal cortex.

Isolation rearing induces changes in the expression of APP isoforms in hippocampus, an area affected by the alterations that occur in schizophrenia.

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P1-9

RATS REARED UNDER ISOLATION SHOW A REDUCTION IN THE EXPRESSION OF β-AMYLOID IN HIPPOCAMPUS AND AMYGDALA.

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The peptide β-Amyloid (Aβ) has been associated to degenerative and non-degenerative processes in the brain. The hippocampal formation is involved in a number of functions such as emotional and social behavior, learning and memory, all affected in neurological disorders. Isolation rearing of rats from weaning has been used as experimental model of affective disorders like schizophrenia. This study aimed at evaluating the changes induced by isolation rearing in the expression of Aβ in the hippocampal formation of rats.

In two groups of Wistar rats (n=6/each) the pups remained with their mothers (6/mother) until weaning (21days) when they were allocated randomly to one of two conditions: 1) grouped, housed 3/cage and handled 3 times/week; 2) isolated, housed individually and handled once/week. After 10 weeks all animals were deeply anaesthetized (50ml/kg of Urethane 25%), perfused and their brains removed. 40-μm sections were used for immunohistochemistry. The immunopositive cells (IC) were counted bilaterally, in 3 sections/rat, in hippocampus, amygdala and entorhinal cortex. Student *t*-test ($p<0.05$).

Although a few number of Aβ - IC was found in all areas of the hippocampus, a dramatic reduction was induced by isolation rearing in all areas (100% in hillus, $p=0.001$; 64% in CA3, $p=0.002$ and 51% in CA1, $p=0.02$). A higher number of Aβ - IC was seen in basolateral and lateral amygdala compared to hippocampus. However, a 100% of reduction was induced by isolation rearing only in lateral amygdala ($p=0.001$). No change was found in entorhinal cortex.

β-Amyloid may be involved on the complex mechanisms triggered in the hippocampus and amygdala during the development of schizophrenia.

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P1-10

THE EFFECT OF MATERNAL SEPARATION ON FEAR AND ANXIETY BEHAVIORS AND ON SPATIAL MEMORY.

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Early life stress seems to put an individual at a greater risk for many mental disorders, such as depression and posttraumatic stress disorder, which may affect the levels of fear and anxiety and also the functions of learning and memory. The aim of this study was to evaluate the levels of anxiety and spatial memory in rats submitted to maternal separation (MS).

Male Wistar rats (n=10) were used. The pups underwent a daily-3h separation from their mothers from PND1-21 and the controls (n=11) were left undisturbed. On PND21, they were housed (4/cage) for 5 weeks before being tested on the elevated plus-maze (EPM). Behavioral responses were scored for 5min: number of entries and time on the open or closed arms and number of stretched attend postures (SAPs). They were retested after 24 hours. Groups were compared by "Student *t*-tests" ($p<0.05$).

Maternal separation induced a non significant increase in both number of entries and time in the open arms on the first test. However, a non significant reduction was induced by MS in both scores when the animals were re-exposed to EPM 24 hours later. The time in the open arms was only 1,8 - 2,0% of the total time in any arm. A significant decrease was induced by MS in the SAPs when the animals were re-exposed to EPM (46.8-51%, $p<0.05$).

Chronic affective stress in early life may affect the spatial memory. However, this effect may be reversed by neuronal plasticity that occurs during the brain development.

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P1-11

BEHAVIOURAL EFFECTS OF DIETARY TRYPOTPHAN MANIPULATIONS ON C57BL/6J AND BALB/C MICE

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Depletion of tryptophan (Trp), the precursor to serotonin has been shown to alter mood and cognition in both humans and rodents. Functional polymorphisms of tryptophan hydroxylase-2 (*Tph2*), the brain serotonin synthesizing enzyme has been shown to be a risk factor in development of mood disorders. Interestingly, BALB/c mice carry a single nucleotide polymorphism in *Tph2*, manifesting as a decrease in serotonergic levels compared to control C57BL/6J mice. Whether this polymorphism affects how mice respond to Trp depletion is unknown. Using a novel dietary manipulation we investigated the impact of normal (0.7% Trp), depleted (0% Trp) or enhanced (1.25% Trp) Trp levels on behaviour and plasma tryptophan levels.

Statistical analysis was performed using one way ANOVA or student T test. Plasma tryptophan levels were assessed using high performance liquid chromatography. C57BL/6J but not BALB/c Trp-depleted mice exhibit significantly higher number of transitions ($p=0.05$) and reduced latency ($p=0.05$) to enter the dark compartment in the light-dark test of anxiety. In the forced swim test of depression-related behaviour no manipulation in either strain produced a pro-depressant effect, with depletion in C57BL/6J but not BALB/c showing a hyperactive response. Interestingly, nesting behaviour was influenced by Trp levels with Trp enhanced animals being better than controls in both strains and Trp depleted animals being poor nest builders over the 24 hour observation period. HPLC analysis showed that depletion reduced plasma tryptophan levels by 86% and 70% in BALB/c and C57BL/6J mice respectively. On the other hand, increases in plasma tryptophan levels of 96% and 100% were seen in each respective strain.

Overall, BALB/c mice, despite having a greater vulnerability to Trp depletion, were resistant to its behavioural effects with the exception of nesting behaviour. Trp enhancement had limited effects on behaviour in either strain.

P1-12

MITOCHONDRIAL LOCALIZATION OF THE FOXO3A TRANSCRIPTION FACTOR.

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Mitochondria are the major source of our brain cell's energy production. Their malfunction is linked to neurological diseases and aging. Mitochondria contain their own DNA which encodes enzymes essential for their functions. Recent studies have shown that a subset of nuclear transcription factors, including CREB (1) or NFκB (2), may be able to translocate to the mitochondria during cell stress, in order to affect transcription of mitochondrially-encoded genes. In the present study we investigated whether members of the FoxO family transcription factors localize to mitochondria and whether this is altered in response to cell stress following seizures.

Using a rat model of unilateral hippocampal seizure-damage produced by intra-amygdala kainic acid (3), subcellular fractionation analyses determined that mitochondrial levels of FoxO3a were significantly higher in the ipsilateral (injured) compared to contralateral (less damaged) hippocampus 4 h after seizures. Electron immunogold microscopy confirmed localization of FoxO3 to the outer and inner mitochondrial membrane. Chromatin immunoprecipitation assay using mitochondrial DNA detected binding of FoxO3a to the D-loop promoter region which contained a consensus site for FoxO binding, after seizures but not in control. Finally, confocal imaging of both primary neurons and immortalized hippocampal cells (HT22) transiently transfected with a FoxO3-GFP construct detected co-localization with Mitotracker red.

These data demonstrate that in addition to cytoplasmic and nuclear localization, the FoxO3a transcription factor localizes to mitochondria. Moreover, cell stress – seizures, induce interaction with mitochondrial DNA. These data identify a potentially novel function for FoxO3a in mitochondrial bioenergetics control and may provide novel targets in neurological diseases such as stroke and epilepsy.

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PRTLI Cycle 4 (NBPI)

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P1-13

5-HT6 RECEPTOR ANTAGONIST SB742457 RECOVERS AN AGE RELATED DEFICIT IN WORKING MEMORY BUT NOT IN SPATIAL MEMORY IN THE RAT

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The serotonergic system is becoming a new objective in the development of treatments for Alzheimer's disease (AD). The serotonergic system has been linked to cognition, depression, psychosis and aggression, and therefore regulation of this system appears to be an attractive potential therapeutic treatment of neurodegenerative disorders.

Serotonin (5-HT) plays an important role in cognition through activation of the serotonergic receptors including the 5-HT6 receptor, which is widely distributed within the CNS, including the striatum and hippocampal formation. This study examined the effects of chronic systemic administration of the 5-HT6 antagonist SB742457 in the delayed non-match to sample (DNMS) task and in the water-plus maze (WPM) task.

The operant DNMS task stimulates and measures working memory in rodents, while the WPM task, a modified version of the Morris Water Maze, is aimed at targeting spatial learning and memory. These tasks are appropriate models to analyze the effects of SB742457 on cognition in an aged population as there are reliable age-related delay-dependent deficits in performance shown for both the DNMS and WPM tasks.

Following a six week training protocol in the DNMS task, both young (3month) and middle aged (12-14month) rats received chronic treatment (3mg/day). This treatment resulted in a recovery of the age-related deficit in the middle aged group, sufficient to match the performance of the young control group. In the WPM task animals received treatment (3mg/day SB742457) 24hr before commencing training and for the duration of the experiment. By contrast, we found no change in the performance of young or middle age animals in this task.

These results suggest that regulation of the serotonergic system enhances working memory, but may not enhance spatial memory in the rat, suggesting that the 5-HT6 antagonist may be of benefit in treating mnemonic aspects of neurodegenerative diseases.

P1-14

TEST-RETEST RELIABILITY ANALYSIS OF EVENT RELATED POTENTIALS.

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Event-related potentials (ERP) provide a direct measure of cortical activity with excellent temporal resolution making it possible to isolate the distinct processing stages underlying perception and cognition. In recent years, ERPs have been increasingly employed as biomarkers in longitudinal clinical trials of new pharmacological agents targeting cognitive deficits. The utility of ERPs as biomarkers is partly dependent on the strength of their stability over time yet very few studies have actually investigated their test-retest reliability. The present study therefore seeks to determine the test-retest reliability of a range of commonly studied ERP markers across a one month period. ERPs were recorded with a 64-channel electroencephalograph (EEG) from 15 healthy participants (age 18-40) at two time points, 4 weeks apart. The time of testing was kept constant for each participant. The participants completed computerised tasks that addressed a range of key cognitive abilities including working memory, sustained attention, error processing, response inhibition and face processing. Test-retest reliability was calculated for the amplitude and latency of several ERP components including the N2, N170, P3a, P3b, and ERN. The stability within and between session was assessed with the split-half method and the Pearson's correlation, respectively. Results are discussed in terms of the reliability of ERP components, the reliability of different tasks to elicit certain components and the suitability of ERPs for clinical research.

P1-15

AUDIO-VISUAL SEARCH IN DEPTH USING 'REAL' AND 'VIRTUAL' ENVIRONMENTS

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It is well known that a sound presented at the same location on the horizontal plane as a visual target can improve the detection of the target by guiding attention to that location[1,2]. We asked whether sound can affect search for a visual target presented in different depths. In separate experiments, we explored aurally aided visual search in 3-dimensional space using 'real' and 'virtual' environments. In Experiment 1, our visual scene consisted of an array of eight face images presented as an array of 4 faces images in a near horizontal location (i.e. within peripersonal space) and 4 images located in a far horizontal location. Each face image was paired with a loudspeaker. The participant's task was to indicate whether the visual target face which was indicated by a flash of an LED light, was either 'near' or 'far'. Sounds were presented simultaneously with the LED light but were either congruent or incongruent with the location of the target. In Experiment 2, we presented virtual scenes of people and the participant's task was to locate a target individual in the visual scene. Congruent and incongruent virtual voice information, containing distance and direction location cues, were paired with the target. In both Experiments, we found that response times were facilitated by a congruent sound. Our findings suggest that sound can have a significant influence on locating visual targets presented in depth in both real and virtual displays and has implications for understanding crossmodal influences in spatial attention and also in the design of realistic virtual environments.

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P1-16

MIDKINE IS A LEARNING-ASSOCIATED PEPTIDE WITH POTENT EFFECTS ON HIPPOCAMPAL NEURITE OUTGROWTH AND HIPPOCAMPAL-DEPENDENT MEMORY CONSOLIDATION.

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Midkine belongs to the pleiotrophin (PTN)/midkine family of peptides and is recognized as a retinoic acid-inducible, developmentally regulated, heparin-binding protein[1]. Midkine null mice have previously been shown to have spatial learning deficits and impaired sensory processing as measured by prepulse inhibition of startle response[2]. We have shown that midkine expression is increased at the level of mRNA and protein in the hippocampal dentate gyrus following two learning paradigms (water maze and passive avoidance). *In situ* hybridization revealed that midkine expressed was highly restricted to regions of the adult brain associated with synaptic plasticity, including the hippocampal dentate gyrus. Taken together, these studies indicate that midkine may represent an effector signal for activity-dependent changes in hippocampal function following learning. In support of this suggestion, midkine was shown to have significant effects on key morphometric parameters of neurite outgrowth (e.g. neurite length and branching) in primary cultures of hippocampal neurons. The effect of midkine was then examined in two separate learning tasks – water maze and olfactory reward learning. Midkine enhanced learning in both paradigms indicating that its pro-cognitive effects are task-independent. Midkine was also capable of reversing isolation rearing-induced deficits in pre-pulse inhibition. Together, these results indicate that midkine is a learning-associated peptide that has potent effects on cellular parameters relevant to hippocampal function and can enhance memory formation *in vivo* in a task-independent manner.

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P1-17

DEFICIENCY IN SIGIRR LEADS TO IMPAIRMENT OF SYNAPTIC PLASTICITY AND HIPPOCAMPAL-DEPENDENT MEMORY

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Single Ig-like IL-1 Related Receptor (SIGIRR) is a member of the toll-like receptor (TLR)/interleukin-1 receptor (IL-1R) family. Unlike other members of this family, SIGIRR does not mediate pro-inflammatory responses (Thomassen et al., 1999) and acts to negatively regulate TLR/IL-1R mediated-signals (Wald et al., 2003). Consistent with this, mice lacking SIGIRR ($SIGIRR^{-/-}$) demonstrate greater susceptibility to microbial infection and exacerbated symptoms in autoimmune disease models (Huang *et al*., 2006; Garlanda *et al*., 2007; Lech et al., 2008).

In the present study, we assessed synaptic transmission and long-term potentiation (LTP) in hippocampal slices of wildtype and $SIGIRR^{-/-}$ mice. We have identified a profound attenuation in the ability of $SIGIRR^{-/-}$ mice to sustain LTP at CA1 synapses. Furthermore, $SIGIRR^{-/-}$ mice demonstrate impaired learning in hippocampal-dependent tasks. We provide evidence that enhanced pro-inflammatory signal transduction involving IL-1β and stress-activated protein kinase may contribute to these deficits in hippocampal function observed in $SIGIRR^{-/-}$ mice.

P1-18

A CD200 FUSION PROTEIN EXERTS ANTI-INFLAMMATORY EFFECTS *IN VITRO* AND *IN VIVO*

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Deficits in cognitive function are associated with neuroinflammatory changes, typified by activation of glial cells and an alteration of the pro- and anti-inflammatory cytokine balance in the brain. CD200 is a membrane-bound glycoprotein expressed on neurons and endothelial cells, which interacts with its cognant receptor (CD200R) expressed on microglia. Previous evidence from this laboratory has suggested that interactions between CD200 and CD200R can maintain microglia in a quiescent state and preserve the balance between pro- and anti-inflammatory cytokines.

Here we report that LPS induced an increase in the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α ($p<0.05$, ANOVA) in mixed glia prepared from neonatal C57BL/6 mice. This was paralleled by enhanced expression of CD40 mRNA ($p<0.05$, ANOVA), a surface marker of microglial activation. Pretreatment of mixed glia with a CD200 fusion protein (CD200Fc) attenuated the LPS-induced changes.

We assessed the ability of CD200Fc to attenuate LPS-induced changes in vivo and report that, while intraperitoneal injection of LPS significantly inhibited long-term potentiation (LTP) in the dentate gyrus, intrahippocampal administration of CD200Fc attenuated this LPS-induced impairment in LTP in Wistar rats.

The data presented here reveal the importance of CD200 in immune regulation and demonstrate the ability of CD200Fc to attenuate LPS-induced changes both *in vitro* and *in vivo*.

P1-19

A NOVEL PROTEIN COMPLEX PICK1-PARKIN-CDC4A LINKING MITOCHONDRIAL DYSFUNCTION TO PARKINSON'S DISEASE

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Parkin (PARK2) is an E3 ligase enzyme responsible for protein degradation in Ubiquitin Proteosomal System (UPS). Mutations in *parkin* manifests as a recessive form of Parkinson's disease, called Autosomal Recessive Juvenile Parkinsonism (ARJP). This neurodegenerative disease involves the death of dopaminergic neurons in the *substantia nigra pars compacta* in the midbrain, occurring in young adults between 20 - 40 years of age. Parkin interacts and ubiquitinates several proteins, which play important roles in mitochondrial function, oxidative stress, cellular toxicity and apoptosis. We are particularly interested in a PICK1-Parkin-Cdc4α protein complex, which may play a role in mitochondrial function and oxidative stress. To decipher the importance of this protein complex, we are generating blocking agents that specifically interfere with the interaction of each of these participating proteins. We have already designed a blocking agent that may hinder the interaction between PICK1 and parkin. We are now testing this agent in protein–protein interaction studies, to validate its biological activity. The effect of this inhibitor will also be evaluated in mitochondrial function and neuronal cell survival. This work may unveil the importance of a PICK1-Parkin-Cdc4α protein complex in mitochondrial dysfunction leading to neuronal death and development of Parkinson's disease.

The work is being supported in part by Science Foundation Ireland.

P1-20

CD200 RECEPTOR-LIGAND INTERACTIONS IN THE SPINAL CORD IN EAE DISEASE PROGRESSION.

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Multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE) are inflammatory demyelinating diseases of the central nervous system characterised by a persistently activated microglial state. Microglial activation is characterised by an increase in the expression of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and an up-regulation in the expression of pro-inflammatory cell surface markers such as CD40. Recent evidence has indicated that microglial activation is modulated by the interaction between CD200, which is expressed on neurons, and its cognate receptor CD200 receptor, which is expressed on microglia [1](Lyons *et al.,* 2007). EAE was induced in C57BL/6 mice by injection of myelin oligodendrocyte glycoprotein (MOG), pertussis toxin (PT) and complete Freund's adjuvant, and 48 hours later by an additional injection of PT. Clinical symptoms were observed over 21 days [2](Reinke *et al.,* 2007) and symptoms consistent with the onset of EAE were observed after 10 days which progressed to hindlimb weakness thereafter. Mice were sacrificed 12 hours and 3, 5, 7, 10 and 21 days post MOG injection and the spinal cord was removed for analysis.

We observed a time-dependent significant increase in mRNA expression of IL-1β ($p<0.01$, ANOVA) and TNFα ($p<0.05$, ANOVA) in the spinal cord 5 days post MOG injection and a significant increase in IL-1β ($p<0.001$, ANOVA) and TNFα ($p<0.05$, ANOVA) protein 10 and 21 days after MOG injection respectively. These changes were accompanied by a significant increase in CD40 mRNA expression 7 days post MOG injection ($p<0.05$, ANOVA). Importantly, the increase in CD40 mRNA was associated with a decrease in CD200 mRNA expression in the spinal cord ($p<0.05$, ANOVA), providing further evidence of an inverse correlation between microglial activation and CD200 expression.

The data indicate that evidence of inflammation in the spinal cord, consistent with microglial activation precedes the onset of clinical symptoms in EAE and suggest that one factor which may contribute to this is an alteration on CD200 receptor-ligand interactions.

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P1-21

SOCIAL STRESS IN ADOLESCENT NRG1 HETEROZYGOUS KNOCKOUT MICE – A PUTATIVE MODEL OF GENE × ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA.

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Schizophrenia is a complex, multifaceted disorder that is associated with both genetic and environmental etiological factors. The onset of schizophrenia typically occurs in early adulthood. In those with a genetic vulnerability to schizophrenia, the experience of stress during this crucial period of development can precipitate and/or exacerbate schizophrenia symptoms. Social factors associated with competitive urban lifestyles may result in phenotypic alterations that contribute to the pathogenesis of schizophrenia [1]. This study seeks to investigate gene × environment interactions in schizophrenia by subjecting mice with a heterozygous deletion of the schizophrenia risk gene neuregulin-1 (NRG1) [2] to chronic social defeat stress during adolescence.

Singly-housed 40 day-old heterozygous NRG1 mutants or wildtype mice (maintained on a C57BL6 background) were placed individually into a conflict box with a dominant mouse until the adolescent was attacked and successfully defeated by the dominant aggressor. Socially defeated and dominant mice were co-housed for the intervening 24hrs, being separated by a transparent partition allowing the exchange of sensory cues only. This was repeated for 10 days. Effects of stress on the adult mouse phenotype were assessed by subjecting the mice to a battery of behavioural tests to measure anxiety, sociability and cognitive function.

Heterozygous NRG1 mice exhibited hyperactivity relative to wildtypes which was attenuated in NRG1 mutants exposed to chronic social defeat stress ($p<0.05$). Social stress induced a decrease in preference for sucrose solution in wildtypes ($p<0.05$) and increased preference in NRG1 mice on day 4 ($p<0.01$) of testing.

It appears that chronic social defeat stress during adolescence alters the behavioural phenotype of NRG1 mutants. These findings suggest that an interaction exists between social stress and the NRG1 gene which may have implications for schizophrenia.

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P1-22

EFFECT OF DISTAL CUE CONFIGURATION LOCATION ON MORRIS WATER MAZE PERFORMANCE: AN IN-DEPTH BEHAVIOURAL AND MOLECULAR ANALYSIS.

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Studies investigating spatial learning and memory, using the Morris watermaze (MWM) task, repeatedly show that completion of the task relies on the formation of allocentric relations using a spatial array of distal cues. One temporal lobe structure involved in establishing these allocentric relations is the hippocampus. In order to fully examine the importance of distal cues, and to attempt to separate out differences in allocentric and egocentric strategies, we investigated the effect of cue location on how animals solve the MWM task. Male Wistar rats (n=14) were divided into two groups: Near-Cues (n=7) and Far-Cues (n=7). The near-cues group had a distal cue configuration that was located close to and directly behind the hidden platform whereas the far-cues group distal cue configuration was located further from the platform. All animals were trained in the MWM for 5 consecutive days, 4 trials/day. Following a series of ANOVAs and t-tests, results from standard measures of acquisition revealed significant differences between the groups' escape latencies, with animals in the far-cues group performing significantly worse than the near-cues group ($p<0.05$). Head direction analyses on the platform did not reveal any significant differences between the groups. However, in-depth behavioural analyses of the animals' swimming tracks revealed differences between the groups, particularly in their thigmotactic behaviours. Differences in their turning behaviours and how they appear to use the cues were also evident. Hippocampal BDNF expression further supported the behavioural results, with far-cues BDNF expression being significantly higher than the near-cues group ($p<0.01$). The behavioural and molecular data suggests when cues are located in close proximity to the goal, animals appear to use the cues as a beacon to find their goal. However, when cues are located far from the goal, animals must infer more to locate the platform position and so use a hippocampal-dependent allocentric strategy.

P1-23

IDENTIFICATION OF NOVEL PROTEINS REGULATING S1P-R AND PAEL-R RECEPTOR TRAFFICKING

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Multiple sclerosis (MS) and Parkinson's disease (PD) are chronic neurodegenerative disorders that cause a wide range of debilitating symptoms. Our aim is to understand the roles of sphingosine-1-phosphate receptors (S1P-Rs) and Parkin-associated endothelial like receptors (PAEL-Rs) as drug targets for MS and PD, respectively. Both S1P-Rs and PAEL-Rs belong to the family of G coupled protein receptors (GCPRs) and are differentially expressed in cells of the central nervous system, namely astrocytes, microglia, oligodendrocytes and neurons. These GPCRs may play vital roles in cellular migration, survival and differentiation in a wide range of cells. We are particularly interested in the mechanisms that govern the surface expression of these GPCRs. The aims of our project are to discover modalities by which the surface expression of S1P-Rs and PAEL-Rs may be regulated. Our working hypothesis is that specific trafficking machineries and routing pathways are involved in the surface expression of these GPCRs. To study the trafficking mechanisms of both the S1P-R and the PAEL-R, we are identifying novel proteins that interact with these receptors, using yeast-two hybrid genome-wide technologies. We will also present the routing pathways of these receptors once internalised. We hope to create methods that regulate these trafficking proteins, alter S1P1-R and PAEL-R surface expression and thereby create new molecular therapies for possible treatment of neurodegenerative diseases such as MS and PD.

This work is supported in part by Science Foundation Ireland and the Health Research Board.

P1-24

WHITE MATTER TRACTS IN EUTHYMIC BIPOLAR 1 DISORDER: A DTI STUDY OF THE CINGULUM BUNDLE AND UNCINATE FASCICULUS

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Evidence from the field of structural neuroimaging implicates subtle white matter abnormalities in bipolar disorder (BD) in brain regions involved in affective regulation and executive function. This preliminary DTI tractography study sought to identify trait-related white matter microstructural abnormalities in the cingulum bundle and uncinate fasciculus (UF) in an entirely euthymic cohort of patients.

DTI data was acquired on 24 euthymic BD type 1 and 45 healthy control subjects using a 64 gradient direction sequence, (b=1300) collected on a Siemens 1.5T MRI scanner. Diagnosis of BD-I was determined by DSM-IV SCID and euthymia confirmed both 1 month prior to, and on the day of testing using standardised mood rating scales (BDI,YMRS,ASRM,HAMD). Exclusion criteria for all subjects included neurological or co-morbid psychiatric disorders, drug and alcohol abuse within the last year, and LOC >5 mins. Whole brain tractography was performed using ExploreDTI and the tracts of interest extracted using anatomically defined 'AND' and 'NOT' gates. Median fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were calculated for the UF and mid-dorsal cingulum.

There was no significant difference in FA or ADC between groups in either the left or the right cingulum or UF ($p<0.05$). There was a significant effect of age on FA in the left cingulum ($p=0.03$) and gender in the right UF, M>F ($p=0.049$). An inter-hemispheric asymmetry in FA, but not ADC, was detected in both tracts: cingulum L>R, UF R>L.

We detected asymmetry in FA consistent with the known lateralisation of brain morphology and function. However, this preliminary sample size may be underpowered to detect further group differences in FA or ADC in the tracts of interest. Future work will expand the sample size and explore High Angular Resolution Diffusion Imaging (HARDI) based estimations of the diffusion signal to improve the sensitivity of tractography based analyses.

P1-25

THE INFLUENCE OF FACIAL EXPRESSION ON ASSOCIATIVE MEMORY PERFORMANCE AND THE RELATIONSHIP TO CORTISOL LEVELS.

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There is a well established link between emotion and memory, whereby emotionally arousing material is generally better remembered than neutral material. Socially/emotionally relevant stimuli, while not arousing per se, may also influence memory performance. Several studies have shown that facial expression can affect subsequent face recall/recognition memory. There is also evidence for a relationship between cortisol levels and emotional face processing, though exact nature of this relationship is not yet clear.

Our primary aim here was to investigate if performance on an associative memory paradigm could be modified by the use of emotional faces. A secondary aim was to determine if there was an association between cortisol levels and emotional face processing/memory.

Thirty young adults (aged 18-29) performed a face-name pairs associative memory task. Participants were randomised into one of three groups, viewing either happy faces, neutral faces, or angry faces. In addition, all participants performed an emotion judgment task, whereby they were required to identify faces as being happy, neutral or angry in expression. Salivary cortisol measurements were taken three times during the course of the testing session.

Participants were found to exhibit poorer delayed recall performance for face-name pairs when the faces were angry, rather than neutral or happy in expression ($p=0.026$). This deficit seemed to stem from an inability to encode/retrieve the angry faces, rather than impaired face-name associative ability, as face recognition was impaired ($p=0.018$) with name recognition preserved ($p>0.05$). There was no association between cortisol levels and face-name pairs task performance. However, higher levels of cortisol were associated ($r=-0.592$, $p=0.005$) with an increased tendency to identify neutral faces as being emotional in the judgment task.

Results will be discussed in full, with reference also to the effects of aging on memory for emotional salient stimuli.

This research was funded by the Health Research Board.

P1-26

DELINEATING THE ROLE OF THE BASAL FOREBRAIN CHOLINERGIC SYSTEM IN DELIRIUM DURING DEMENTIA USING THE MURINE-p75-SAPORIN IMMUNOTOXIN

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It is known that the basal forebrain cholinergic system shows significant degeneration during Alzheimer's disease. Existing dementia is the greatest risk factor for development of delirium and systemic infection is a very frequent trigger for these episodes, thus it seems likely that cholinergic hypofunction plays a role in delirium during dementia. We have previously shown that systemic inflammatory insults induce exaggerated CNS inflammation in animals with existing neurodegeneration, via microglial priming, and that these insults have both acute and lasting negative consequences for the disease state. In this study, the murine-p75-saporin immunotoxin (mu-p75-sap) has been used to selectively lesion the cholinergic neurons of the basal forebrain in mice, thus mimicking the early stages of dementia-associated cholinergic loss. We hypothesised that mimicking systemic infection using lipopolysaccharide (LPS) would induce acute working memory deficits in mu-p75-sap-lesioned animals that would not be apparent in normal animals similarly challenged with LPS. Limited selective lesions were performed by stereotaxic injection of mu-p75-sap intracerebroventricularly (0.2μg or 0.04μg, or sterile saline). Characterisation of the acute inflammatory response following mu-p75-sap lesion revealed increased IL-6, TNF-α and IFN-β at three and 7 days followed by resolution by 14 days. Immunohistochemical staining for choline acetyltransferase (ChAT), NeuN and IBA-1 has allowed characterisation of the basal forebrain cholinergic lesions in response to both doses of mu-p75-sap. At twenty days post-surgery mu-p75-sap-lesioned animals were impaired on a Y maze reference memory task at a high but not low dose of the toxin. Animals at both doses could perform T maze working memory tests but following systemic challenge with LPS, only mu-p75-sap-lesioned animals showed acute working memory deficits, with control animals showing no impairment. This novel model of acute cognitive dysfunction superimposed on existing neurodegeneration should allow mechanistic studies of acute cholinergic dysfunction during episodes of delirium.

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P1-27

ELECTROPHYSIOLOGICAL INDICES OF ATTENTIONAL DECREMENTS IN MILD COGNITIVE IMPAIRMENT

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Amnestic mild cognitive impairment (aMCI) is classified primarily via substantial episodic memory deficits in the absence of a dementia diagnosis. We investigated the degrees to which attentional versus memory encoding decrements might contribute to such deficits, by analysing event-related potentials (ERPs) acquired during encoding trials of a modified Sternberg word recognition task with low (4 items) and high (8 items) memory load conditions. These measures and memory accuracy data were compared between 15 participants with aMCI (ages 58-84) and 15 matched, healthy older adults (ages 57-81). Recognition accuracy was significantly higher in controls than aMCI participants, in the high-load condition ($p<0.05$). In posterior ERPs the N1 was significantly larger ($p<0.01$) and the P2 significantly smaller ($p<0.05$) in controls versus aMCI participants. These differences were most pronounced in the high-load condition. Neither P1 amplitude nor any peak latency differences were observed between the samples. We interpret these outcomes to primarily reflect attentional decrements in aMCI, albeit these do not preclude memory encoding/retrieval deficits. Differing ERP current source patterns were revealed (using standardised LORETA) between the groups for the N1 component only; occipito-parietal N1 sources were identified bilaterally in the controls but unilaterally in the aMCI sample. These and other data indicate that healthy older adults generally can recruit additional brain regions, via attentional control, to successfully maintain a certain level of cognitive performance; whereas aMCI individuals generally may not.

Part of this research was completed as part of a wider programme of research within the TRIL Centre, (Technology Research for Independent Living). The TRIL Centre is a multi-disciplinary research centre, bringing together researchers from UCD, TCD, NUIG & Intel, funded by Intel and IDA Ireland. www.trilcentre.org

P1-28

IDENTIFICATION OF CAPTODIAMINE AS A PUTATIVE ANTIDEPRESSANT

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Using a behavioural tier we re-evaluated a series of clinically-safe drugs which were removed by the FDA during the Drug Efficacy Study Implementation programme in the period 1968-1974. Chronic treatment (8 days) of C57Bl6 mice with drug doses (3-5 mg/kg) previously used in the clinic revealed captodiamine to exhibit an anxiolytic action in the open-field and elevated X-maze paradigm and to have cognition-enhancing actions in recognition and spatial memory tasks. Captodiamine was also found to reduce latency to despair in the forced swim test but was without effect on sensorimotor processing (prepulse inhibition). The effects of captodiamine on behavioural despair combined with its cognition-enhancing actions suggested this drug to be a putative antidepressant. Furthermore, receptor displacement studies demonstrated captodiamine to have significant affinities for the σ1, D3 and $5HT_{2C}$ receptors which have been previously implicated as drug targets in the treatment of depression. Captodiamine was demonstrated to be an agonist at the σ1 receptor, as the rimcazole σ1 receptor-specific antagonist blocked its action in the forced swim test, an agonist at the D3 receptor, as demonstrated by its blockade of electrical field-induced relaxation of the rat pylorus, and a $5HT_{2C}$ receptor antagonist, as judged by its ability to block 5HT-induced calcium release in $5HT_{2C}$ receptor-transfected HEK cells. Enantiomeric analysis revealed the antidepressant action of captodiamine to reside in the R-enantiomer which had the highest affinity for the $5HT_{2C}$ receptor ($5HT_{2C}$ receptor: R=1.6 ηM; S=44.9 ηM; σ1 receptor: R=0.094 μM; S=0.036 μM; D3 receptor: R=0.96 μM; S=0.31 μM). The ability of captodiamine to modulate BDNF and GDNF expression in a brain region-specific manner is currently being used as a surrogate marker to understand the unique polyvalent pharmacology of this putative antidepressant.

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P1-29

THE GEOMETRY AND INFORMATION CARRYING CAPACITY OF SPIKE TRAINS

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Information propagates through the brain in the form of spike trains, however, it is difficult to measure the quantity of information these spike trains contain. Existing methods can be difficult to calculate and do not necessarily respect all the properties of the spike train. We believe we have a novel way to improve on this by making use of the metric geometry of spike trains, combined with information theory.

Each spike train was treated as a continuous time interval, contained in a metric space. A metric was used to obtain the distribution of the neural noise, and from this the variance of the noise and the power constraint were calculated. The capacity of a spike train was subsequently obtained. The time-discreteness of the input to the inter-neuron channel was also found.

We have applied our methods to a range of different electrophysiological data sets which have been given to us by experimental labs with whom we communicate.

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P1-30

THE β_2 ADRENOCEPTOR AGONIST-CLENBUTEROL ATTENUATES KAINIC ACID-INDUCED NEUROINFLAMMATION AND APOPTOSIS IN THE HIPPOCAMPUS: A ROLE FOR BDNF

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Excitotoxicity is a mechanism of neuronal cell death implicated in a range of neurodegenerative conditions. Systemic administration of the excitotoxin kainic acid induces cell loss and tissue damage in the hippocampus, resulting in apoptosis, inflammation and an increase in the protective neurotrophin- brain derived neurotrophic factor (BDNF). Increased BDNF expression is considered a compensatory response to kainic acid-induced tissue damage. The endogenous catecholamine neurotransmitter, noradrenaline has previously been shown to have anti-inflammatory and neuroprotective properties and signalling via the β_2 adrenoceptor has been associated with neuroprotection. In this study we examined the effect of the β_2 adrenoceptor agonist- Clenbuterol on kainic acid-induced inflammation and apoptosis in the hippocampus. BDNF expression was also determined to assess any association with clenbuterol-induced effects. Adult male Wistar rats were administered clenbuterol (0.5 mg/kg) one hour prior to kainic acid (10 mg/kg) administration. Twenty four hours later the animals were euthanized and the hippocampus was retrieved. Expression of the inflammatory markers interferon gamma (IFN-γ) and inducible nitric oxide synthase (iNOS) was quantified using real-time PCR. BDNF expression and concentration were measured using RT-PCR and a commercially available ELISA (Promega) respectively. Expression of the apoptotic marker Caspase-3 was determined by RT-PCR and caspase-3 activity was measured with a commercially available assay kit (Biomol). Statistical analysis was performed using ANOVA followed by a Newman-Keul's post hoc comparison test, where appropriate, to determine significant differences between treatment groups ($P < 0.05$). Pre-treatment with clenbuterol resulted in an amelioration of kainic acid-induced IFN-γ and iNOS expression. Kainic acid induced caspase 3 activity was decreased following pre-treatment with clenbuterol. Expression and concentrations of the protective neurotrophin-BDNF were increased following pre-treatment with clenbuterol. The results of this study indicate that clenbuterol is anti-inflammatory and anti-apoptotic following Kainic acid induced neruoinflammation and further displays neuroprotective properties by increasing BDNF expression in the hippocampus. In conclusion, the β_2 adrenoceptor agonist clenbuterol possesses anti-inflammatory and anti-apoptotic properties against excitotoxin-induced neuroinflammation and apoptosis. The extent to which these properties rescue kainic-acid induced neuronal cell loss in the hippocampus remains to be determined.

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P1-31

AGE-RELATED BEHAVIOURAL DEFICITS IN RATS CHRONICALLY TREATED WITH AMYLOID-β PEPTIDE

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The aging process is accompanied by a progressive decline in the performance of both physical and cognitive tasks. As the brain ages it becomes less effective in overcoming challenges such as those produced by infections, traumas or surgeries. Alzheimer's disease is an age-related neurodegenerative condition associated with cognitive dysfunction, which is typified by deposition of amyloid-β-containing plaques. One of the forms of amyloid found in plaques is the amyloid-β_{1-42} peptide which is considered to be cytotoxic as well as immunogenic.

Young (3 months) and aged (18-21 months) male Wistar rats were implanted with Alzet osmotic minipumps delivering either amyloid-β_{40-1} peptide (control) or a cocktail of amyloid-β_{1-40}+ amyloid-β_{1-42}. Animals were sedated with ketamine/Xylazine and anaesthetized with isofluorane (mask) for the duration of the implantation. Carprofen (subcutaneous) was used for postsurgical analgesia. After 28 days of amyloid-β or control treatment, animals were trained in the Morris Water-Maze over a five-day period. Each rat completed eight x 60 seconds trials on the first day and six x 60 seconds trials on the remaining days.

Aged, amyloid-β-treated animals took significantly longer to find the hidden platform in the water-maze than the young control-treated rats ($p<0.05$, ANOVA) and the young amyloid-β-treated rats ($p<0.01$). The aged control-treated rats also took longer to reach the platform than the young amyloid-β-treated animals ($p<0.05$, T-test). No difference in the escape times was found between the two groups of young animals.

This findings point to the important role aging plays on cognitive decline as well as the reduced effectiveness of the aged brain to cope with the challenge induced by amyloid-β perfusion.

P1-32

THE EFFECT OF Δ^9-TETRAHYDROCANNABINOL ON POST TRANSLATIONAL MODIFIERS OF THE PRO-APOPTOTIC TUMOUR SUPPRESSOR PROTEIN p53.

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We have previously reported that the predominant psychoactive phytocannabinoid, Δ^9-Tetrahydrocannabinol (Δ^9-THC), induces apoptosis in cerebral cortical neurones *in vitro* and *in vivo*[1,2]. Δ^9-THC-induced apoptosis involves p53 signaling[1]. The activity, stability and intracellular location of p53 can be modified by the post translational addition of certain proteins *e.g.,* Murine Double minute 2 (Mdm2) and Small Ubiquitin-like MOdifyer 1 (SUMO-1).

To investigate the effect of Δ^9-THC on the p53 interacting proteins, Mdm2 and SUMO-1, protein expression was assessed in cultured cerebral cortical neurones by western immunoblot and immunocytochemistry. The effect of Δ^9-THC on the level of SUMO-1-conjugated p53 was determined by co-immunoprecipitation and immunocytochemistry. CB_1 receptor expression was also determined using immunocytochemistry.

Δ^9-THC **(**5μM**)** induced an increase in the expression of the non-p53-inhibiting isoform of Mdm2 (p72Mdm2), from 0.33±0.03 to 0.56±0.06 arbitrary units (mean±SEM; $p<0.001$, Student Newman Keuls, n=6) within 5 minutes. This coincided with the Δ^9-THC-induced increase in phosphorylated p53 (serine 15). Δ^9-THC (5μM, 15 min) significantly increased the level of unconjugated SUMO-1 protein in the cytosol from 81.27±12.39 to 134.70±17.49 arbitrary units (mean±SEM; $p<0.05$; Student's t-test, n=4). Δ^9-THC also induced the removal of SUMO-1 from p53 as shown by immunoprecipitation and immunocytochemistry. The CB_1 receptor antagonist, AM251 (10μM), prevented the Δ^9-THC-induced deconjugation of p53 and SUMO-1. CB_1 receptor immunocytochemistry demonstrated that SUMO-1 colocalises with the CB_1 receptors.

The ability of Δ^9-THC to induce changes in Mdm2 provides additional evidence that the p53 pathway is pertinent in Δ^9-THC signalling in the brain. Furthermore, the observation that Δ^9-THC has an impact on the SUMO regulatory system is exciting considering that the system has a role in synaptic function.

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P1-33

THE ROLE OF GSK-3β IN INFLAMMATION INDUCED CHANGES IN EMBRYONIC RAT HIPPOCAMPAL CELL FATE.

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Glycogen synthase kinase-3 beta (GSK-3β) is a key regulator of hippocampal neurogenesis which occurs in both the adult and embryonic brain. Hippocampal neurogenesis is impaired in neurodegenerative diseases such as Alzheimer's disease and in many psychiatric disorders. Inflammation is also associated with the neuropathology of these disorders, due to the sustained activation of microglia and release of the pro-inflammatory cytokine interleukin-1β (IL-1β), which is detrimental to neuronal survival.

The aim of this study was to assess the effect of IL-1β on GSK-3β protein expression in hippocampal neural precursor cells (HNPCs) and to assess the effect of GSK-3β inhibition on lippolysaccaride (LPS) induced pro-inflammatory cytokine release in cortical glial cultures. Embryonic day 18 rat hippocampi were isolated and cells were proliferated for 7 days *in vitro* (DIV) in the presence or absence of IL-1β (10ng/ml). HNPCs were immunocytochemically stained for GSK-3β with doublecortin (newly-born neurons), nestin (undifferentiated NPCs), and glial fibrillary acidic protein (astrocytes). Mixed glial cultures were prepared from postnatal day two rat cortex; after 14DIV cells were treated with LPS (50ng/ml) and SB216763 (GSK-3β inhibitor) (10μM). TNF-α and IL-1β levels in cell supernatant were measured using ELISA.

GSK-3β was present in astrocytes, newly-born neurons and undifferentiated NPCs. IL-1β significantly increased the percentage of undifferentiated NPCs ($p<0.001$), newly-born neurons ($p<0.05$) and astrocytes ($p<0.001$) expressing GSK-3β (Student's t-test, n=3). SB216763 treatment blocked the LPS induced release of IL-1β ($p<0.05$) and TNF-α ($p<0.001$) from cortical glial cultures (ANOVA, n=5/6).

GSK-3β maybe involved in the observed IL-1β-induced increase in gliogenesis. LPS-induced release of IL-1β and TNF-α may be mediated via GSK-3β. Investigating GSK-3β, in an inflammatory environment, may provide important information for the development of appropriate treatments for neurodegenerative and psychiatric disorders.

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P1-34

BRIEF SACRAL NERVE ROOT STIMULATION INCREASES CORTICAL SOMATOSENSORY POTENTIAL EVOKED BY ELECTRICAL STIMULATION OF THE ANAL CANAL IN AN EXPERIMENTAL MODEL.

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Faecal incontinence may be associated with pudendal nerve damage sustained during traumatic childbirth[1]. Sacral nerve stimulation (SNS) has been used to treat this condition, but the mechanism of action is unclear. It is our hypothesis that affected individuals develop a sensory deprivation syndrome and sacral neuromodulation potentiates sensory input to the cortex. The aim of this study was to compare somatosensory evoked potentials (SEP) following anal canal stimulation before and after acute sacral neuromodulation.

Fourteen female virgin Wistar rats (body mass: 200-250g) were used. Two groups were constructed, group 1: control and group 2: animals treated with SNS. Animals were anaesthetised with urethane (1.5g kg^{-1} i.p.). An extradural recording array was placed 2mm lateral and 2mm caudal to bregma. In both groups a cathode placed in the anal canal was used to provide triggered stimulation at 1Hz (amplitude: 10volts and pulse duration 0.1ms). A concentric needle stimulating electrode was placed in the left S1 sacral foramen in all animals, but the control group did not receive electrical current. Sixteen SEP were signal averaged (500 sweeps) in the all groups, before and after applying 500sec of sacral neuromodulation.

The SEP amplitude in the control groups (group 1) decreased from $14 \pm 3\mu V$ to $11 \pm 2\mu V$ over 25 minutes following anal canal stimulation (not significant). When SNS was applied to group 2, the SEP amplitude increased from $7 \pm 1\mu V$ to $13 \pm 3\mu V$ sustained over 25mins ($P = 0.001$, two way ANOVA).

The findings support the hypothesis that even brief sacral neuromodulation can increase sensory input from the anal canal to the somatosensory cortex.

This work was supported by a grant from the Health Research Board, Ireland.

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P1-35

DEVELOPMENTAL EXPOSURE TO 17β-ESTRADIOL DOES NOT ALTER NEURAL CELL FATE IN WISTAR RATS.

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There is concern that chronic low-dose exposure of the developing foetus to environmental endocrine disrupting compounds (EDCs) may result in subtle neurological deficits that lead to enduring behavioural deficits. As previous work in our laboratory has demonstrated EDCs to drive cell fate towards the neuronal phenotype *in vitro*, we determined if the 17β-estradiol EDC exerted a similar effect on the developing hippocampal formation. Pregnant Wistar rats received 17β-estradiol (0.5 or 5μg/kg/day by gavage) from gestational day 1 until weaning (postnatal day 25). On postnatal day 30, the pups were killed, their brains fixed with 4% paraformaldehyde, and coronal sections (12μm) obtained at the level hippocampus (-3.3 mm with respect to bregma). Alternate sections were immunohistochemically stained for neuron-specific enolase (NSE) and glial fibrillary acidic protein (GFAP). Hoechst 33258 was used to visualize the total cell nuclei. No gross anatomical changes were observed in the structure of the hippocampus in the 17β-estradiol-exposed animals compared to controls as judged by width of the suprapyramidal blade (P=0.4015), infrapyramidal blade (P = 0.8754), the apex (P=0.4245) or total area (P = 0.463) of the dentate gyrus. Moreover, no difference in neuronal cell fate was apparent when NSE-positive cells were quantified in the apex (P=0.6747), hilus (P=0.3276); CA3 (P=0.7656) and CA1 (P=0.6356) regions of the hippocampal formation. The 17β-estradiol treatment did not modulate glial cell numbers, however, the number of radial glial cells spanning the CA1 region was found to be significantly increased (P=0.0077). In conclusion, developmental exposure to low doses of 17β-estradiol has little impact on the gross structural architecture of the hippocampus or its neuronal and glial cell complement.

P1-36

WHAT IS A NEURON'S FIRING RATE?

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For such an obvious and commonly used a concept, there is no clear, universally accepted, method for calculating the time dependent firing rate of a neuron in an experiment with a limited number of trials. However, the issue of how the firing rate is calculate, and how it is defined, is important when addressing the role of the temporal structure of spike timing in neural coding. In fact, some studies using spike train metric methods which appear to support a strong role for spike timing in neural coding can be reinterpreted as demonstrating the fine temporal structure of the firing rate.

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P1-37

WORDS IN THE BRAINS LANGUAGE: A MISMATCH NEGATIVITY STUDY

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Language, memory and neuronal mechanisms are reciprocally connected in the human brain. Cortical mechanisms can be investigated using a specific Event Related Potential (ERP), called Mismatch Negativity (MMN). MMN is greatly dependent on phonological feature specific information. However, there are limited MMN studies using "natural", finely controlled speech stimuli.

The aims were (i) to develop natural-sounding English word and pseudoword speech stimuli, using a new method for strictly controlling feature-specific information. (ii) To determine the robustness of MMN responses to these stimuli in healthy young adults (n=17).

Experimental stimuli included one word and one pseudoword: peace and "peash". The researchers recorded (1) multiple repetitions of these stimuli uttered by a male native speaker of (Hiberno) English and (2) selected stimuli from these repetitions, whose vowels matched in fundamental frequency (F0), mean energy and overall duration. To create the final stimuli, cross splicing was used. These stimuli were presented in two, reverse single contrast paradigms (each stimulus acted as a "standard" (probability 90%) in one contrast and as a "deviant" (probability 10%) in the reverse contrast).

Carefully controlled natural speech stimuli were created. Discrimination testing has shown a 100% correct identification of difference between the two stimuli. Results to date using the MMN paradigm have confirmed an enhanced MMN response for real word stimuli compared to pseudoword stimuli. This real word-related enhancement provides evidence to support the "word advantage effect", thought to reflect the activation of language-specific memory traces in the brain for words.

The method outlined above will facilitate a range of accurate natural speech stimuli for use in MMN studies. These may be more ecologically valid than stimuli developed using previous methods. Building on these results, investigation of this theory through MMN studies of disordered language (aphasia) may lead to a greater understanding of real brain mechanisms.

We would like to acknowledge Science Foundation Ireland for funding this work.

P1-38

AUTOBIOGRAPHICAL MEMORY IN AMNESTIC MILD COGNITIVE IMPAIRMENT: EXPLORATION OF AUTONOETIC CONSCIOUSNESS AND CONTEXT-DEPENDENT MEMORY

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Autonoetic consciousness refers to the ability to mentally transport oneself back in subjective time to relive elements of, or all, of a past event, and is compromised in the early stages of Alzheimer's disease (AD). Here we investigate potential deficits in autonoesis in amnestic Mild Cognitive Impairment (aMCI, n=16) compared with healthy elderly controls (n=18) during autobiographical memory (ABM) recall using the Episodic Autobiographical Memory Interview (EAMI[1]). aMCI participants exhibited significant deficits in personal semantic and event detail ABM recall. Recall of an event that occurred one week previously was tested in the same spatiotemporal context, and provided the greatest group dissociation, with elderly controls benefitting from a context-dependent memory effect. This reinstantiation of context did not ameliorate the emerging anterograde deficits in the aMCI group, nor did it imbue participants' memories with autonoetic consciousness. Reliving judgments were comparable in both groups, despite aMCI participants' compromised capacity to generate vivid, self-referential visual imagery and re-experience the original emotion of the event. Such experiential elements are critical for autonoesis and the present findings reflect the unravelling of the recollective experience in aMCI, offering further support for a prodromal stage of AD.

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P1-39

STIMULATION OF THE TRANSSULFURATION PATHWAY BY GLIOTOXINS IN C6 GLIOMA CELLS

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L-αaminoadipate (L-αAA) and L-β-*N*-oxalyl-amino-L-alanine (L-BOAA) belong to a group of L-glutamate analogues that are toxic to astrocytes and are known collectively as gliotoxins. Both compounds target the x_c^- cystine-glutamate exchanger, leading to a reduced intracellular concentration of cysteine and, consequently, a considerable reduction in the major antioxidant, glutathione (GSH). Recently, a functional transsulfuration pathway has been identified in astrocytes, in which cysteine can be supplied from methionine and thus contribute to the pool of cysteine required for GSH synthesis. In this study, we have used gliotoxin-mediated inhibition of the x_c^- exchanger to evaluate the relative contribution of the exchanger and the transsulfuration pathway to the supply of cysteine. Statistical analysis was determined by one-way or two-way ANOVA, as required. Incubation of C6 glioma cells with either gliotoxin significantly inhibited the x_c^- exchanger and reduced GSH content of the cells to 44% and 46% of control, respectively, after 24 h. The cysteine content was 34% and 26% of control, respectively. Blockade of the transsulfuration pathway with propargylglycine (PPG) caused a 23% ($P<0.05$) reduction in GSH. A further reduction in GSH was observed when the cells were co-incubated with L-BOAA (to 63% of control, $P<0.001$), but not when the cells were co-incubated with PPG and L-αAA. Neither gliotoxin had any effect on cystathionine-γ-lyase, the rate-limiting enzyme of the transsulfuration pathway, whereas L-αAA, but not L-BOAA, significantly inhibited γ-glutamylcysteine synthase (to 73% of control, $P<0.05$). Depletion of GSH by inhibition of the x_c^- exchanger caused a significant ($P<0.001$) increase in expression of cystathionine-γ-lyase, such that, after 48 h incubation with the gliotoxins, the contribution of the transsulfuration pathway to GSH synthesis was 50%. It is concluded that an increased flux through the transsulfuration pathway promotes *de novo* synthesis of GSH when the supply of cysteine via the x_c^- exchanger is limited.

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P1-40

PINK1: MUTATIONS IN WHICH CAUSE PARKINSONISM, IS ALSO DEFECTIVE IN ALZHEIMER' DISEASE

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Mutations in the serine threonine kinase PINK1 (PTEN inducible kinase-1) cause autosomal recessive forms of Parkinson's disease (PD). These loss of function mutations draw significant attention to understanding how PINK1 protects the brain from degeneration in PD, in addition, to determining whether PINK1 dysfunction is part of the neurodegenerative process of other diseases, particularly Alzheimer's disease (AD).

The aim of this study was to determine whether alterations in PINK1 status occur in AD brain, and its relationship to amyloid-β (Aβ) and neurofibrillary tangle (NFT) pathology. Frozen temporal cortex tissue and paraffin embedded hippocampal sections from AD and control cases were obtained from the Netherlands Brain Bank, with informed donor consent and ethical approval.

Endogenous PINK1 was detected at ~ 64 kDa in human brain, with specificity confirmed showing absence of this immunoreactive band in mice where PINK1 had been deleted. Western blot analysis of PINK1 levels detected a highly significant reduction in PINK1 levels in the cytosol of AD cases (n = 8), with a trend towards increased PINK1 levels in AD membrane fractions (n = 8) compared to matched controls (n = 8).

Immunofluorescence microscopy of control hippocampal sections (n = 5) showed PINK1 is predominantly neuronal, with high levels of expression in pyramidal neurons of CA regions, and subiculum, localising throughout the cell soma, but generally absent from the nucleus. In AD hippocampus (n = 5) neuronal PINK1 expression was reduced but could be increased in subgroups of neurons some of which contained NFTs, and was also increased in glia in some AD cases. PINK1 colocalised with immunostained Aβ plaques and surrounding PHF-1 labelled tau pathology at degenerating terminals of entorhinal cortical neurons. Together the results implicate PINK1 for the first time in AD pathogenesis and stress the importance of understanding the function of this kinase in human brain.

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P1-41

P3 ABNORMALITIES IN MULTIPLE SCLEROSIS AS A FUNCTION OF OLIGOADENYLATE SYNTHETASE GENOTYPE

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Cognitive impairment (CI) may occur in up to 65% of multiple sclerosis (MS) patients. Cognitive event-related potentials (time-locked EEG; ERPs), provide an excellent tool for measuring the time-course of processing in the cortex. An increase in P3 latency is a reflection of CI. Type 1 interferons up-regulate oligoadenylate synthetase 1 (OAS1); a SNP in exon 7 of OAS1 results in differential RNAseL enzyme activity; the G allele confers high, the A allele low, activity. Differential OAS1 enzyme activity dependent on OAS1 genotype may determine in part the degree of upregulation of endogenous interferons. Patients possessing only the A allele (AA) have decreased OAS1 anti-inflammatory activity in comparison to those with the G allele (AG or GG). We hypothesized that patients with the AA allele would have CI (reflected in lower PASAT scores and delayed P3 latency) when compared to AG and GG patients.

We compared patients with the AA allele (n=8; mean age = 42, SD) to patients with the AG alleles (n=10; mean age = 36). Participants completed both 2-stimulus (P3b) and 3-stimulus (P3a) auditory oddball tasks whilst data were recorded from a 136-channel EEG array. Participants also completed the Paced Auditory Serial Addition Test (PASAT).

Neither the age nor EDSS scores were significantly different. The mean PASAT score was significantly different between groups (AA = 45%, AG= 82%; Mann-Whitney U, $Z = -2.89$, $p<.005$). The mean P3b latency at Pz was significantly different between groups (AA = 478 ms, AG= 366 ms; Mann-Whitney U, $Z = -2.22$, $p<.05$). The mean P3a latency at Fz was significantly different between groups (AA = 345 ms, AG= 273 ms; Mann-Whitney U, $Z = -2.08$, $p<.05$).

There is greater CI in MS patients with the AA genotype in comparison to MS patients with the GG genotype.

P1-42

A METHOD FOR THE RAPID ASSESSMENT OF VISUAL PROCESSING LATENCIES IN MULTIPLE SCLEROSIS

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The speed with which visual information is conducted from retina to cortex is an important measure in assessing a number of neurological disorders. For example, optic neuritis is often the indicator of multiple sclerosis (MS). In clinical testing, conduction speed is typically measured using electroencephalography (EEG), an inexpensive and noninvasive technique. The stimulation typically consists of several hundred repetitions of discrete visual stimuli because of the low signal-to-noise ratio (SNR) of EEG. Such testing is extremely time consuming. Previously, we described a method – the VESPA – for obtaining neural responses, with high SNR, more rapidly than with the standard approach. The advantage of this method stems from its use of continuous visual stimulation. We applied the VESPA to the assessment of visual information conduction in MS patients.

We obtained VESPAs in 2-4 minutes for 39 multiple sclerosis patients (20 relapsing remitting MS, 19 secondary progressive MS) and 19 controls. The mean MS age was 42 yrs (SD: 12, range 19-61), mean illness duration was 14 yrs (SD 13, range 1.5-44 yrs), and the mean EDSS was 3 (SD 2.5, range 0-8). The mean control age was 38.95 yrs (SD 10, range 28-60.27 yrs). Only subjects with clear VESPA responses were included in the analysis – (10 controls, 14 RR, 11 SP).

Clear latency differences were seen between the groups as indicated by a 1-way ANOVA ($F_{2,34} = 5.84$, $p < 0.01$). Post-hoc analysis indicated that this was driven by a shorter P1 latency for controls than for both RR ($t = -3.2$, $p < 0.005$) and SP patients ($t = -3.4$, $p < 0.005$). No latency difference was seen between patient groups ($p = 0.64$).

The short amount of testing time required to obtain such dramatic differences suggests the VESPA as a useful tool in clinical testing.

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P1-43

INDUCTION OF BURST-FIRING MEDIATED LONG-TERM DEPRESSION IS INDEPENDENT OF IONOTROPIC EPSPs.

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Burst-firing is a prevalent action potential firing mode of many neocortical neurons during slow-wave sleep. We have previously shown that burst-firing leads to associative long-term depression (LTD) of excitatory synaptic connections between neocortical pyramidal neurons (burst-LTD, ref. 1,2). To elucidate the physiological mechanism of burst-LTD we recorded composite excitatory synaptic potentials (EPSPs) in layer V pyramidal neurons in acute slices of rat somatosensory cortex with the whole-cell patch-clamp technique and assessed the role of AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptor mediated EPSPs for burst-LTD induction. An initial control sequence of composite EPSPs was elicited at low frequencies (0.2 Hz) by extracellular stimulation electrodes. This was followed by a pairing period consisting of pre- and postsynaptic stimuli separated by 10 ms and repeated 70 times. During the pairing sequence AMPA receptors were transiently blocked with the reversible antagonist DCPG (*R*-3,4-Dicarboxyphenylglycine, 0.4 mM). After conditioning and washout of DCPG EPSPs were again recorded for up to 30 min. Amplitudes of EPSPs were significantly depressed to (mean ± SEM) 76 ± 5.5% by the burst-pairings ($p = 0.0024$, t-test, $n = 9$). This amount of LTD was not significantly different from LTD obtained previously with AMPA receptors intact (59 ± 9%, ref.1, $p=0.18$). In additional experiments without conditioning we verified that the washout of DCPG was complete within the same time period used in the pairing protocol.

We conclude that fast ionotropic EPSPs are not essential for burst-LTD induction at this glutamatergic synapse.

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P1-44

THE IMPACT OF FUNCTIONAL BRAIN CONNECTIVITY ON PREDICTION AND THERAPY EVALUATION IN MAJOR DEPRESSION

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The increasing morbidity of depression is one of the reasons why discovering the most effective treatment of the disease has become a very important challenge for medicine and neuroscience. To do so biological markers would be helpful that can track changes during the treatment or predict response. The aim of the study was to find out how an antidepressant trial with one of two medications (mirtazapine or venlafaxine) changes functional brain connectivity between orbitofrontal cortex (OFC) and other brain regions involved in emotion processing and to find markers for response prediction to this antidepressant treatment.

Twenty-three drug-free patients suffering from major depression were examined with an fMRI face matching task to obtain the baseline for their functional brain connectivity. Next they were randomly divided into groups treated with mirtazapine and venlafaxine, respectively. After 4 weeks of therapy the follow-up scan was performed. fMRI data were analyzed using SPM5. Factorial analysis was used with $p<0.05$ and FWE correction.

Responders to treatment were characterized by higher functional OFC connectivity with the primary motor cortex and the right prefrontal cortex, however, lower activation in cerebellum before the therapy begins. A decrease in functional connectivity between OFC and amygdala, cingulate gyrus and sensory cortex was observed after treatment. In the case of participants receiving mirtazapine there was a fall in connectivity between OFC and left cingulate gyrus, left amygdala, temporal cortex and sensory cortex. Venlafaxine resulted in a significant decrease of OFC coupling with cerebellum and an increase in coupling with the in left amygdala and left frontal cortex.

Higher OFC connectivity with motor cortex and prefrontal cortex seems to predict a good clinical response to antidepressant treatment. Therefore, OFC connectivity may be a suitable marker for response prediction. Interestingly, mirtazapine and venlafaxine show alternative effects on OFC connectivity with venlafaxine increasing and mirtazpine decreasing frontal-limbic connectivity.

P1-45

AUDIO-VISUAL SPEECH PROCESSING IN OLDER ADULTS

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Research has shown that older people obtain a higher benefit from multisensory information than a younger population. As normal speech recognition is affected by both the auditory input and the visual lip-movements of the speaker in young adults, we investigated multisensory integration in an older population manipulating the availability of the auditory and visual information in speech. In two tasks we presented participants with words (Exp. 1) and sentences (Exp.2) in audio only (visual stimulus pixelated) or in audio-visual (AV) conditions. In Experiment 2 we also manipulated the semantic context of the sentence to assess whether AV integration is affected by top-down semantic processing. Results showed that older adults are more susceptible to perceiving an integrated audio-visual speech event, even when there is a discrepancy between the auditory and visual information (Exp.1). In contrast, speech perception in older persons benefits from congruent audio-visual inputs relative to auditory information alone. Furthermore, recall performance for speech events is greater for audio-visual than auditory only speech (Exp.2). We also found that sentence context (meaningful or not) differentially affected AV integration. Our findings have implications on our understanding of how ageing affects efficient multisensory integration for the perception of speech.

This research was conducted as one of the studies of the Technology Research for Independent Living (TRIL) centre.

P1-46

THE EFFECTS OF ALERTNESS ON SELECTIVE ATTENTION

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It has been proposed that there is a hierarchy of attentional subsystems in which the basic intensity subsystems of alertness and arousal fuel the more complicated attentional subsystems, which serve selective and divided attention.[1] In order to investigate if selective attention can be improved by increasing alertness, we trained normal, healthy adults to either alert or relax while performing a selective attention task. We hypothesised that, due to increased alertness, the Alert Group would show improvements in performance while the Relaxation Group, due to lowered alertness, would show reduced performance.

The selective attention task was a computerised verbal report task in which participants reported target red letters while ignoring distracter blue letters, displayed on screen. This test was designed to enable estimation of certain parameters of visual selective attention according to the Theory of Visual Attention[2].

Participants in the Alert Group were trained to increase their alertness periodically using a posture shift and deep breath to boost physiological arousal, a self command to sustain attention and skin conductance biofeedback to show the increase in autonomic arousal with each alert. Relaxation training involved skin conductance biofeedback, in which a series of interactive screens encouraged participants to relax and allow their skin conductance to decrease.

Contrary to hypotheses, mixed ANOVAs revealed that both the Alert (n = 14) and Relaxation (n = 15) groups significantly improved their Short Term Memory (*K*), $F(1, 27) = 10.114$, $p < .01$, and Sensory Processing Speed (*S*), $F(1, 27) = 19.529$, $p < .001$. Perceptual Threshold (T_0) and Selective Attention (*Alpha*) did not show a significant change. It is possible that both alertness and relaxation improved sustained attention to task. We are currently running a practice control group in order to determine whether these improvements are true effects of training or are simply practice effects.

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P1-47

MIXED EMOTIONS: AUDITION CAN MODULATE THE VISUAL PERCEPTION OF THE EMOTION OF A CROWD.

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The ability to recognize the emotional state of another person or persons is an important social skill. Moreover, efficient emotional perception determines the appropriate response action. Although many studies have investigated the processes involved in investigating the perception of emotion from individual facial expressions or body postures, very little is known about how we perceive emotions from a crowd of individuals. Furthermore, our understanding of how the visual and auditory senses combine to influence the perception of the emotion of a crowd is poor. We previously found that the emotion conveyed by a crowd can be accurately determined using vision only and that the visual categorization of a crowd is efficient even when the emotion is not consistent across the individuals in the crowd. In the current study we investigated the role of auditory information on the perception of the visual emotion of the crowds. Our stimuli comprised of audio-visual dynamic displays of crowds of varying levels of emotional consistency, from highly consistent to ambiguous. The emotions expressed were anger, fear, happiness and sadness. The auditory emotional cue was paired with each visual display such that it was consistent with one of the emotions visually displayed. We used a 4-AFC design and the participant's task was to categorise the visual emotion but to ignore the auditory information. We found that the auditory emotion significantly biased the perception of the emotion in the visual crowd, particularly when the emotion was visually ambiguous (e.g. half of the individuals in a crowd were fearful whereas the other half were sad). Our findings suggest that auditory emotional information can modulate the visual perception of the emotion of a crowd and have important implications for our understanding of emotional cognition.

P1-48

Bifidobacterium infantis 35624 REDUCES VISCERAL HYPERACTIVITY IN A RAT MODEL OF CHRONIC STRESS

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Irritable Bowel Syndrome is characterized by recurrent abdominal pain and altering bowel habit with a high percentage of patients displaying comorbid anxiety. This disorder currently affects a significant percentage of the population and can have detrimental effects on the quality of life. In this study we evaluated the efficacy of three probiotics in reducing visceral pain in a visceral normosensitive (Sprague-Dawley) and visceral hypersensitive (Wistar-Kyoto) rat strain. We also investigate if these probiotics may have anxiolytic effects. Following 14 days oral gavage of *Lactobacillus salivarius* UCC188, *Bifidobacterium infantis* 35624 or *Bifidobacterium breve* UCC2003 both Sprague-Dawley (SD) and Wistar-Kyoto (WKY) rats were exposed to a novel stress, the open field arena. Behaviour in the open field was recorded. Colorectal distension (CRD) was then carried out on both SD and WKY rats to determine if these probiotics reduced visceral pain by recording pain behaviours during CRD. It was found that there was a difference in the open field between strains but not between probiotics groups within each strain. WKY rats appear more anxious in the open field arena; however, probiotic treatment did not reduce this. The probiotic *B. infantis* 35624 did reduce visceral pain behaviours in both rat strains. It significantly increased the threshold pressure of the first pain behaviour and also reduced the total number pain behaviours during the colorectal distension. While none of the probiotics tested displayed an anxiolytic effect, the *B. infantis* 35624 was effective in reducing visceral pain confirming that certain probiotics may be effective in treating certain symptoms of IBS.

P1-49

GLOBAL DOWNRELULATION OF MIRNAS IN TEMPORAL LOBE EPILEPSY

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miRNAs (miRs) are a growing family of small (~22nt) non-protein coding genes which are predicted to regulate protein expression through base-pairing with the 3'UTR of their target mRNAs[1]. To explore whether miR function is important in temporal lobe epilepsy we screened expression in human epileptic hippocampus and compared findings with mice rendered epileptic following status epilepticus.

Using age/gender matched hippocampal specimens (4 control & 4 temporal lobe resections obtained from Beaumont Hospital with pre-determined sclerosis) we ran large scale expression screens (Taqman Low Density Array Cards which amplify 384 miRs) on a 7900HT Fast real-time PCR system. We observed lower expression of ~30 miRs in TLE compared to control, including miR27a and miR132. No miRs were significantly higher in TLE than control. Western blot analysis of patient samples determined that Dicer, the rate limiting enzyme in miR biogenesis, was downregulated and cleaved. RT-PCR analysis of hippocampus from epileptic mice also detected significantly lower expression of miR27a and miR132. Finally, to verify whether a post mortem delay influenced the human data we analyzed expression of a set of miRs in mouse brain left at room temperature for 8 h, which demonstrated no significant miR changes.

Our findings suggest that miR downregulation in TLE may the result of a chronic disease process wherein the precise balance of miR expression is altered due to abnormal Dicer processing within the cell and identifies candidates for therapeutic manipulation.

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P1-50

THE ROLE OF AGEING ON EFFICIENT AUDIO-VISUAL INTEGRATION IN THE BRAIN: AN EEG STUDY

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Older adults integrate information across the senses more than younger adults. The consequences of this are that perception in an older person can benefit more than younger when congruent multisensory inputs are presented, but perception is more impaired when irrelevant sensory inputs bring distracting information (Poliakoff et al., 2006a). We have recently reported that a relatively simple, audio-visual flash illusion (Shams, Kamitani & Shimojo, 2000) can discriminate between perceptual performance in older relative to younger adults in that older adults are more susceptible to this multisensory illusion over larger time delays between visual and aditory events (Setti, Burke, Newell, 2008). More interestingly, we found that older participants with a history of falling are also more susceptible to the illusion than their age-match counterparts who are not prone to falls. Differences in sensory acuity did not account for these effects, suggesting that the effects are manifested centrally.

In the present study we assessed temporal correlates of this multsensory impairment in the brain by comparing older relative to younger participants using EEG. We adapted a behavioural paradigm, the temporal order judgement (TOJ) task, which requires judgements of the relative order of crossmodal events (a visual flash or auditory beep). It has been shown that older adults are more impaired at this task than younger adults (Poliakoff et al., 2006b). Specifically, we manipulated the delay between the visual and the auditory events and recorded both behavioural responses and the EEG signal during the task. We hypothesised poorer performance for older adults in the TOJ and a different time course of brain activation across the two groups. Our results will help elucidate the time course of the integration of multisensory events in ageing and help compare the integrity of the cortical processes involved in perception across younger and older populations.

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P1-51

SIMVASTATIN MODULATES HIPPOCAMPAL NEURONAL EXCITABILITY AND SYNAPTIC PLASTICITY IN C57/BLACK6J MICE.

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The potential therapeutic effects of statins on cerebral ischemia and Alzheimer's disease have been investigated recently. Chronic treatment with simvastatin can improve learning and memory in mouse behavioural tasks[1]. Here, we have examined the effects of acute and chronic simvastatin treatment on paired pulse facilitation (PPF), neuronal excitability and synaptic plasticity in the form of long term potentiation (LTP) in the hippocampal CA1 region. Extra cellular EPSPs were recorded in the CA1 region of in vitro hippocampal slices from C57 black6J mice. Antidromic action potentials (APs) were evoked by stimulating the alveus and recorded in the CA1 cell body region. Stable recordings were obtained for at least 20min before application of simvastatin or LTP induction. LTP was induced using trains of stimuli applied to the Schaffer-collateral pathway at either 100 or 200Hz. No significant difference was observed in the magnitude of LTP induced by either frequency of stimulation. Acute application of simvastatin prior to LTP induction decreased LTP magnitude compared to control. Following chronic simvastatin treatment however (0.04%, in the diet for 6 months), LTP induced using 100Hz HFS was not significantly different to levels recorded in 8 or 16 month old animals. Acute application of 35μM of simvastatin for 35min increased the EPSP slope compared to vehicle, whereas 10μM simvastatin did not alter the EPSP slope. Simvastatin also significantly decreased the PPF ratio at 35min indicating possible effects on neurotransmitter release. APs recorded in slices from 8week old animals treated acutely with simvastatin (35μM) increased significantly compared to vehicle control. However, acute application of simvastatin had no effect on APs recorded in slices from chronically treated animals compared to untreated animals. These results suggest that simvastatin can alter intrinsic excitability and synaptic plasticity.

Supported by the Irish Health Research Board.

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P1-52

MESENCHYMAL STEM CELLS FROM THE GREEN FLUORESCENT PROTEIN TRANSGENIC RAT ARE HYPOIMMUNOGENIC FOLLOWING TRANSPLANTATION TO THE INTACT ADULT RAT STRIATUM

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A major technical limitation in pre-clinical cell replacement research has been the ability to discriminate between cells of donor and host origin post-transplantation. In recent years, this has been substantially improved by the availability of transgenic animals which express 'reporter' genes such as green fluorescent protein (GFP). This experiment sought to determine the usefulness of one such transgenic reporter rat to assess the survival of bone marrow-derived rat mesenchymal stem cells (MSCs) following direct transplantation to the intact adult rat brain. We also sought to determine if the expression of GFP in the brain impacted on the survival of the MSCs or affected the host's neuro-immune response to the cells.

Male Sprague Dawley rats (n=60) received intrastriatal injections under isofluorane gaseous anaesthesia (2-5 % in oxygen) of sterile transplantation medium, 100,000 normal MSCs or 100,000 GFP-MSCs extracted from the bone marrow of Sprague Dawley rats transgenic for enhanced GFP (eGFP under the ubiquitous CAG promoter). The rats were sacrificed by terminal anaesthesia (50 mg/kg pentobarbital) and transcardially perfused with saline and 4% paraformaldehyde 1, 4, 7, 28 and 42 days post-transplantation. The brains were then processed for fluorescent microscopy and immunohistochemical staining for astrocyte and microglial markers.

GFP-MSCs were evident at all time points examined although their survival declined over time ($P<0.0001$, one-way ANOVA). Graft volume estimates comparing normal and GFP-MSCs revealed that GFP expression did not adversely affect the survival of the stem cells in the brain ($P=0.37$, ns, two-way ANOVA). Furthermore, immunostaining for astrocytes and microglia revealed that expression of the reporter protein did not affect the immunogenicity of the stem cells.

Overall, these data indicate the usefulness of GFP for investigating the survival of MSCs following transplantation to the brain. However, the mechanisms responsible for the poor survival of the stem cells must be elucidated if these cells are ever to become truly useful for cell-based therapies for neurodegenerative disorders.

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P1-53

THE ENDURING EFFECT OF COGNITION ENHANCING DRUGS ON GENE EXPRESSION IN THE RODENT HIPPOCAMPUS

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The hippocampus plays a critical role in cognitive processes such as learning and memory, and its function has been shown to be positively influenced by cognition enhancing drugs. Such drugs have many different primary mechanisms of action and produce a cognition enhancement that persists after cessation of drug administration suggestive of long-lasting beneficial alterations to brain function likely mediated by change in gene expression and/or enduring alteration in nerve cell connectivity.

In this study, we have explored the transcriptome of several known cognition enhancing drug classes. We administered galanthamine, nefiracetam, ABS205 and curcumin to adult rats, daily, for 8 days and, 24h after the final injection, dissected out the hippocampal dentate gyrus and microarrayed this tissue for alterations in gene expression. For each drug treatment we obtained the total number of genes significantly regulated ($p < 0.05$); galanthamine (832 genes), nefiracetam (399), ABS205 (602) and curcumin (472), at a fold-change value of 1.5. There was a large overlap between galanthamine and ABS205 (78 genes in common), and between nefiracetam and curcumin (52 genes) however, no single gene was regulated by all four drugs suggesting that any commonality of effect lay in signalling pathways rather than the individual genes. We next identified several signalling cascades that are modulated in the same direction but at differing points by all four drugs. Using real-time PCR, we have validated eight gene expression changes within these signal cascades including *EfnB1*, *EfnA4* and *EphB1*, drivers of the ephrin growth guidance signal.

In summary, we have shown that while these cognition enhancing drugs differ in their mechanisms of action, they engage the same key signalling pathways. Future studies will test whether modulation of these key pathways is responsible for the procognitive actions of these cognition enhancing agents.

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P1-54

INTRACEREBRAL INFUSION OF ROTENONE INTO THE STRIATUM OR SUBSTANTIA NIGRA CAUSES BEHAVIOURAL DEFICITS AND NIGROSTRIATAL DEGENERATION ASSOCIATED WITH PARKINSON'S DISEASE.

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The lack of valid animal models is a major limitation in the search for novel therapies for Parkinson's disease (PD). Recently, the pesticide rotenone has successfully incorporated the main hallmarks of the disease in a more progressive manner than previously devised models. Systemic administration of rotenone, however, causes peripheral toxicity to such an extent that precludes it as a valid model. This experiment sought to determine the effect on motor function and nigrostriatal degeneration of infusing rotenone into specific brain structures associated with PD.

Male Sprague Dawley rats underwent behavioural testing employing the corridor and stepping tests prior to surgery. Performance matched groups (n=6) were unilaterally infused into the substantia nigra (0.3 µg rotenone or 5% DMSO control) or striatum (4 x 0.3 µg rotenone or 5% DMSO control) under isofluorane gaseous anaesthesia (2-5% in oxygen). Post-infusion behavioural testing was carried out. Rats were sacrificed by terminal anaesthesia (50 mg/kg pentobarbital) and transcardially perfused with saline and 4 % paraformaldehyde. Brains were processed for immunohistochemistry.

No significant difference in weight was recorded between treatment groups. Behavioural tests showed a significant decrease in motor function contralateral to the side of the lesion in striatally infused animals in both the corridor and stepping tests ($p < 0.05$, Unpaired t-test) as compared to controls. Tyrosine hydroxylase (TH) immunohistochemistry showed a significant decrease in the nigral TH-positive cell body count ($p < 0.05$, Unpaired t-test) and a significant decrease in striatal TH-positive terminals ($p < 0.05$, Unpaired t-test) after substantia nigra or striatal infusion of rotenone, respectively, as compared to controls.

This study demonstrates that striatal infusion of rotenone causes deficits associated with PD and does so in a non-toxic manner. However, a varying dose study needs to be carried out to determine if there is a dose-related effect of intra-striatal rotenone on motor function and nigrostriatal degeneration.

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P1-55

UNCOVERING THE NEURAL SIGNATURE OF LAPSING ATTENTION: ELECTROPHYSIOLOGICAL PREDICTORS OF HUMAN ERROR ARE APPARENT UP TO 20s IN ADVANCE

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The extent to which human error can be predicted by monitoring changes in brain activity is uncertain yet has important theoretical and practical implications. The present study examined changes in a range of electrophysiological signals preceding a lapse on a specially designed test of sustained attention. Twenty-one participants performed a continuous temporal expectancy task which involved monitoring a stream of regularly alternating patterned stimuli in order to detect a rarely occurring target stimulus whose duration was 40% longer. The task was designed to place continuous demands on attentional resources and hence to elicit frequent errors. Variations in a variety of attention-sensitive EEG and event-related potential measures were analysed in an epoch extending up to 30 seconds prior to target stimulus onset. Our results indicated that errors were consistently preceded by an endogenous increase in alpha band activity (8-14Hz) beginning approximately 20 seconds before the error actually occurred. Errors were also preceded by shorter-term decreases in the amplitude of two stimulus-related components: the frontal P3 which traces the timing of task stimuli and the contingent-negative variation which is sensitive to target anticipation and motor preparation. In contrast, visual evoked potentials did not distinguish between hits and misses in the pre-target interval suggesting that the efficacy of ongoing basic visual processing was unaffected by lapsing attention. Our results show that the specific neural signatures of attentional lapses are registered in the EEG up to 20 seconds prior to an error and identify new avenues for the development of novel feedback protocols.

P2-1

INHIBITION OF THE PURINERGIC RECEPTOR $P2X_7$, ATTENUATES CASPASE-1 ACTIVATION AND IL-1β RELEASE IN RAT MIXED GLIAL CULTURES TREATED WITH ADENOSINE TRIPHOSPHATE

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The $P2X_7$ receptor, a member of the purinergic receptor family, is an ion-gated channel which is activated by high extracellular concentrations of adenosine triphosphate (ATP)) and which is expressed on cortical rat microglia and astrocytes. Activation of $P2X_7$ receptors has previously been associated with several neurological conditions. Lipopolysaccaride (LPS)-primed mixed glial cultures were shown to release the inflammatory cytokine IL-1β, in response to ATP treatment in a dose-dependent manner and, although LPS also stimulated release of TNFα and IL-6, ATP failed to exert any additional effect. A selective $P2X_7$ antagonist, GSK 1370319, significantly reduced the release IL-1β from LPS-primed mixed glial cultures in response to ATP but IL-1β mRNA expression was unaffected by the drug. TNFα and IL-6 released from similarly-treated cultures were unchanged by treatment with the $P2X_7$ antagonist. ATP dose-dependently increased activation of caspase-1 in mixed glia and which was significantly reduced in GSK 1370319-treated cells. These results taken together indicate that inhibition of $P2X_7$ receptors, by GSK 137019, attenuates caspase-1-dependent release of IL-1β.

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P2-2

THE AGE-RELATED INCREASE IN MICROGLIAL ACTIVATION IN THE RAT HIPPOCAMPUS IS COUPLED WITH INCREASED NOGO-B EXPRESSION.

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Several factors are likely to contribute to the deterioration in neuronal function which has been consistently reported in aged animals. Among these changes are an increase in activation of caspase 3, a marker of deterioration in neuronal function and increased microglial activation in the hippocampus. Here we report that these age-related changes are coupled with an increase in expression of Nogo-B, which is a member of a family of proteins which are known to inhibit axonal regeneration (1, 2).

Hippocampal tissue obtained from groups of young (3 months) and aged (22-23 months) male Wistar rats was assessed for evidence of microglial activation, changes in activities of caspases 8 and 3 and for expression of Nogo-B and the synaptic vesicle protein, synaptophysin. The evidence indicates that there were parallel age-related increases in expression of Nogo-B ($p<0.01$; Student's t-test) and expression of MHCII ($p<0.05$; Student's t-test) and CD11b ($p<0.001$; Student's t-test) which are markers of microglial activation; these changes were accompanied by a decrease in the synaptic vesicle protein synaptophysin ($p<0.01$; Student's t-test) and an increased activation of caspases 8 ($p<0.001$; Student's t-test) and 3 ($p<0.001$; Student's t-test). Importantly, incubation of cultured mixed glia in the presence of Nogo-B significantly increased the expression of MHCII ($p<0.01$; Student's t-test) and CD11b ($p<0.01$; Student's t-test) mRNA, while incubation of cultured neurons in the presence of Nogo-B significantly enhanced activation of caspases 8 ($p<0.001$; 1-way ANOVA) and 3 ($p<0.001$; 1-way ANOVA) in a concentration-dependent manner.

The data suggest that the age-related increase in Nogo-B may, by increasing activity of caspases contribute to the age-related deterioration in neuronal function and to the associated increase in microglial activation.

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P2-3

NEUROPROTECTIVE EFFECTS OF HISTAMINE IN PC12 CELLS

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Histamine is a biogenic amine, commonly associated with inflammatory processes. It also has a neuromodulatory role within the CNS where activation of pre-synaptic H3 receptors leads to changes in cognition, arousal and locomotion among other functions. More recently, a neuroprotective role for histamine has been suggested. The aim of this study was to investigate the effects of histamine, its analogues and selective histamine receptor antagonists / inverse agonists on cell viability and neurite outgrowth in PC12 cells. Protective drug effects were evaluated in the presence and absence of tunicamycin (5μg/ml), which reduced PC12 cell viability as measured by MTT assay. Preliminary results indicate a protective effect with 24 hour histamine (100μM) or carnosine (5mM) pre-treatment and 5mM carnosine also offers protection when co-administered with tunicamycin - an effect not seen with histamine co-treatment. Selective antagonists / inverse agonists at histamine receptors were also examined. The H3 inverse agonist thioperamide demonstrated a trend towards neuroprotection at higher concentrations (100μM) and further studies are underway to confirm this finding. These include dual fluorescent staining with calcein-am and propidium iodide for both qualitative microscopy and quantitative spectrophotometric validation. In parallel, to determine effects of these drugs on neurite outgrowth, PC12 cells were differentiated over a period of 7 days in NGF (50ng/ml). Images were taken 1, 2, 4 and 6 days after drug treatment and neurite and branch lengths were measured. Both histamine and thioperamide increased lengths at concentrations of 10-30μM, while the H2 inverse agonist cimetidine increased lengths up to the maximum concentration tested of 100μM. In conclusion, histamine, carnosine and thioperamide demonstrated a trend towards neuroprotection at higher concentrations and increased neurite outgrowth occurred in the presence of histamine, cimetidine and thioperamide.

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P2-4

EVENT-RELATED POTENTIALS REVEAL HEMISPHERIC LATERALIZATION ON A LANGUAGE TASK IN CHILDREN AT-RISK FOR PSYCHOSIS

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Schizophrenia is typically characterized by language and motor deficits and also impairment in thinking patterns, often manifested as auditory hallucinations.

62-channel EEG was recorded during a computerized version of the British Picture Vocabulary Scale (BPVS) receptive language task, in which adolescents symptomatic for developing psychosis (N=12) and matched controls (N=14) were presented with four line drawings depicting various scenes and situations. Participants were required to select the picture that most closely corresponded to a spoken word. Distinct waveform differences were observed in the visual and auditory phases of the task, with larger visual components for controls. Auditory, correct and incorrect potentials were larger for controls in the left hemisphere and more pronounced for the high-risk group in the right.

These data suggest the possibility of an impaired left hemisphere circuit for language in high-risk children, which may necessitate the recruitment of additional right hemisphere structures to compensate for this deficit. These findings show that children with psychotic-type experiences have right-lateralized ERP activity with respect to controls while engaged in a language task, which may reflect the subtle changes in brain development that may herald the onset of a psychotic disorder.

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P2-5

GUT PEPTIDE HORMONES GHRELIN AND OBESTATIN DIFFERENTIALLY EFFECT STRUCTURE AND SYNAPTIC FUNCTION OF RAT HIPPOCAMPAL NEURONES *IN VITRO*

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Ghrelin and obestatin, both products of the ghrelin gene which have been implicated in regulating appetite, have also been shown to have pro-cognitive effects *in vivo*. However, it is unclear if cognitive effects result from direct effects on relevant brain structures (e.g. hippocampus), or if any interaction occurs between the peptides. We examined the direct effect of both peptides, alone and in combination, on neuronal structure and synaptic function *in-vitro*, by exposing primary hippocampal neuronal cultures to a range of doses of ghrelin, obestatin, or both (0.05, 0.5, 1.25, 5 and 50μM in each case) for 48 hours. Overall complexity of neurite branching was assessed by calculating the area under curve (AUC) of Sholl plots. No dose of ghrelin or obestatin had an effect on AUC relative to control (130±19, n=20), but a significant increase was seen at 5μM dose when both peptides were co-applied (204±18, n=20, $p<0.05$, ANOVA). Additionally, while no ghrelin doses increased the length of the longest neurite relative to control (65±6 μm, n=20), obestatin caused an increase at the 0.5μM (96±11 μm, n=20, $p<0.05$) and 5μM (93±11 μm, n=20, $p<0.05$) doses, and no increases were seen when both peptides were co-applied. Synaptic release rate was calculated from the half-life of FM 1-43 destaining with 65mM KCl stimulation. Ghrelin at a dose of 5μM increased the release half-life (32.1±0.8 s, n=29, $p<0.05$, ANOVA), as did obestatin at 0.05μM (41.7±0.4 s, n=17, $p<0.05$), 0.5μM (31.8±1.5 s, n=50, $p<0.05$) and 50μM (33.2±1.6 s, n=22, $p<0.05$) doses, relative to control (21.5±1.8 s, n=14). No effect on synaptic release was seen when both peptides were co-administered. While the peptides have direct effects on structure and function of hippocampal neurones, no simple dose response relationship or interaction was found, suggesting an underlying complexity in their signalling which has yet to be elucidated.

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P2-6

DEVELOPMENTAL EMERGENCE OF BEHAVIOURAL, NEUROCHEMICAL, AND ULTRASTRUCTURAL DEFICITS IN A PRECLINICAL MODEL OF SCHIZOPHRENIA.

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The neurodevelopmental hypothesis of schizophrenia suggests early brain insults lead to perturbations of normal brain development and the inexorable emergence of the adult psychopathological phenotype. Converging evidence has implicated the prefrontal cortex (PFC) as a major brain locus of dysfunction in schizophrenia which, through a complex and ill-defined sequence of developmental events, ultimately leads to hypofunctional glutamatergic neurotransmission and reciprocal cortical-subcortical disinhibition of striatal dopamine release through GABAergic interneurons. Much of this information is derived from studies on post-mortem tissue from individuals in whom schizophrenia is stable and entrenched and fails to explain the genesis of the disorder. Addressing the critical sequence of molecular, neurotransmitter and synaptic disruptions that lead to schizophrenia presents extreme difficulties in the human dimension and further progress is only likely to come from translational studies in animal models that accurately model core features of the disease. We have used isolation rearing of Wistar rats as a model of schizophrenia and demonstrated the associated sensorimotor deficits, as measured by a pre-pulse inhibition paradigm, to emerge in an age-dependent manner and lead to reduced glutamatergic tone and synaptic deficits within the adult PFC. Further, our transcriptional profiling studies have revealed an initial decoupling of GABAergic-glutamatergic transmission and predict excessive excitation to proceed the emergence of the sensorimotor deficits. These studies further validate the isolation rearing model of schizophrenia and provide insight into the earliest molecular dysregulations that may provide a basis to understand the developmental emergence of schizophrenia.

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P2-7

BEHAVIOURAL AND TRANSCRIPTIONAL PROFILES OF RATS DISPLAYING HIGH AND LOW LEVELS OF CO-OPERATIVITY.

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Co-operation is found to occur widely in human society, even when it is at a cost to those involved. This would indicate that the act of social co-operation in itself must be innately rewarding and that differences in the underlying biological mechanism must underpin the varying degrees of cooperation seen across individuals. Here we describe an animal model that allows separation of inter-individual degrees of co-operation from other neurobehavioural characteristics. Two food-restricted cage-mates are separated in an apparatus divided by a transparent Perspex wall with numerous holes to facilitate visual, olfactory and auditory interactions. Each chamber contained a food hopper connected to a lever that allowed delivery of a food pellet to the partner animal in the absence of receiving a personal reward. The propensity of animals to display reciprocal delivery of food over 7 days was used to define their degree of co-operativity. Animals above the 75th percentile were defined as displaying high levels of co-operativity (mean lever press per day = 9.8 ± 0.31) while animals below the 25th percentile were defined as displaying low levels (mean lever press per day = 4.5 ± 0.35) and the performance of these groups was significantly different by 2-way ANOVA ($P<0.0001$). Neurobehavioural analysis revealed this effect was task specific as no significant difference ($P<0.05$) between the groups was apparent on measures of social interaction, anxiety (elevated X-maze), learning ability (water maze and olfactory discrimination) or sensorimotor processing (prepulse inhibition of acoustic startle). Comparison using microarray technology revealed 113 genes differentially expressed between the groups ($p<0.01$; fold change>1.5), analysis of which may help define the neural mechanisms underlying cooperative behaviour.

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P2-8

AN ANIMAL MODEL OF DELIRIUM DURING DEMENTIA: SYSTEMIC INFLAMMATION INDUCES ACUTE WORKING MEMORY DEFICITS IN THE PRIMED BRAIN.

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Delirium is an acute and sudden cognitive impairment, with particular disruption of attention, which is highly prevalent in the aged and demented population. Episodes of delirium are frequently triggered by systemic infection and such episodes accelerate the process of dementia. We have previously demonstrated that microglia are primed by neurodegeneration to respond more robustly to systemic challenges. In the current study we exploit this phenomenon to propose a novel model of delirium during dementia. This model replicates aspects of the cognitive/attentional dysfunction inherent in delirium by mimicking a key biological context in which it is experienced: systemic inflammation during dementia. We demonstrate that hippocampal synaptic loss and accompanying microglial activation in the ME7 model of prion disease predisposes these animals to experiencing working memory deficits when treated systemically with lipopolysaccharide (LPS). Similar, or greater, LPS challenges do not affect hippocampus-dependent working memory in normal animals. ME7 animals treated with LPS show heightened and prolonged mRNA levels for key inflammatory mediators in the CNS, compared to normal LPS-treated animals, despite equivalent levels of cytokines in the circulation. Perivascular parenchymal microglial IL-1β was detectable only in ME7 animals treated with LPS. The steroidal anti-inflammatory drug dexamethasone prevented these LPS-induced working memory impairments. Future work will examine the mechanisms by which the working memory deficits are induced in this model. Specifically, the roles of prostaglandin E2 and IL-1β production in the CNS and in the periphery will be investigated.

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P2-9

A FULLY AUTOMATED METHOD FOR ARTIFACT DETECTION IN HIGH-DENSITY EEG DATA

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Recently, researchers studying electroencephalography (EEG) have employed high-density EEG arrays (greater than 128 channels). Detecting artifacts produced in EEG data by muscle activity, eye blinks and electrical noise across such arrays is time-consuming, and the rejection criteria for artifacts varies across studies. Independent component analysis (ICA) is able to separate brain activation processes or artifacts whose time waveforms are (maximally) independent of each other. The aim of this research was to harness ICA to develop a fully automated method for artifact detection in high-density EEG data.

A number of 128-channel EEG datasets, both simulated and real (including patient data), were first highpass-, lowpass- and notch-filtered. In the present approach, noisy data were identified by creating dynamic thresholds for the data properties using a cut-off determined by standard deviation. Electrodes were referenced to Fz. Noisy channels were interpolated using an inverse distance approach. Noisy epochs were removed across all channels. An ICA matrix was then calculated and noisy components removed (e.g. eye blink component(s) and white noise components). The remaining components were then re-mixed to scalp space. This method was tested against manual and semi-automated approaches (standard 100uV thresholds), and each was ranked by time taken to process, improvement in signal-to-noise ratio (quantified as signal variance post-stimulus), and number of clean epochs remaining.

In all cases, the automated detection and rejection method surpassed the performance of manual and semi-automated approaches, across all measures. The decrease in signal variance was greater than 30% in almost all cases, and at least 5% more epochs were retained using the automated method.

An automated artifact detection method increased detection of artifacts in high-density EEG data, was faster and more objective than manual or semi-automatic approaches.

P2-10

REMOTE MEMORY IMPAIRMENT IN UNIPOLAR DEPRESSION

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Neurocognitive impairments in attention and working memory are well known to accompany major depressive episodes. However, the effect of depression on retrospective memory is still unclear. The main objective of this work is to examine retrospective memory function during a major depressive episode. We hypothesise that depressed patients will perform worse than healthy controls on measures of retrospective memory.

In this case-control study a neurocognitive test battery was administered to patients with unipolar depression (n=21) during inpatient treatment for a depressive episode (DSM-IV criteria), and to matched healthy controls (n=21). Both public events and autobiographical retrospective memories were assessed, using a specially constructed Events Questionnaire and the Autobiographical Memory Interview Short-Form respectively. The Events Questionnaire examines public events memory for the first year prior to assessment and the 15 years preceding that in three separate five year blocks. Severity of depression in patients, and absence of depression in controls, was assessed using the Hamilton 24-item rating scale for depression (HRSD 24).

The mean HRSD 24 score for patients was 29.05 (SD 6.7). No significant differences were found between depressed and control groups on measures of pre-morbid IQ ($t=1.2$, $p=0.24$), age ($t=0.696$, $p=0.49$) or gender ($\chi 2=0.96$, $p=0.33$). No difference was found between depressed patients and controls on measures of public events memory both within each time period and overall ($p=0.99$). In contrast, depressed patients were found to perform significantly worse than healthy controls on autobiographical memory recall ($p=0.007$).

Results indicate that depressed patients are less able to recall personal events compared to controls, but show no impairment on recall of public events. This finding suggests a dissociation between autobiographical and public events memory in patients suffering from depression.

P2-11

ENDOCANNABINOIDS PREVENT LYSOSOMAL MEMBRANE DESTABILISATION EVOKED BY TREATMENT WITH β-AMYLOID IN RAT CULTURED CORTICAL NEURONES

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Lysosomal dysfunction and destabilisation have been implicated in a variety of neurodegenerative events, including the apoptotic pathway evoked by Aβ (1). The endocannabinoid system is emerging as a promising neuroprotective target for the treatment of AD. It provides neuroprotection against excitotoxicity, ischemia, inflammation, and more significantly against the harmful affects of Aβ (2). Thus, the aim of this research was to explore the ability of the endocannabinoid, anandamide (AEA), to maintain lysosomal membrane integrity and confer neuroprotection.

To monitor lysosomal stability, cultured cortical neurones from one day old Wistar rats were incubated with acridine orange (AO; 5µg/ml) for 10 minutes followed by treatment with $A\beta_{1-40}$ (2µM) ± anandamide (AEA; 10nM) for 6 hours. Cathepsin-L activity was measured using a commercially available kit. Expression of lysosomal associated membrane proteins, LAMP1/2, was assessed by western immunoblotting.

AO fluorescence intensity at 633nm was reduced from 130±18 (mean fluorescence units±SEM) in control cells to 52±10 in cells treated with $A\beta_{1-40}$ ($p<0.01$, ANOVA, n=5) and this was prevented by AEA. Cathepsin-L activity was increased from 3.7±0.5 (relative fluorescent units, mean±SEM) to 7.6±1.2 by $A\beta_{1-40}$ ($p<0.05$, ANOVA, n=5) and this was reduced to 3.5±0.9 with AEA ($p<0.05$, ANOVA, n=5). LAMP1 expression was decreased from 2.70±0.29 (arbitrary units, mean±SEM) to 1.74±0.08 in cells treated with $A\beta_{1-40}$ compared with control ($p<0.05$, ANOVA, n=5) and this was prevented by AEA. LAMP2 expression was increased from 3.7±0.15 (arbitrary units, mean±SEM) to 5.9±0.23 by $A\beta_{1-40}$ ($p<0.001$, ANOVA, n=5) and this was reduced to 3.9±0.058 with AEA. TUNEL positive cells were reduced from 24.54±0.96% (mean±SEM) in cells treated with $A\beta_{1-40}$ to 7.80±0.75% in control cells ($p<0.001$, ANOVA, n=5).

We demonstrate that the endocannabinoid, AEA, prevents the $A\beta_{1-40}$ –induced lysosomal membrane destabilisation, and the subsequent release of the lysosomal enzyme, cathepsin-L. Similarly, AEA prevents the $A\beta_{1-40}$-evoked changes in LAMP1 and LAMP2 expression. Modification of the lysosomal branch of the apoptotic cascade by endocannabinoids could be a therapeutic strategy of relevance for AD.

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P2-12

THE BONE MORPHOGENETIC PROTEIN INHIBITORS CHORDIN, GREMLIN AND NOGGIN DIFFERENTIALLY REGULATE DENDRITIC STRUCTURE, NEURONAL ACTIVITY AND SPATIAL LEARNING

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Many components of the bone morphogenetic protein (BMP) signaling pathway including BMP2, 4, 7 and 10 and BMP inhibitors (BMPIs) chordin and gremlin are present in the adult hippocampus. Recent studies looking at the chordin knockout mouse have implicated inhibition of BMP signaling in control of synaptic transmission, plasticity and learning.

Here, we have compared the BMPIs chordin, gremlin and noggin for effects on neuronal structure and activity in organotypic hippocampal slices of P6-P9 Wistar neonates and spatial memory consolidation in adult Wistar rats. Chordin dose-dependently increased neuritic outgrowth of hippocampal neurons, whilst gremlin and noggin had no effect ($p<0.05$; Dunnett's Multiple Comparison Test). Chordin and gremlin (100ng/ml) caused a significant increase in spontaneous neuronal activity as judged by transient increases in intracellular calcium ($p<0.0001$; Mann Whitney Test). Conversely, hippocampal cells treated with noggin showed a significant decrease in spontaneous activity ($p<0.001$). In vivo, hippocampal BMP signaling was regulated as part of the normal memory cascade. pSmad expression was significantly down regulated in all regions of hippocampus 1-2 hours following water-maze training ($p<0.0001$; Mann Whitney Test). Recombinant chordin (5µg) injected intracerebroventricularly enhanced acquisition and recall of spatial watermaze task ($p<0.05$; Two-Way ANOVA).

Taken together these results indicate that the BMP inhibitors chordin, gremlin and noggin differentially affect the dendritic structuring and activity of hippocampal neurons as well as spatial memory consolidation.

This work was funded by Science Foundation Ireland.

P2-13

THE ROLE OF THE ENDOCANNABINOID SYSTEM IN THE RAT DORSOLATERAL PERIAQUEDUCTAL GREY IN FEAR-CONDITIONED ANALGESIA

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Fear-conditioned analgesia (FCA) is the profound suppression of pain during exposure to conditioned aversive stimuli[1]. Endocannabinoids in the periaqueductal grey (PAG) modulate nociception and unconditioned stress-induced analgesia[2], however, their role in conditioned fear-induced analgesia is unknown. The present study examined the effect of intra-dorsolateral (dl)PAG administration of URB597, an inhibitor of fatty acid amide hydrolase (FAAH), the enzyme which degrades the endocannabinoid anandamide, or rimonabant, a cannabinoid$_1$ (CB_1) receptor antagonist, on formalin-induced nociceptive behaviour and FCA. Male Lister-hooded rats (230-300g, n=6-9) were stereotaxically implanted with guide cannulae into the right dlPAG under isoflurane anaesthesia. The fear-conditioning paradigm used was footshock paired with context (non-footshocked (NFC) controls included). Intra-plantar injection of 2.5% formalin into right hindpaw was used to assess nociceptive behaviour during re-exposure to the conditioned context 24hrs post-footshock. Rats received intra dlPAG administration of 0.2µl of URB597 (0.1 mM), rimonabant (2mM) or vehicle (Veh) (100%DMSO) 15 minutes prior to re-exposure to the context. Pain behaviours were assessed over a 15 min period. All data were analysed by ANOVA followed by Fisher's LSD post hoc test where appropriate and $p<0.05$ was deemed significant.

Re-exposure of rats to the context resulted in a significant reduction of formalin-evoked nociceptive behaviour (Composite pain score (CPS): NFC-Veh 0.68$\pm$0.15 *vs.* FC-Veh 0.19$\pm$0.11, $p<0.5$). Administration of URB597 significantly reduced formalin-evoked pain behaviour in NFC rats (CPS: NFC-Veh 0.68$\pm$0.15 *vs.* NFC-URB 0.20$\pm$0.06, $p<0.01$) but not in FC rats. Administration of rimonabant (Rim) did not alter formalin-evoked nociceptive behaviour in NFC rats but significantly attenuated FCA (FC-Veh 0.19$\pm$ 0.11 vs. FC-Rim 0.70$\pm$0.19, $p<0.05$).

In summary, direct administration of an inhibitor of endocannabinoid degradation into the dlPAG elicits an antinociceptive effect in the rat formalin test. In addition, pharmacological blockade of CB_1 receptors attenuates FCA, indicating a functional role for CB_1 receptors in the dlPAG in mediating FCA.

This work was supported by a grant from Science Foundation Ireland. W.M. Olango is a recipient of an EMBARK Postgraduate Fellowship from The Irish Research Council for Science, Engineering and Technology.

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P2-14

SYNAPTIC INPUT TO NEUROPEPTIDE Y (NPY) IMMUNOREACTIVE NEURONES IN THE AMYGDALA OF PHARMACORESISTANT TEMPORAL LOBE EPILEPSY PATIENTS

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The lateral nucleus serves as the main sensory input of the amygdala and is well known for its involvement in the feed forward and feedback inhibitory role in generation of epileptic foci in pharmacoresistant temporal lobe epilepsy (TLE) patients.
The NPY neurones being among the most abundant immunoreactive neurones in the region were studied at both a light and electron microscopic level. This is a single blind study amongst a population of patients who have undergone amygdalo-hippocampectomy for recalcitrant seizures not amenable to antiepileptic medication.

This quantitative study is amongst two groups, Ammon's horn (AHS) and non-AHS group, looking at the excitatory and inhibitory driving forces acting on NPY neurons in the human epileptic amygdala.

The immunostained amygdala was sectioned utilising an ultramicrotome to obtain both semi- and ultrathin sections for both light and electron microscopic analysis. Results so far show that damage of the amygdala in TLE reveal local alterations in the inhibitory circuitries that may contribute to a lower seizure threshold and greater excitability within the amgdala.

P2-15

ENVIRONMENT AND ANTIPSYCHOTIC DRUG TREATMENT SHAPE CORTICAL-BRAINSTEM CONNECTIVITY. MICRODIALYSIS STUDIES IN ANIMAL MODELS OF SCHIZOPHRENIA.

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Carlsson's accelerator/brake hypothesis of schizophrenia[1] which proposes the loss of a frontal cortical brake on ventral tegmental area (VTA) dopamine was tested in the socially isolated and maternally deprived rat models of schizophrenia by investigating the activation of the medial prefrontal cortical (mPfc) D_2 receptor on VTA glutamate and GABA transmission. Toward this aim, intra-mPfc and VTA microdialysis was employed in freely moving male Wistar rats to investigate the effects of intra-mPfc pergolide (1 μM, 60 mins) on dialysate VTA glutamate and GABA release, alone and in the presence of chronic clozapine (5 mg/kg *i.p.* daily, 10 days). A two-factor ANOVA was employed for significance where $P \leq 0.05$ was deemed significant (n=6-7 animals per group). Vehicle-treated rats acted as controls.

Basal dialysate glutamate levels were similar in all three groups while GABA was reduced by 55% in the isolated rat ($p=0.0066$ v's social control). Clozapine had no effect on basal dialysate glutamate or GABA levels. Intra-mPfc pergolide rapidly reduced VTA glutamate by -96% ($p<0.001$ v's non-treated control) and VTA GABA by -24% ($p=0.023$) in the social control rat but increased VTA GABA by +90% in the isolated rat ($p=0.016$ v's control). Clozapine counteracted the intra-mPfc pergolide-induced reduction in VTA glutamate from -32% to +9% (v's basal) in the social control rat ($p=0.0103$ v's vehicle-treated group, ANOVA) while it reversed the intra-mPfc pergolide-induced increase in VTA glutamate to a decrease (*i.e.* from +23% to -21%, $p=0.0085$) in the isolated rat. Clozapine also reversed the intra-mPfc pergolide-induced increase in VTA GABA in the isolated rat from +99% to -9% ($p=0.0324$).

The findings confirm the cortical brake on the VTA in the social control rat operating *via* a frontal D_2 receptor-mediated inhibition of both corticofugal glutamate and local interneuronal VTA GABA release - which is abnormal or absent in the two animal models. Furthermore, the ability of clozapine to reverse the pergolide effect in the social controls and normalize it in the isolated rat suggests a role for clozapine in maintaining this brake on the VTA. These findings demonstrate the ability of both environment and antipsychotic drugs to shape brain plasticity.

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P2-16

EFFECTS OF MATERNAL IMMUNE ACTIVATION IN UTERO ON BEHAVIOUR IN THE OFFSPRING OF MICE WITH HETEROZYGOUS DELETION OF THE SCHIZOPHRENIA RISK GENE NEUREGULIN 1: MODELLING GENE × ENVIRONMENT INTERACTION IN SCHIZOPHRENIA

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It is well documented that a large number of risk genes have been associated with schizophrenia; these include DTNBP1, DISC1 and NRG1. Although genetic factors are established, contribution from early environmental factors is also indicated. Viral infection during pregnancy has been associated with increased risk for schizophrenia in the offspring. Polyriboinosinic–polyribocytidilic acid (PolyI: C) is a known immune system activator. Behavioural abnormalities related to schizophrenia have been described in the offspring of pregnant dams treated with PolyI: C (1). Neuregulin 1 (NRG1) is one of the genes associated most consistently with risk for schizophrenia.

Using C57BL/6 breeding pairs, ppregnancy was confirmed by the presence of a vaginal plug and was considered gestation day 0 (GD0). Pregnant dams on GD 9 received a single injection (5mg/kg i.p.) of PolyI: C or vehicle.

Behavioural analysis began at postnatal day 35 (PND 35). We have previously reported (2) that social affiliative behaviour is intact but social novelty preference is impaired in mice with heterozygous deletion of NRG1. Social affiliative behaviour was assessed using the sociability and preference for social novelty paradigm (2), in terms of time spent with: (i) an unfamiliar conspecific vs. an empty chamber (sociability) or (ii) an unfamiliar conspecific vs. a chamber containing a familiar conspecific (preference for social novelty).

A pilot study conducted in C57BL/6 mice showed that during the sociability phase mice spent more time in the chamber containing *Stranger 1* (246.3 sec. ±36.1) than in the opposite empty chamber (157.2 sec. ± 14.3). In the social novelty preference phase, C57BL/6 mice demonstrated a preference for spending time in the chamber containing now familiar *Stranger 2* (255.7 sec.±28.0) rather than in the opposite chamber containing *Stranger 1* (169.6 sec. ±27.3). The effects of maternal immune activation on these behaviours in offspring are now being determined.

These studies were supported by Science Foundation Ireland

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P2-17

LITHIUM INCREASES HIPPOCAMPAL CELL PROLIFERATION AND ALTERS BEHAVIOUR IN A HIGH ANXIETY MOUSE STRAIN: EFFECTS OF CHRONIC IMMOBILISATION STRESS.

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Lithium, the major pharmacotherapy for bipolar disorder, is also an effective add-on agent in antidepressant-refractory depression. Although the precise molecular mechanisms underlying its antidepressant effects remain unresolved, it has been reported that chronic lithium treatment can prevent stress-induced changes in behaviour and adult hippocampal neurogenesis in rats. Unfortunately, comparable stress studies in adult mice are lacking. The development of a reliable stress model that induces analogous changes in adult mouse brain and behaviour is important because the characterization of genetically-modified mice in such a model could identify novel targets of antidepressant activity.

The present study examined the utility of a chronic immobilisation stress (CIS) paradigm for inducing changes in mouse behaviour and neurogenesis in the adult hippocampus. Male mice of the high-anxiety BALB/cOLaHsd strain were fed a lithium-supplemented diet (0.2%) or control diet for 21 days. During the last 10 days of the diet, mice underwent immobilisation stress (2h/day) for 10 days, while non-stressed controls remained in their homecages. One day following termination of CIS, mice were either tested in the forced swim test (FST) or were injected with the cell proliferation marker, BrdU (75mg/kg, i.p. X 4 injections every 2h). Interestingly, analysis by two-way ANOVA revealed that CIS did not significantly alter immobility time in the FST or the number of BrdU-positive cells in the subgranular zone or the hilus, but it did prevent body weight gain. In contrast, lithium reduced immobility in the FST and increased the number of BrdU-positive cells in the subgranular zone of both non-stressed and stressed mice ($P < 0.05$). Taken together, these data confirm the neurogenic and antidepressant properties of lithium in this mouse strain but do not support the utility of this CIS paradigm for inducing changes in the FST or cell proliferation in the adult mouse hippocampus.

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P2-18

ABERRANT BEHAVIOURAL AND PHYSIOLOGICAL RESPONSES TO A SYSTEMIC IMMUNE CHALLENGE IN THE WISTAR KYOTO RAT

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The efficiency of the innate immune response is crucial for the priming of acquired immunity and survival of an organism. Inappropriate immune responses are associated with stress related disorders. The neuroendocrine system is a major pathway of communication between the central nervous system and the immune system. Dysfunction of the neuroendocrine system leads to inefficient communication between the two major systems of the body. Stress may have different effects on immune function depending whether it is presented in an acute, which may be immuno-enhancing or chronic fashion, which may be immunosuppressive. The Wistar Kyoto (WKY) rat is genetically predisposed to high-anxiety behaviour and displays disturbances of the hypothalamic pituitary adrenal axis.

Our aim was to study the effect of an acute immune challenge on behavioural and physiological parameters in a stress-prone preclinical model of IBS. LPS at a dose of 01.mg/kg or saline (1ml/kg) was administered to WKY or Sprague Dawley (SD) rats. Following this challenge, visceral hypersensitivity (2 hours later), food and water intake as well as social interaction behaviour (2, 6, 24 hours) were analysed. Interleukin (IL)-1β and IL-6 concentration were analysed in the plasma and mRNA of these cytokines were measured in the brain.

It was noted that WKY rats display visceral hypersensitivity compared to the SD rats at baseline. Only SD rats showed an increase in visceral hypersensitivity following the LPS challenge. Food and water intake decreased significantly in SD rats only and they also showed the greatest reduction in social interaction. An altered immune response was also noted with regard to the cytokine measurements in the WKY compared to the SD controls.

The genetically stressful background of the WKY rat influences the manner in which they respond to infection. This can contribute to the further understanding of the impact of stress on the immune function.

P2-19

THE EFFECT OF GENERAL ANAESTHETIC AGENTS ON HIPPOCAMPAL NEURONAL STRUCTURE AND PSA-NCAM EXPRESSION.

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Post Operative Cognitive Dysfunction (POCD) is a well-established entity that contributes substantially to post-operative morbidity and resource utilisation. Data relating to the direct contribution of individual general anaesthetic agents toward the development of POCD are lacking.

The neural cell adhesion molecule (NCAM) plays an important role in activity-dependent synaptic plasticity and, glycosylation with polysialic acid (PSA) has been shown to be necessary for memory consolidation. Anaesthetics may interfere directly with synaptic plasticity by altering neuronal structure, gene expression and PSA-NCAM expression.

We studied the effects of isoflurane and propofol on hippocampal neuronal structure and PSA-NCAM expression using organotypic hippocampal cultures. We examined the expression of PSA-NCAM in the CA1, CA3 and dentate gyrus at 24, 48 & 72 hours following exposure to clinically relevant doses of isoflurane or propofol for 2 hours using standard immunofluorescence techniques. We also examined the effects of these agents on hippocampal neuronal structure (spatial expansion of neuritic arborisation and total neuritic length).

There were no significant changes in the expression of PSA-NCAM in any region at any time point between isoflurane and controls. However, within the isoflurane group, the expression of PSA-NCAM was significantly decreased in the DG and CA3 hippocampal neurons at 72 hours relative to 24 and 48 hours time points. There were significant differences between the slices treated with propofol for 2 hours and corresponding controls at discrete time points, particularly in the CA1 region.

Quantitative analysis of total neuritic length 72 hours following treatment revealed that exposure to isoflurane resulted in increased total neuritic length relative to controls. Propofol reduced the total neuritic length relative to the control group, but this effect did not achieve significance. Scholl analysis of the overall spatial extent of neuritic arborization showed that isoflurane increased the spatial distribution of the neuritic, whereas exposure to propofol appeared to stunt neuritic arborisation relative to control neurons, although not significantly.

P2-20

APPswe/PS1dE9 MICE EXHIBIT BEHAVIOURAL DEFICITS AND INCREASED MICROGLIAL ACTIVATION.

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Alzheimer's Disease (AD) is associated with impaired memory and neuronal degeneration and amyloid-beta (Aβ) is believed to play a crucial role in these alterations in brain function. In this study APPswe/PS1dE9 mice, which overexpress amyloid precursor protein (APPswe) and presenilin 1 (PS1dE9) and which exhibit an age-related increase in Aβ deposition in the brain, were used as an animal model of AD. It was hypothesized that, in comparison with wildtype mice, the increased Aβ deposition in the transgenic mice would be associated with microglial activation and would exert a negative impact on spatial learning.

Spatial learning was investigated using the Morris Water Maze. No difference was found between groups during the acquisition phase however during the reversal phase, the pathlength to find the escape platform was significantly increased in APPswe/PS1dE9 mice compared with wildtype animals. This suggests an impairment in plasticity in these animals. Aβ plaque load was assessed using confocal microscopy and a significant plaque burden was observed in the hippocampus and cortex of the APPswe/PS1dE9 mice while no plaques were observed in wildtype mice. Microglial activation was assessed by evaluating expression of cell surface markers on isolated cells prepared from brains of transgenic and wildtype mice using flow cytometry. Expression of MHCII on CD11b-positive cells isolated from the brains of APPswe/PS1dE9 mice was significantly greater than its expression on CDllb-positive cells isolated from wildtype mice.

These data indicate that the increased plaque burden in the brains of APPswe/PS1dE9 transgenic mice is associated with increased microglial activation and impaired spatial learning.

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P2-21

IDENTIFICATION OF FUNCTIONAL GENE REGULATORY ELEMENTS IN THE HIPPOCAMPUS OF A RAT MODEL OF SCHIZOPHRENIA USING FAIRE-SEQ

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It is well established that multiple genetic and environmental factors contribute to schizophrenia (scz). It is hypothesised that these factors interact at critical periods in early development to create a defective epigenetic state within certain brain structures. This causes dysregulation of connectivity and functionality, resulting in onset of disease symptomatology. The DNA regions that are most likely affected under this hypothesis are the functional regulatory elements that control the activation of genes in different cell types, at different stages of development. Most of these elements are located far from existing genomic landmarks and the vast majority remain unidentified.

Here, we present the use of a next-generation sequencing platform to identify functional elements in the isolation reared rat model for schizophrenia. Sequencing libraries were generated using FAIRE (formaldehyde-assisted isolation of regulatory elements) isolated DNA from the hippocampus of isolated (Iso) and social control (Soc) rats. These samples were sequenced using a Genome Analyzer II (Illumina) to produce a genome-wide map of regulatory elements in the rat hippocampus.

In total, 66,338 significant peaks were detected across the two groups. >80% of these fall within, or flank, known gene sequences, indicating that active elements are being detected by this method. Furthermore, by comparing the active elements in Iso versus Soc samples, we have identified regions which distinguish the model from controls, several of which are in the region of scz candidate genes.

Taken together, we have begun to identify the underlying epigenetic mechanisms of expressional control, which may contribute to Schizophrenia disease characteristics.

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P2-22

THE TRANSCRIPTION COFACTOR MKL REGULATES HIPPOCAMPAL MEMORY-ASSOCIATED NEURONAL STRUCTURAL REORGANISATION

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The megakaryocytic acute leukaemia (MAL) family of serum response factor (SRF) co-activators have recently been identified as key components of a signalling pathway linking changes in the actin cytoskeleton to SRF-mediated gene expression. *In vitro* studies have shown that MAL proteins associate with monomeric G-actin in the cytoplasm, but undergo Rho-A induced translocation to the nucleus where they associate with SRF and stimulate transcription of several structural genes.
Here, we set out to better understand the role of MAL proteins in neuronal morphology and to investigate if they function in the synaptic restructuring required for memory consolidation. We find that targeted siRNA disruption of MAL expression significantly alters the growth and development of hippocampal neurons in culture ($p<0.001$; one-way ANOVA and Dunnett's post-test). Specifically, it seems that increased expression of MAL2 promotes, and knocked down of MAL2 decreases, neuritic growth and branching. Furthermore we demonstrate that MAL accumulates *in vivo* in the nucleus of granular and pyramidal neurons of the ventral hippocampus 3h, but not immediately, following passive avoidance training of Wistar rats ($p<0.01$; Kolmogorov-Smirnov test). This nuclear translocation coincides with a learning-specific increase in the expression levels of 3 MAL-regulated genes, *Tpm3*, *α-SMA* and *Snai2* ($p<0.05$, Student's t-test), suggesting that MAL is transcriptionally active at this time.
Our findings suggest that MAL is shuttled to the nucleus of cardinal cell populations in the hippocampus during memory consolidation and may contribute to the transcriptional programme driving synaptic reorganisation that underpins long-term information storage in this region.

KJM is a Science Foundation Ireland Investigator.

P2-23

SUBCHRONIC ADOLESCENT EXPOSURE TO DELTA-9-TETRAHYDROCANNABINOL IN COMT KNOCKOUT MICE: IMPACT ON SCHIZOPHRENIA-RELEVANT PHENOTYPES

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Clinical studies have indicated cannabis use to confer a two-fold increase in risk for subsequent onset of psychosis, with adolescent-onset use conveying even higher risk. This increased susceptibility is likely mediated via a disruptive effect of cannabis during a critical period of brain development. Genotype plays a role, as there is evidence that a high activity COMT polymorphism moderates the effects of adolescent exposure to cannabis on risk for adult psychosis. COMT is an enzyme that facilitates the degradation of dopamine in the synapse and deletion at chromosome 22q11, which contains the COMT gene, has been linked with elevated risk for psychosis.

In the present study, mice mutant for the COMT gene (COMT 'knockouts') were chronically treated with delta-9-tetrahydrocannabinol (THC, the psychoactive component of cannabis; 4.0 and 8.0 mg/kg over 20 days) during either adolescence (postnatal day 32-52) or adulthood (postnatal day 70-90). The effects of THC exposure were then assessed in adulthood across behavioural phenotypes relevant for psychosis: basal exploratory activity, social interaction (as measured in the sociability and social novelty preference test), several indices of cognition, including object recognition memory, spatial working memory (spontaneous alternation, delayed alternation) and anxiety (elevated plus maze). COMT genotype selectively modified the adult effects of chronic THC, when given during either adolescence or adulthood, at the levels of social cognition and object recognition memory. However, adolescent-treated COMT mutants demonstrated more pronounced abnormalities following chronic THC across psychosis-relevant behavioural endophenotypes (heightened exploratory activity, spatial working memory deficits) compared with adult-treated mutants and controls. It is proposed that examination of the effect of genotype on responsivity to environmental manipulations at specific developmental stages illuminates the relative contribution of, and interaction between, genes and adverse environmental factors in the expression of the psychosis phenotype.

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P2-24

HOW TO PREDICT AN ERROR: DEVELOPMENT OF SINGLE-TRIAL ELECTROPHYSIOLOGICAL CLASSIFIERS TO IDENTIFY LAPSES OF ATTENTION

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Lapses of attention are often the cause of human error, as in the distracted driver who runs a red light. Detecting when these lapses of attention occur inspire an important field of cognitive science. Previous studies showed that changes in brain activity before an error predicted the occurrence of this error. For instance, O'Connell et al.[1] showed that electrophysiological activity of the brain changed up to 20 seconds before missing a target on a test of sustained attention.

Although these results are compelling, they only concern the performance of a group of participants. It would be an important step if we could predict errors at the level of an individual or even a single trial. Some researchers successfully developed computational models that associate patterns of brain activity with a type of answer. These models have been able to differentiate brain patterns of single participants looking at different categories of objects, both in fMRI and EEG techniques.

Using similar computational models, we investigated if it was possible to classify correct and incorrect responses preceding a target on a test of sustained attention. Using the data of O'Connell et al. (2009), we analyzed four-second epochs preceding a target. We built multiple classifiers using a combination of well known methods and compared their performance. The results are discussed in terms of classification accuracy and the potential for an on-line predictive method for errors before they occur.

1. Redmond G. O'Connell, Paul M. Dockree, Ian H. Robertson, Mark A. Bellgrove, John J. Foxe, and Simon P. Kelly Uncovering the Neural Signature of Lapsing Attention: Electrophysiological Signals Predict Errors up to 20 s before They Occur. J. Neurosci. 2009 29: 8604-8611

P2-25

STOP NULL MICE DISPLAY PHENOTYPES RELATED TO THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Although several genes have been reliably associated with risk for schizophrenia, it is unclear how these genes might relate to individual psychopathological, cognitive or biological aspects of schizophrenia. Stable tubule-only polypeptide [STOP] proteins are involved in the cold stability of microtubules, brain development and connectivity, synaptic plasticity and neurotransmission. STOP null mice show abnormalities in synaptic protein mRNAs similar to those reported in schizophrenia. STOP null mice display several phenotypes reminiscent of the positive symptoms and cognitive deficits observed in schizophrenia including: hyperactivity, hypersensitivity to behavioural effects of psychostimulants, deficits in PPI and recognition memory. The negative symptoms of schizophrenia include anhedonia, avolition, and social withdrawal. The objective of the present study was to investigate whether phenotypic differences are observed between STOP null mice *vs*. wildtypes (WT) across the following animal models of negative symptom-like features: sucrose preference test, the forced swim test (FST). Using a two-bottle preference test, it was found that STOP null mice displayed a reduced preference for a sucrose solution *vs*. water relative to WT mice ($p < 0.05$); these data indicate a putative anhedonia phenotype in STOP null mice. In the FST, no difference was found in either total duration or latency to first episode of immobility between WT and STOP null mice. However, STOP null mice displayed significantly fewer climbing movements in the FST relative to WT ($p < 0.05$). Prior treatment with the antidepressant desipramine (8mg/kg) selectively restored a normal climbing profile in STOP null mice ($p < 0.05$), without altering immobility or climbing behaviour in WT mice, suggesting that the phenotypic decrease in climbing behaviour may represent a behavioural index of depressive-like behaviour in STOP null mice. In summary, the present results would suggest that improved characterisation of the role of STOP gene in schizophrenia has the potential to provide insight into the pathophysiological basis of negative symptoms in this disorder.

P2-26

HIPPOCAMPAL REDUCTION IN MAJOR DEPRESSION AND NORMAL PREFRONTAL CORTEX DEVELOPMENT IS ASSOCIATED WITH CHILDHOOD STRESS

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Early emotional stress is associated with a life-long burden of risk for later depression and stressful life events contribute to the development of depressive episodes particular in genetically vulnerable subjects. However, the association between stress, depression and brain structure has yet not been clarified in humans. In this study we investigated whether structural brain alterations are associated with childhood stress. Patients with major depression from the University Hospital, Department of Psychiatry, Ludwig-Maximilians-University Munich, and age as well as gender matched control subjects from the community were recruited. They were investigated using high-resolution magnetic resonance imaging (MRI). Region of interest analysis of the hippocampus, whole brain voxel-based morphometry (VBM) and assessment of childhood stress as well as cumulative illness duration was carried out.

Significantly smaller hippocampal ($p<0.05$) and prefrontal gray matter volume ($p<0.05$, FWE corrected) was observed in patients with major depression compared to healthy controls. Smaller hippocampal volumes were significantly associated with more childhood stress in male patients and with cumulative illness duration in female patients. Physical neglect during childhood was associated with prefrontal gray matter volume in healthy subjects.

Other yet unknown biological factors seem to contribute to the association of childhood stress and hippocampal development in male subjects who later become depressed. Whether the association between stress and structural changes is related to genetic vulnerability should be investigated in future studies.

P2-27

CROSSMODAL INTEGRATION IN COMPLEX DYNAMIC SCENES

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Crossmodal influences in spatial perception have been well documented in recent years. While there has been much research into the visual effects on sound localization (e.g ventriloquist effect), relatively little is known about how sound can affect visual localization in a scene. Moreover, very little is known about how sounds can influence attentional deployment during a visual search task. Here we investigated whether sound can affect visual search performance when the target is a dynamic object embedded in a dynamic display. In Experiment 1, participants had to judge whether a visual target was present or absent in a display containing varying number of distractor items. Auditory information was either congruent, incongruent with the moving direction of the visual target, or sound was absent. In Experiment 2, participants conducted an odd-one-out task in a similar dynamic display but here sound was either congruent or incongruent with the intermittent appearance of the visual target in the display (or sound was absent). In both experiments, we found that sound significantly affected visual search performance. Furthermore, explicit instructions to either ignore or attend to the sound had no effect on the overall findings. However, in Experiment 1 in particular, sound information did not facilitate the detection of the visual target directly but seemed instead to be used to facilitate multi-object tracking in order to eliminate non-target objects during the search process. Our findings suggest that sound can affect visual search in dynamic displays and have important implications for our understanding of multisensory influences target detection in realistic scenes.

P2-28

TREATMENT WITH THE β_2-ADRENOCEPTOR AGONIST CLENBUTEROL ACTIVATES THE CENTRAL INTERLEUKIN-1 SYSTEM WITHOUT PROVOKING DEPRESSIVE OR ANXIETY-LIKE BEHAVIOUR IN RATS

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The inflammatory cytokine IL-1β in expressed in the central nervous system and plays a number of physiological roles in the CNS. In contrast, excessive production of this inflammatory cytokine, particularly in the context of microglial activation, has been implicated in the neurodegenerative process, and also in the pathogenesis of psychiatric disorders such a depression and anxiety. We have recently demonstrated that the brain permeable β_2-adrenoceptor agonist clenbuterol selectively activates the central IL-1 system without inducing expression of other inflammatory cytokines including TNF-α, IL-6 and IFN-γ. Moreover, we have shown that this induction of IL-1β is short-lived and accompanied by increased expression of IL-1 receptor antagonist (IL-1ra) and IL-1 type II receptor (IL-1RII); two negative regulators of the IL-1 system. Double immunohistochemical staining that clenbuterol-induced IL-1β expression is localised to astrocytes as opposed to microglia, and this is supported by the fact that clenbuterol treatment consistently induces expression of the astrocytic activation marker GFAP, whilst having little effect on expression of the microglial activation marker CD11b.

As central IL-1β expression has been previously been implicated in precipitating anxiety and depressive behaviours, in this study we examined the impact of chronic treatment with clenbuterol (30μg/kg; bid; 21 days) on anxiety behaviour using the elevated plus maze and open field tests, and examined the anhedonia using the saccharin preference test as an indicator of depressive behaviour. As we previously observed, clenbuterol induced central IL-1β expression which was accompanied by expression of IL-1ra and IL-1RII. Despite this induction of IL-1β, clenbuterol failed to induce anxiety or depressive behaviour in these animals. This study demonstrates that selective activation the central IL-1 system in a controlled manner does not induce a depressive or anxious behavioural phenotype in rats.

P2-29

THE β_2-ADRENOCEPTOR AGONIST CLENBUTEROL ACTIVATES ASTROCYTES AND REDUCES AMYLOID-β CONCENTRATIONS AND RAGE EXPRESSION IN RAT CORTEX AND HIPPOCAMPUS

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Alzheimer's disease is a neurodegenerative disease characterized by chronic inflammation and the accumulation of amyloid-β plaques and neurofibrillary tangles. Noradrenaline acting at β_2-adrenoceptors on glial cells has anti-inflammatory and neurotrophic properties, and it has been suggested that a loss of central noradrenergic tone may contribute to the development of Alzheimer's disease by facilitating chronic neuroinflammation and amyloid-β deposition.

In this study we report that chronic treatment with long-acting β_2-adrenoceptor agonist clenbuterol (30μg/kg; bid; 14 days) results in a significant induction of GFAP mRNA expression in rat cortex and hippocampus, indicating astrocytic activation. In parallel, clenbuterol treatment significantly reduced amyloid-$\beta_{1\text{-}40}$ and amyloid-$\beta_{1\text{-}42}$ concentrations in both brain regions. We suggest that this reduction in amyloid-β concentrations occurs due to increased degradation, as opposed to an inhibition of synthesis. In this regard, we demonstrate that clenbuterol induces expression of matrix metalloproteinase-2 (MMP-2) in cortex and hippocampus; an enzyme that is known to degrade amyloid-β. In contrast, we found no evidence that clenbuterol could influence amyloid-β synthesis, as expression of amyloid precursor protein, α-secretase (ADAM-10 or ADAM-17) or γ-secretase (Presenillin 1 or 2) were not altered following clenbuterol treatment. Furthermore, clenbuterol treatment significantly reduced expression of the receptor for advanced glycation end products (RAGE) in both hippocampus and cortex; a receptor implicated in mediating amyloid-β-induced neurotoxicity.

Ultimately these data indicate that β_2-adrenoceptor activation activates astrocytes and limits the actions of amyloid-β by clearing the protein, and also by reducing expression of RAGE. These results indicate that the β_2-adrenoceptor may represent a new target for pharmacological intervention in the treatment of Alzheimer's disease.

P2-30

EFFECTS OF TUMOUR NECROSIS FACTOR-α ON PROLIFERATION AND DIFFERENTATION OF EMBRYONIC RAT HIPPOCAMPAL NEURAL PRECURSOR CELLS: A ROLE FOR HES1.

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Neurogenesis in embryonic and adult brain occurs due to the presence of neural precursor cells (NPCs). Tumour necrosis factor-α (TNFα) is a pro-inflammatory cytokine, which negatively influences neuronal survival and function. Hairy enhancer of split-1 (Hes1) is an anti-neurogenic basic helix-loop-helix transcription factor. This study's aim was to examine the effects of TNFα on neuronal and astroglial proliferation, differentiation, and Hes1 expression in hippocampal neurosphere cultures.

Neurospheres, prepared from embryonic day 18 Sprague Dawley rat hippocampus, were proliferated for 7 days *in vitro* (DIV) in the presence of TNFα (10ng/ml). 5-Bromo-2'deoxyuridine (BrdU) (0.2μM) was added 12 hours before fixation. Immunocytochemistry was performed for BrdU/doublecortin (proliferating newly-born neurons) or BrdU/glial fibrillary acidic protein (GFAP) (proliferating astrocytes). TNFα didn't affect the percentage of proliferating newly-born neurons but significantly decreased the percentage of proliferating astrocytes (50±4.6%) compared with control cells (67±4.2%) (Student's t-test; $p<0.05$; n=3). When cells from these neurospheres were differentiated for 7DIV, TNFα treatment during proliferation didn't affect cell differentiation toward astrocytic or neuronal lineage. RT-PCR showed TNFα didn't affect gene expression of Hes1 or the TNFα receptors, TNF-R1 and TNF-R2.

In a separate study, cells from neurospheres were differentiated for 7DIV in the presence of TNFα (10ng/ml) and stained for β_{III}-tubulin (post-mitotic neurons), doublecortin and GFAP. In contrast to the findings of the proliferation experiments, TNFα treatment during differentiation significantly reduced the percentages of newly-born neurons (5±0.7%) and post-mitotic neurons (10±1.2%) compared to control cells (9±0.7% and 32±1.4% respectively). Conversely, TNFα significantly increased the percentage of astrocytes (82±1.4%) compared to control cells (60±1.3%) (Student's t-test; $p<0.01$; n=3). RT-PCR demonstrated increased expression of Hes1, TNFR-1 and TNF-R2 after TNFα treatment during differentiation.

Exposure of hippocampal NPCs to TNFα during differentiation negatively influences neurogenesis. Hes1 upregulation, along with increased expression of TNFα receptors may provide a mechanism for TNFα to impair neurogenesis.

P2-31

METHAMPHETAMINE EFFECTS ON CELL VIABILITY, BDNF LEVELS AND NEURITE OUTGROWTH IN PC12 CELLS.

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Methamphetamine has been described as a very potent psychomotor stimulant which can cause neurotoxic damage in vitro and in vivo [1]. PC 12 cells have dopaminergic characteristics [2] and can be used as a model to evaluate methamphetamine toxicity. Previously, in this laboratory, we found that methamphetamine caused a decrease in cell viability and increased BDNF level in undifferentiated PC12 cells [3]. The objective of this study was to examine the effect of methamphetamine in differentiated PC12 cells and correlate these findings with undifferentiated cells. Cell viability was measured by MTT assay, BDNF expression was measured by ELISA and neurite outgrowth was measured by morphological assessment [4]. PC12 cells were seeded on poly-L-lysine coated wells at a density of 1x 10^5/ml for ELISA or 0.5x 10^5/ml for morphology and MTT analysis. For undifferentiated PC12 cells, cells were allowed 24 hours to adhere on the plates before drug treatment. To differentiate the cells 50ng/ml NGF in media was used for 7 days prior to drug treatment. Cells were treated with MA (1mM, 3mM, 6mM or 15mM), staurosporine (STS) 2mM (positive control) or medium (negative control) for 24 hours. The results (table 1) showed that methamphetamine and STS reduced cell viability in both undifferentiated (U) and differentiated (D) cells. Methamphetamine also caused an increase in BDNF levels in both undifferentiated (U) and differentiated (D) cells. BDNF levels were higher in differentiated PC12 cells than undifferentiated cells, STS had no effect on BDNF expression. In differentiated PC12 cells methamphetamine caused a decrease in neurite length. Further elucidation of the mechanism by which methamphetamine reduces cell viability is needed as is a better understanding of the role of BDNF following methamphetamine treatment.

Table 1

Group	Cell viability (% of control)		BDNF (pg/mg protein)		Neurite outgrowth (µM)
	U	D	U	D	D
Control	100±15	100±7.8	7±0.98	58±8.4[a]	12±1.2
1mM	60±17[*]	60±7.1[*]	12±0.9[*]	101±15[*]	12±3.1
3mM	42.±19[*]	60±7.4[*]	19±1.0[*]	141±55[*]	4±0.82[*]
6mM	13±1.5[*]	11±1.8[*]	23±1.2[*]	112±11[*]	0.46±0.16[*]
15mM	6±1.8[*]	5±0.9[*]	24±0.8[*]	108±11[*]	0.15±0.07[*]
STS	6±2.2[*]	51±7.4[*]	8±0.9	67±2.4	10.5±1.7

Results (n=3) are expressed as mean ± S.E.M. All data were analysed using one way ANOVA, followed by Student-Newman-Keuls test. [*]$p<0.05$ vs. Control. [a]Significantly different from respective undifferentiated group (U).

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P2-32

SIMILAR TEMPORAL OSCILLATIONS IN HIPPOCAMPAL NF-κB FOLLOWING SPATIAL LEARNING IN RATS AND HIGH-FREQUENCY STIMULATION OF ORGANOTYPIC SLICE CULTURES

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Learning and the initial molecular events associated with memory formation are thought to be heavily dependent upon new protein synthesis. Consequently, transcription factors have been implicated in driving this cognitive process. The sensory triggers that culminate in formation of a memory trace have been modelled experimentally by administration of an external high-frequency electrical stimulus (HFS) to those neuronal circuits involved in memory formation. In this study we investigated the temporal regulation of NF-κB, a key transcription factor recently implicated in hippocampal-dependent synaptic plasticity, following both spatial learning in the rat hippocampus and post-HFS to the outer molecular layer of the dentate gyrus (DG) in organotypic hippocampal slices. NF-κB has been shown to translocate to the nucleus following neuronal activation and increases in intracellular calcium levels and is, therefore, an ideal candidate to drive waves of transcription associated with the memory consolidation process. Using a combination of immunofluorescence, confocal microscopy and an automated image analysis system, we demonstrate similar temporal oscillations in the activated p65 subunit of NF-κB in the CA1 and dentate gyrus neuronal populations of the rat hippocampus following both water maze training and HFS. NF-κB decreased in the majority of CA1 (Kolmogorov-Smirnov test, $p<0.001$, D-statistic = 0.150) and dentate neurons (K-S test, $p<0.001$, D-statistic = 0.121) 2 h post-training. These decreases were recapitulated *in vitro* post-HFS (CA1: K-S test, $p<0.001$, D-statistic = 0.175; DG: K-S test, $p<0.001$, D-statistic = 0.106). At the 3 h time-point post-training, however, NF-κB activity increased in the CA1 region (K-S test, $p<0.001$, D-statistic = 0.121). These increases were also evident *in vitro* post-HFS with the CA1 and dentate regions (CA1: K-S test, $p<0.001$, D-statistic = 0.074; DG: K-S test, $p<0.001$, D-statistic = 0.141). Our results indicate marked similarities in the temporal regulation of NF-κB activity following both a learning event and an externally-administered HFS, suggesting that both stimuli may trigger common tightly regulated transcriptional programmes.

P2-33

THE SPATIO-TEMPORAL AND CELLULAR EXPRESSION PATTERN OF CD200 IN THE DEVELOPING AND ADULT C57/BL6 MICE BRAIN

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CD200, a cell surface glycoprotein elicits suppressive effects on myeloid cells including microglia by interacting with the CD200 receptor contributing to immune privileged status of the central nervous system. The immature brain exhibits distinct morphological and physiological characteristics determining a peculiar response to injury showing an aggravated susceptibility to excitotoxicity and pro-inflammatory cytokines along with an exacerbated inflammatory response. In these contexts the aim of the present study is to characterize the spatio-temporal and cellular expression of CD200 in the developing and adult mice brain by immunohistochemistry. Wild-type C57/BL6 mice postnatal day- 1,3,5,7,10,14,21 and adult were perfused intracardially under ketamine anaesthesia. Brains were removed, cryoprotected, frozen and cut into 30 μm sections. CD200 is highly expressed in gray matter regions including cerebral cortex, hippocampus and striatum where immunoreactivity appeared surrounding neurons in all age groups displaying an age dependent decrease in intensity through the early postnatal period to adult. Blood vessels labelled by Tomato lectin, expressed CD200 at all ages but were more pronounced in P21 and adult. A distinct CD200 labelling was observed in the hippocampal fissure (hf) along with the meninges in all ages with decreasing intensity from P1 to adult. Many oval to round meagrely ramified cells not stained by either NeuN or Iba1, but some of them labelled with GFAP were present all across the hf in postnatal groups but were much reduced or absent in adult mice. At P21 and adult, hippocampal CD200 was mainly found as a stronger labelling in the inner commissural-associational zone of the molecular layer than in the outer molecular layer of DG. Microglial cells were not found to be labelled with CD200. These data indicate that CD200 expression mediates immune regulation in neonates. Further study with CD200R will shed light on their role in the exacerbated inflammatory response in neonates.

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P2-34

CROSS MODAL TRAINING EFFECTS IN THE LEARNING OF NATURALNESS PERCEPTION

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The effect of learning and expertise has been observed in many visual perception studies, including texture [1], faces, and objects [2]. However, it is unclear whether improved performance following training is restricted to the trained modality, or whether this effect can transfer across to a non-trained modality. Additionally, the neural processes underlying learning within and across modalities remain unexplored. This study aimed to investigate the behavioural and functional cross-modal effects of training on the perception of textures as natural. Specifically, participants were trained on fabric stimuli and asked to categorise them as 'natural' (derived from nature) or 'not natural'. The stimuli consisted of a set of 32 fabric samples that systematically varied from natural (e.g. cotton) to not natural (e.g. acrylic), and which were either finely or coarsely weaved. The stimuli were divided for training (fine vs. coarse), such that participants were trained visually on one half and tactilely on the other. Visual categorisation performance on the full stimulus set and functional data were collected before and after an extensive training session. In this way, within (visual-visual) and across (tactile-visual) modality performance could be assessed.

Behaviourally, the within modality training condition produced a significant increase in categorisation accuracy after training. Further, visual performance benefitted from tactile training, thus behavioural cross-modal effects were observed. Preliminary functional analyses suggest differences in both sensory regions and multisensory regions. Our results indicate the influence of training on unimodal and cross-modal texture perception.

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P2-35

PRIMARY DEPRESSION AND INTERFERON-ALPHA INDUCED DEPRESSION: COMPARISON OF SYMPTOM PROFILES.

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Interferon-alpha (IFN-α) is currently the only FDA approved treatment for Hepatitis C. However treatment is often complicated by a number of physical, behavioural and psychological side effects, one of the most debilitating of which is that it can lead to depression in up to 50% of patients [1].

The aim was to compare the depression induced by IFN-α to a primary depression in order to see how similar or different the symptoms exhibited by the two patient groups are. Twenty-seven patients with HCV due to start treatment with IFN-α were recruited from the Hepatology Centre at St. James's Hospital, and administered a diagnostic interview and the 24 item HAM-D at baseline and week 8 of treatment. Those patients who developed depression were then compared to age, sex, and depression severity matched medically healthy depressed patients from St. Patrick's hospital. Results were analysed using matched and independent T-tests.

From week 0 to 8 of treatment there is a significant increase in depressive symptoms ($t(27), =-4.5, p<0.05$). Of the 27 patients currently tested 2 developed a major depressive disorder with melancholic features and 4 developed a mild depressive episode.

When compared to patients with a primary depression patients on IFN-α reported having significantly more somatic symptoms ($t(10)=4, p<0.01$) and significantly fewer psychic symptoms than depressed patients ($t(10)=-5, p<0.01$). Within each group, patients taking IFN-α have a significantly greater proportion of their symptoms explained by sickness than by psychic symptoms ($t(5)=5.2, p<0.01$). However, depressed patients show no difference in the proportion of psychic and somatic symptoms.

IFN-α does cause a change in mood, however, results from the current study indicate this is more a results of the side effects of treatment as somatic effects constitute of majority of the HAM-D profile.

This work was supported by a 4-year grant from the Health Research Board, Ireland.

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P2-36

$GABA_B$ RECEPTOR ACTIVATION DURING EARLY ADOLESCENCE AFFECTS ADULT ANXIETY BEHAVIOUR

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Vulnerability to anxiety disorders is believed to be influenced by the interaction between environmental and genetic factors at discreet periods during brain development. One such period, in rodents, is proposed to be early adolescence (P14 to P28), a pre-weaning period when the animal develops its repertoire of behavioural responses in preparation for adulthood.

A growing body of evidence indicates that the $GABA_B$ receptor plays a key role in modulating anxiety-related behaviour. Indeed, $GABA_B$ receptor positive modulators/agonists have anxiolytic effects when administered to adult mice in a host of behavioural tests. The role the $GABA_B$ receptors plays in th development of normal anxiety behaviour in this critical adolescent period is unclear. Thus we hypothesised that treating mice with a $GABA_B$ receptor agonist during early adolescence could also induce long term alterations in emotionality in adulthood.

BALB/c mice were treated with the selective $GABA_B$ receptor agonist, R-baclofen (2 mg/kg, s.c) or vehicle, (P14 to P28), and allowed to mature to adulthood. These mice were then tested (P62 onwards) in a battery of behavioural tests comprising; the stress induced hyperthermia (SIH) test, defensive marble burying (DMB), elevated-plus maze (EPM) and the forced swim test (FST). Results were analysed via T-test.

Postnatal R-baclofen treatment resulted in a trend towards an increased hyperthermic response to a stressor in the SIH test and increased anxiety-like behaviour in the EPM ($P<0.01$) but not in the DMB. In the FST, animals treated with R-baclofen during early adolescence trended towards a significant increase in immobility. Taken together, these data suggest that $GABA_B$ receptor-mediated signalling during postnatal development plays an important role in the establishment of adult anxiety levels. The molecular basis of this and its interactions with the 5-HT system remain to be unravelled.

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P2-37

AFFECTIVE STRESS IN DIFFERENT PERIODS OF BRAIN DEVELOPMENT INDUCES DISTINCT PATTERNS OF EXPLORATION OF A NEW OBJECT.

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The aim was to evaluate if chronic isolation in different periods of brain development affects the recognition memory and the exploration of a new object. Pups (n=12) remained with their mothers (6/mother) until weaning (PND21) when were allocated to: 1) grouped, housed 4/cage; 2) isolated, housed individually. Social isolation: Rats (140g; n=12) were allocated in the same conditions. Behavioral tests began after ten weeks. Maternal separation (MS): Pups were either separated from their mothers for 180min (MS180) or left undisturbed (n=11) from PND1-21 when were housed 4/cage for 5 weeks before testing. On the first day rats were submitted to a habituation session (5min). After 24h rats were given 5-min training trial exposed to two identical objects (A1/A2). On the short-term memory (STM), 90 min after training, rats were allowed to explore a familiar object (A) and a different one (B). On the long-term memory (LTM), 24h after training, the object A and a third different one (C) were used. Exploration: Time exploring both objects. Recognition index: $T_B/(T_A+T_B)$ or $T_C/(T_A+T_C)$. Student *t*-tests ($p<0.05$).

No change in the index of recognition was induced by any condition of isolation in the sessions. However, isolation from weaning induced a significant decrease (36%, p=0.001) in the total exploration of the objects on LTM while MS induced a significant increase (33%, p=0.01). Isolation of adult rats induced no alteration in this behavior.

Isolation reared rats do not remain motivated in the exploration of objects, according to emotional features of schizophrenia. In contrast, the neuronal plasticity seems to reverse the possible effects of the MS in this behavior.

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P2-38

SOCIAL ISOLATION OF YOUNG ADULT RATS INDUCES AN INCREASE IN THE EXPRESSION OF AMPA GLUTAMATE RECEPTORS IN HIPPOCAMPUS.

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Studies using postmorten human brains with depression and animal models have shown that glutamate is involved in this disorder. The social isolation is a chronic affective stress largely used as experimental model of depression. The aim of this study was to investigate the changes in GluR1 and GluR2 expression induced by social isolation of young adult rats in the hippocampal formation.

Male Wistar rats (140g) were allocated randomly to one of two conditions (n=6/each): 1) grouped, housed 4/cage and handled 3 times/week; 2) isolated, housed individually and handled once/week. After 10 weeks all animals were deeply anaesthetized (50ml/kg of Urethane 25%), perfused and their brains removed. 40-μm sections were used for immunohistochemistry. The immunopositive cells (IC) were counted bilaterally, in 3 sections/rat, in hippocampus, amygdala and entorhinal cortex. Student *t*-test ($p<0.05$).

Social isolation induced a significant increase in GluR1- IC in CA3 (90%, $p=0.004$) and CA1 (270%, $p=0.001$) of the hippocampus. However, no change was found in the hillus of dentate gyrus ($p>0.05$). In contrast to hippocampus, a significant decrease in GluR1- IC was induced by isolation in lateral (18.3%, $p=0.015$) but not in basolateral amygdala. No alterations were found in both GluR1 and GluR2 in entorhinal cortex. No change in GluR2 was also found in the hillus of hippocampus. GluR2 was not detected in CA3 and CA1 and in the lateral and basolateral amygdala.

Social isolation of adult rats induces an increase in GluR1 expression in hippocampus suggesting that glutamatergic neurotransmission through this receptor may be involved on the brain mechanisms altered in psychiatric disorders like depression.

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P2-39

ISOLATION REARING INDUCES A DECREASE IN THE EXPRESSION OF AMPA GLUTAMATE RECEPTORS IN HIPPOCAMPAL FORMATION IN RATS.

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Reduced glutamatergic signaling may contribute to cognitive dysfunction in schizophrenia. Isolation rearing of rats from weaning has been used as experimental model of schizophrenia. This study aimed at evaluating the changes in GluR1 and GluR2 expression induced by isolation rearing in the hippocampal formation of rats.

In two groups of Wistar rats (n=6/each) the pups remained with their mothers (6/mother) until weaning (21 days) when they were allocated randomly to one of two conditions: 1) grouped, housed 3/cage and handled 3 times/week; 2) isolated, housed individually and handled once/week. After 10 weeks all animals were deeply anaesthetized (50ml/kg of Urethane 25%), perfused and their brains removed. 40-μm sections were used for immunohistochemistry. The immunopositive cells (IC) were counted bilaterally, in 3 sections/rat, in hippocampus, amygdala and entorhinal cortex. Student *t*-test ($p<0.05$).

Isolation rearing induced a significant decrease in GluR1- and GluR2- IC in hippocampus. For GluR1 the reduction was 31% in the hillus ($p=0.02$) and 47% in CA3 ($p=0.002$) while for GluR2 the reduction was 57% only in the hillus ($p=0.001$). IC were not seen in CA3 for GluR2 or in CA1 and CA2 for either GluR1 or 2 in grouped and isolated rats. It was found an almost significant decrease (18,5%) in GluR1 in basolateral ($p=0,066$) but not in lateral ($p=0.898$) amygdala in isolated rats. In contrast, GluR2 were not detected in any nucleus of the amygdala. No change was found in entorhinal cortex.

Isolation rearing from weaning induces alterations in AMPA glutamate receptors in hippocampus and amygdala similar to those reported for human brains with schizophrenia.

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P2-40

CHRONIC INGESTION OF ETHANOL INDUCES A DECREASE IN THE EXPRESSION OF GLUR1 SUBUNIT IN HIPPOCAMPUS OF RATS.

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Long-term alcohol abuse produces serious, harmful effects on a variety of the body's organ systems leading to cognitive, behavioral, motor and neural deficits. Glutamate is involved in both physiological functions and pathological processes of the brain through distinct receptors. Evidence show that AMPA GluR1 subunit plays a role in mediation of synaptic plasticity and cognition impairment. The aim of this work was to investigate the changes induced by chronic ingestion of ethanol on the expression of glutamate AMPA receptors in rat hippocampus.

Male Wistar Rats (150g, n=8-12) were treated with water (control) or 5%-20% of ethanol, increasing 5% per week (habituation), and 20% maintained for 15, 60 or 90 days (chronic ingestion). After each time all animals were deeply anaesthetized (50ml/kg of Urethane 25%), perfused and their brains removed. 40-μm sections were used for immunohistochemistry. The immunopositive cells were counted bilaterally, in 3 sections/rat, in hippocampus. Groups were compared by Student "*t*" test or Anova followed by Duncan test and the level of significance was $p<0.05$.

Chronic ingestion of ethanol for 90 days induced a significant decrease in the expression of GluR1 AMPA receptors in hippocampus compared to 15 days (21%) and 60 days (29%) of ingestion ($p=0.001$, Anova). However, no change was found when the ethanol groups were compared to control groups in each time, individually.

A decrease in the expression of GluR1 AMPA receptors contribute to the imbalance on glutamatergic neurotransmission in hippocampus induced by long-term ethanol ingestion.

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P2-41

IN VITRO EVALUATION OF RNAI-MEDIATED SUPPRESSION OF THYROTROPIN RELEASING HORMONE DEGRADING ECTOENZYME EXPRESSION.

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Thyrotropin releasing hormone degrading ectoenzyme (TRH-DE) (EC 3.4.19.6) is a neuropeptide-specific neuropeptidase that is responsible for the inactivation of the naturally-occurring neuroactive peptide thyrotropin releasing hormone (TRH). Central TRH actions are recognised to provide therapeutic benefit for a broad range of central nervous system (CNS) disorders; however, the bioavailability of TRH critically limits investigation into its CNS functions. Inhibition of TRH-DE activity offers an attractive means to prevent TRH degradation and thereby enhance the bioavailability of endogenous or exogenously administered TRH. Thus, inhibitors of TRH-DE have important applications as investigative and therapeutic agents. Inhibition of TRH-DE as a means of enhancing TRH signalling is attractive since, due to the remarkable specificity of TRH-DE for TRH, it should amplify TRH signals exclusively.

TRH-DE activity may be altered through TRH-DE protein inhibition or suppression of gene expression. The current study presents novel RNA interference (RNAi) based compounds that suppress TRH-DE and provide an innovative means to enhance TRH bioavailability, which may represent an alternative or complimentary tool to site-directed TRH-DE inhibitors (1). Notably, H&MsiRNA suppressed human TRH-DE expression in transiently transfected Cos7 cells by $63.3\pm18.1\%$ ($p<0.05$), mouse TRH-DE expression was suppressed by $45.5\pm18.7\%$ ($p<0.05$) and rat TRH-DE RNA suppressed by $64.9\pm1.9\%$ ($p<0.05$) relative to a control non-targeting siRNA. H&M&RsiRNA suppressed human TRH-DE expression by $61.8\pm16.1\%$ ($p<0.05$), mouse TRH-DE expression was suppressed by $62.7\pm1.2\%$ ($p<0.05$) and rat TRH-DE suppressed by $82.7\pm4.0\%$ ($p<0.05$), as evaluated by real time RT-PCR. Western blot analyses of Cos7 cells which were co-transfected with plasmid expressing the rat TRH-DE gene and various TRH-DE-targeting siRNAs were carried out using a rat TRH-DE-specific antibody.

A particular advantage offered by RNAi-mediated TRH-DE suppression is the opportunity to generate suppression agents that are tissue or cell specific, thereby modulating TRH-DE expression in cell types relevant to a variety of CNS disorders.

This research was supported by the Health Research Board of Ireland and Science Foundation Ireland.

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P2-42

CAFFEINE PROMOTES MDMA "ECSTASY"-INDUCED DOPAMINE RELEASE IN STRIATAL AND HYPOTHALAMIC TISSUE SLICES; A ROLE FOR ADENOSINE A_1 RECEPTORS

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Caffeine has been previously reported in our laboratory to promote lethality and profoundly exacerbate the hyperthermic, tachycardic and neurotoxic response to 3,4-methylenedioxymethamphetamine (MDMA "Ecstasy") in an animal model [McNamara et al., (2006) Neuropharmacology 50: 69-80]. To elucidate central mechanisms underlying this toxicity, we have reported that depletion of central catecholamines but not serotonin blocks MDMA-induced toxicity and its exacerbation by caffeine. As MDMA is a potent releaser of the catecholamine dopamine, and caffeine also influences dopamine release in the brain, the aim of this study was to determine the effect of caffeine on MDMA-induced dopamine release. We examined dopamine release in the striatum and hypothalamus, two key brain structures prominent in central dopaminergic transmission. The striatum and hypothalamus were dissected from brains obtained from adult male Sprague Dawley rats. Tissue slices (750μm) were pre-loaded with [^{3}H] dopamine (0,1μM) and superfused with MDMA (30-300μM) or caffeine using a Brandel tissue superfusion system. [^{3}H] dopamine release from tissue slices was quantified in superfusates using liquid scintillation spectroscopy. All data were analysed by ANOVA and differences between treatment groups were obtained where $P< 0.05$ (Student Newman Keuls test). MDMA (100 and 300μM) induced a dose dependent increase in dopamine release in striatal and hypothalamic tissue slices. Caffeine (100μM) provoked dopamine release in the striatum under similar conditions. When striatal tissue slices were superfused with a sub-active dose of MDMA (30μM) in combination with caffeine (100μM), caffeine significantly enhanced MDMA-induced dopamine release, provoking a greater response than that obtained following either caffeine or MDMA applications alone. These synergistic effects observed in the striatum were different to those obtained in hypothalamic slices as both caffeine (100μM) and MDMA (30μM) alone, or in combination, failed to influence dopamine release. Caffeine (100μM) however significantly attenuated MDMA (100μM)-induced dopamine release from hypothalamic tissue slices. As adenosine A_1 receptors play an important role in regulating dopamine release and caffeine is a non selective adenosine receptor antagonist, the role of adenosine A_1 receptor blockade was determined. DPCPX (1μM), a selective adenosine A_1 receptor antagonist, produced a similar effect to caffeine on MDMA-induced dopamine release from both striatal and hypothalamic slices. In conclusion, caffeine differentially regulates MDMA-induced dopamine release, potentiating or attenuating MDMA-induced dopamine release in the striatum and hypothalamus respectively and these effects are most likely mediated by adenosine A_1 receptor blockade. Dopamine release may play an important role in the potentially lethal interaction between caffeine and MDMA, but it is likely that different mechanisms are involved in different regions of dopamine circuitry. The involvement of post-synaptic mechanisms should also be investigated to clarify the mechanisms by which caffeine exacerbates MDMA-induced toxicity.

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P2-43

EXAMINATION OF NOCICEPTIVE BEHAVIOUR AND STRESS REACTIVITY IN SUSCEPTIBILITY GENE MUTANT MODELS OF SCHIZOPHRENIA: FOCUS ON COMT AND NEUREGULIN-1

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Numerous experimental studies have reported altered pain sensitivity in patients with schizophrenia; a recent review found that 16 of 19 studies reported a significant abnormality in pain or thermal perception in patients with schizophrenia [1]. In non-clinical samples, catechol-O-methyltransferase (COMT) Met158 low-activity allele carriers report higher subjective ratings of experimentally-induced pain; COMT is a primary inactivator of dopamine in the prefrontal cortex, and polymorphisms in the COMT gene have been associated with schizophrenia. COMT genotype has also been shown to modulate the psychosis- inducing effects of stress [2]. In the present study, we sought to elaborate a possible gene × environment interaction between selected schizophrenia risk genes and stress/pain sensitivity by comparing nociceptive behaviour and stress responsivity in two schizophrenia susceptibility gene mutant mouse models: the COMT knockout (KO) and heterozygous neuregulin-1 (NRG1) KO mouse. Nociceptive behaviour was measured using the hot plate and tail flick paradigms. Stress responsivity was examined using the light/dark emergence test. In the hot plate test, thermal pain sensitivity was decreased in NRG1 KO mice ($p < 0.05$), but unchanged in COMT mutants. Pain sensitivity, as measured in the tail flick test, was significantly increased in COMT KO mice relative to controls ($p< 0.05$), while NRG1 KO mice displayed significantly reduced sensitivity ($p< 0.05$) compared to the wild-type mice. Altered stress responsivity was also observed in both susceptibility gene mutants. It is suggested that susceptibility genes for schizophrenia can influence the consequences of environmental exposures. Given the inconsistency of evidence linking many susceptibility genes to schizophrenia, genetic risk status may interact with exposure to environmental adversities.

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P2-44

CANNABINOID CB_1 RECEPTOR EXPRESSION IS REDUCED FOLLOWING TERMINAL LESION OF THE NIGROSTRIATAL PATHWAY IN THE RAT

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The endocannabinoid system is emerging as a potential target for the treatment of movement disorders affecting the basal ganglia, such as Parkinson's disease (PD). The highest level of the CB_1 subtype of cannabinoid receptor in the brain is in the basal ganglia, particularly within the substantia nigra (SN). This experiment looked at changes in CB_1 receptor expression in two commonly-used rat models of PD, where the neurotoxin 6-hydroxydopamine is injected into either the axons or terminals of the nigrostriatal pathway.

Male Lister Hooded rats underwent stereotaxic injection of 6-hydroxydopamine into the medial forebrain bundle (MFB) (n=41) or the nigrostriatal terminals (n=16) under isofluorane gaseous anaesthesia (2-5% in oxygen). On days 1, 3, 7, 14 and 28 post-lesion, rats were sacrificed by terminal anaesthesia (50 mg/kg pentobarbital) and transcardially perfused with saline and 4% paraformaldehyde. The brains were processed for immunohistochemistry. Density of staining in the SN and striatum was quantified using Image J software.

Following MFB lesion there was a transient increase in CB_1 receptor expression in the substantia nigra *pars reticulata* (SN*pr*). Following the terminal lesion, there was a progressive decline in CB_1 receptor expression in the SN*pr* (Day 1= 99.7±7.9%; Day 3= 70.8±10.5%; Day 7= 64.5±2.3%; Day 14= 55.5±4.4%; Day 28= 51.6±15.7%, data expressed as a percentage of the intact side ± SEM). DARPP-32 immunohistochemistry carried out on striatal sections indicated that injection of 6-hydroxydopamine at the terminals resulted in decreased striatal volume over time (Day 1= 111.32±4.02; Day 3= 106.04±11.34; Day 7= 92.21±4.57; Day 14= 88.20±2.90; Day 28= 83.64±9.40, data expressed as a percentage of intact side ± SEM) which correlated significantly with decreased CB_1 receptor expression in the SN*pr* ($r=0.60$, $P<0.05$).

Expression of the CB_1 subtype of cannabinoid receptor is significantly downregulated in the nigrostriatal terminal lesion model of Parkinson's disease, apparently caused by non-specific damage by 6-hydroxydopamine of striatonigral neurons, on which CB_1 receptors are located pre-synaptically in the SN*pr*. The MFB hemi-parkinsonian model may be more suited to investigating drugs targeting the cannabinoid system in an effort to identify novel therapies for Parkinson's disease.

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P2-45

CHRONIC ARICEPT (DONEPEZIL) TREATMENT AMELIORATES AGE-RELATED DEFICITS IN A HIPPOCAMPAL-ASSOCIATED SPATIAL MEMORY TASK

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Aricept (ARI) has been approved by the Food and Drug Administration (FDA) for treatment of mild to moderate Alzheimer's disease (AD) since 1996. More recently in 2006, the FDA approved ARI as a treatment for severe AD and it has been proven to significantly improve cognitive function in patients suffering from dementia due to AD[1]. ARI acts via the inhibition of acetylcholinesterase (AchE), which consequently enhances cholinergic synaptic activity and transmission in the cortex. It is well established that reduced cholinergic transmission correlates with memory loss in Alzheimer's patients and cholinergic neurons are greatly diminished in the early stages of AD and this is concurrent with the onset of memory impairments.

Here, we examine acute and chronic ARI administration in an animal model of naturalistic senescence in the middle-aged (MA) rat (12-18 mo), in whom reliable behavioural, neurophysiological and neurochemical differences appear compared to young (YG) (3 mo). Treatment with ARI (3mg/kg/day, p.o.) lasted for 37 days and a spatial task involving a water plus maze (WPM) was carried out at three different time-points (Days 1, 14 and 37).

The task was sensitive to age group [F (1,318) =89.08, P<0.0001] with YG group outperforming MA. Within treatment group we found a substantial and sustained improvement in acquisition with MA-ARI rats compared to MA-CTL in session 2 [t=11.31, P<0.001] and 3 [t=28.03, P<0.05].

These data suggest ARI enhances acquisition of spatial reference learning tasks in MA animals. YG animals on the other hand had slight improvements only in the second session t=3.619, P<0.001]. MA-ARI performed no different to YG-ARI [P=0.4]. We conclude that ARI greatly influences behavioural acquisition in MA but not as much in YG animals. In conclusion, chronic ARI treatment rescues age-related deficits in a hippocampal-associated spatial task.

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P2-46

MODULATORY EFFECTS OF TNFα AND GLUTAMATE PRETREATMENT ON CALCIUM HOMEOSTASIS & GLUTAMATE-INDUCED CALCIUM INFLUX IN RAT ORGANOTYPIC HIPPOCAMPAL CULTURES.

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Glutamate-induced excitotoxicity contributes to neuronal damage during a cerebral ischemic event such as stroke. Physiological levels of glutamate and proinflammatory cytokines, such as TNFα, play a role in the regulation of synaptic plasticity within the hippocampus. Pathophysiological levels, which occur during stroke, cause dysregulation of these processes, enhancing vulnerability of these cells to the ischemic insult. However, previous studies have shown that a transient ischemic attack (TIA) within 72 h of a stroke may attenuate its clinical severity. We developed an *in vitro* TIA model using organotypic hippocampal cultures. Hippocampal slices (400 μm) were cultured from P7 male Wistar rats (humanely killed - decapitated) using a modified technique of Stoppini *et al*. (1991). After 6 days, cultures were exposed to glutamate (30 μM) or TNFα (5 ng/ml) for 30 min, then allowed 24 h recovery. As calcium is an established mediator of glutamate excitotoxicity, we investigated whether glutamate / TNFα preconditioning alters glutamate-induced calcium influx after the recovery period using Fluo-4. Basal calcium homeostasis was examined using ratiometric dye Indo-1. One way ANOVA with Bonferroni post-test was preformed for all data sets (μ±SEM). Indo-1 analysis showed a small but significant lowering of baseline calcium 24 h after pretreatment with TNFα / glutamate (glutamate; 81.7± 1.3, TNFα; 79.2±1.0 *Vs*. control; 100.0±1.4, $p<0.001$). These pretreatments also resulted in a significant reduction in glutamate-induced calcium influx (glutamate 37.4±0.8; TNFα; 51.8±2.9 *Vs*. control; 100.0±1.8, $p<0.001$). Co-application of TNFα with the mGluR5 antagonist, MPEP (10 μM), resulted in significant amplification of TNFα's preconditioning effect (TNFα & MPEP; 39.6±0.7, TNFα only; 51.8±2.9, $p<0.001$). Co-application of the NMDAR antagonist, D-AP5 (100 μM) did not significantly alter the glutamate preconditioning effect. We conclude that TNFα preconditioning may be a result of both TNFR and mGluR5 receptor activity, whereas NMDAR activation during preconditioning with glutamate may be less important.

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P2-47

ELUCIDATING THE CORTICAL CORRELATES OF THE PERCEPTION OF NATURALNESS

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The ability to readily discriminate between natural things and synthetic mimics in the environment is a skill which is not only important for the survival of many species but also has significant consumer value. This ability relies on the acuity of the different senses, the material characteristics of the stimuli, past knowledge and experience and the goal of the behaviour. In a large study, conducted as part of a science exhibition, we investigated the relative contribution of vision and touch to the categorization of a set of different fabric stimuli as natural. The stimuli were comprised of 42 fabric samples, which varied systematically from natural to synthetic. We also examined whether this categorization performance correlated with other judgments such as roughness, pleasantness, familiarity, softness, value and hedonics using a 7-point scale. We found that perceived naturalness was strongly correlated with value and hedonics. Specifically, natural stimuli were rated as more valuable and were liked more.

In a second experiment, we examined the brain activations associated with the perception of naturalness using a subset of these stimuli and cross-correlated these activations with ratings of value and hedonics. We found that whilst each modality contributes to the perception of naturalness independently, there are some brain areas activated for naturalness perception independent of modality. Although other correlates of naturalness differentially affected brain activations these differences were not generally observed in sensory cortices. These results have implications on our understanding of how the senses contribute to more higher-order decisions related to the perception of texture.

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P2-48

AGE RELATED CHANGES IN CIRCADIAN CLOCK GENE EXPRESSION IN THE MOUSE BRAIN.

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Circadian rhythms are generated by a network of transcriptional and translational loops in the expression of a panel of clock genes. Many of the output rhythms controlled by this system are significantly affected by ageing, although the mechanistic basis for this is not well understood. The master circadian clock in mammals is the suprachiasmatic nucleus (SCN), but it now understood that several other brain sites can function as slave or quasi-autonomous circadian oscillators. The aim of this study was to investigate the effect of ageing on the daily oscillation of clock gene protein products in the mouse brain.

Clock gene protein expression in the brain was measured by means of immunohistochemistry, in groups of young (3 months) and older (16 months) mice every 4 hours over a 24-hour cycle. We describe novel rhythmic expression of CLOCK and/or BMAL1 in young mouse brain, including the arcuate, paraventricular and dorsomedial nuclei of the hypothalamus, the hippocampus, the central and basolateral nuclei of the amygdala, the basolateral nucleus of the accessory olfactory tract, the lateral habenula and the paraventricular nucleus of the thalamus. Both CLCOK and BMAL1 showed constitutive expression in the suprachiasmatic nucleus.

ANOVA revealed a significant main effect of ageing for mean CLOCK ($F1,173 = 72$, $p< 0.001$), and BMAL1 ($F_{1,191} = 81.3$, $p<0.001$), with significant interactions between time and age for CLOCK ($F_{5,\ 173} = 13.76$, $p < 0.001$) and BMAL1 ($F_{5,\ 191} = 5.72$, $p < 0.001$), as well as significant interactions between age and region for CLOCK ($F15,\ 173=3.13$, $p<0.001$) and BMAL1 ($F_{15,191}=2.018$, $p<0.05$). Ageing altered the magnitude and acrophase of expression in the extra-SCN regions (as assessed by single cosinor method), with rhythmicity either being lost or phase-delayed. These results indicate hitherto unsuspected roles for CLOCK and BMAL1 in non-SCN brain circadian oscillators, and suggest that desynchrony of the brain circadian system may be a significant contributor to age-related circadian dysfunction.

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P2-49

STDP INDUCES MAINLY LTD IN RAT PREFRONTAL CORTEX AND LTP IN SOMATOSENSORY CORTEX

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The induction of long-term potentiation (LTP) and long-term depression (LTD) of just suprathreshold excitatory postsynaptic currents (EPSCs) was investigated in proximal synapses in rat somatosensory cortex (SSC) and prefrontal cortex (PFC), an area which has been largely neglected for studies of long-term plasticity. Synaptic plasticity was induced by spike timing dependent plasticity (STDP) protocol. Two STDP protocols were employed, either a single presynaptic action potential (AP) preceding 3 postsynaptic APs (50-100 Hz) by 10 ms, repeated 50 times at a frequency of 0.1 Hz, or 5 presynaptic APs preceeding 5 postsynaptic APs both at 50 Hz and presynaptic APs leading postsynaptic APs by 5 ms.

The main finding of the present study is that STDP protocols with a positive delay predominantly induced a postsynaptic LTP in SSC and presynaptically expressed LTD in PFC. LTD in PFC (74 ± 4% of test amplitude) was observed in the majority of experiments (13 out of 24) and was dependent on activation of NMDAR and endocannabinoids. The NMDAR blocker AP5 completely prevented synaptic plasticity in most cells, while application of AM251, a selective CB1 receptor antagonist, strongly inhibited the induction of LTD by the STDP and led to the induction of presynaptic NO-dependent LTP in 5 of 8 cells (134 ± 4% of test). LTP in PFC was observed in 5 out of 6 pyramidal cells and was NMDAR dependent.

It is proposed that a likely reason for the predominate induction of anti-Hebbian presynaptic LTD in PFC is a low NMDAR activation. In agreement with this, I-V curve of isolated NMDAR currents in PFC is shallower in the region between -20 and -60 mV than in SSC.

Differential effects of STDP protocol on plasticity in PFC and SSC may reflect the difference in mechanisms of information processing in these cortical regions.

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