Welcome to Early Career Neuroscientists’ Day 2015

The members of the ECND 2015 Steering Committee would like to take this opportunity to welcome you to an exciting, challenging and informative day of talks, posters and sessions on the various aspects of neuroscience in all its guises.

The last such event (which ran under the title of Young Neuroscientists’ Day) took place in 2010 and was a joint venture between the Universities of Cardiff and Bristol. This year we are delighted to be running under the GW4 banner and as such the Committee has benefitted from the combined efforts of members from all four institutions: Bath, Bristol, Cardiff and Exeter. We are grateful to GW4 for their support in hosting the event’s website and providing prizes.

Organisation for ECND 2015 began back in November 2014 when we were scoping out potential venues and has culminated in a fantastic programme with plenaries from Professors Adrian Harwood and Anne Rosser; contributions from invited speakers in Scientific Techniques, Alternative Careers, Public Engagement and Academic Careers; oral presentation from Early Career Researchers from across GW4; a host of fascinating posters on a wealth of subjects; and lots of time to network and engage. We are confident that the outcome will be satisfying and useful. Take advantage of the various sessions and activities - speak to people, share and discuss your research, get the insider view on how to make the best of your PhD and a career in neuroscience. There are 100 + delegates present in At-Bristol, do make full use of their knowledge and expertise.

Today would not have been possible without the generous support of our many sponsors (see listings and ads in this booklet), some of whom are exhibiting today. At the back of this booklet you will find a stamp page- we would encourage you to visit every exhibitor, see and hear about what they have to offer. As an added incentive, each stall will stamp the appropriate block on the page. Completed pages should be submitted in the clearly labelled box by 16:00 for a chance to win a prize-draw at the end of the day.

Thank you for coming. We very much look forward to meeting you, and hope to do so again in the world of neuroscience in the years ahead.

The ENCD 2015 Steering Committee
The Early Career Neuroscientists’ Day Steering Committee

Catherine Brown          Bristol
Vanessa Davies           Cardiff
Julia Heckenast          Cardiff
Stefan Hirschberg        Bristol
Clara Humpston           Cardiff
Jo Palandri              Bath
Hazel Phillips           Bristol
Tom Phillips             Bristol
Emma Robson              Bath
Hannah Smithers          Exeter
Lydia Staniaszek         Exeter
Michelle Taylor          Bristol

The Early Career Neuroscientists’ Day Scientific Committee

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Vanessa Davies            Cardiff
Rachel Harris             Bristol
Clara Humpston            Cardiff
Kira Rienecker            Cardiff
Hannah Smithers           Exeter
Lydia Staniaszek          Exeter
PROGRAMME

08.45 – 09.30  Registration and poster set up

09.30 – 10.30  Opening Address:
Professor Neil Scolding (Director of Bristol Neuroscience)

Plenary talk:
Professor Adrian Harwood (Technical Director of the Neuroscience and Mental Health Research Institute, Cardiff University)
Team science and the pursuit of interdisciplinary neuroscience

10.30 – 11.30  Poster Session A – with coffee

11.30 – 12.30  Talks by GW4 collaborators & British Association for Psychopharmacology
Chair: Dr Vanessa Davies

11.30-11.50  Dr Matt Jones (University of Bristol)
Circuit psychiatry Severnside-style

11.50-12.10  Dr Anthony Isles (Cardiff University)
The GW4 Epigenetics consortium; relevance to neuroscience

12.10-12.30  Professor Jo Neill, President-Elect British Association for Psychopharmacology (University of Manchester)
The British Association for Psychopharmacology: Why you should join

12.30-13.15  Lunch

13.15-14.45  Parallel Breakout sessions (1)

Breakout 1: Scientific Techniques
Chair: Aurelien Bunga (Cardiff University)

13.15-13.30  Dr Tom Lancaster (Cardiff University)
Magnetic resonance imaging 1: Brain macrostructure and the BOLD response
13.30-13.45  Dr Mark Drakesmith (Cardiff University)
*Techniques for structural brain imaging*

13.45-14.00  Dr Jonathan Witton (University of Bristol)
*Using electrophysiology to understand neuronal network function in health and disease*

14.00-14.15  Dr Gurpreet Balrey (Sigma-Aldrich)
*CRISPR*

14.15-14.30  Matt Devall (University of Exeter)
*Making the most of it: New insights into mitochondrial methylation from publically aware data*

**Breakout 2: Alternative Careers**
*Chair: Dr Vanessa Davies (Cardiff University)*

13.15-13.35  Dr Nick Jenkins (Tertiary Manager, Eppendorf UK Ltd)
*Give sales a chance*

13.35-13.55  Dr Hazel Phillips (Research Development Manager, University of Bristol)
*Academia and beyond*

13.55-14.15  Dr Jason Li (CEO, Proteintech)
*Benchside to Businessman*

14.15-14.35  Dr Poppy Mulvaney (Prime Decision)
*Behavioural insights: Utilising research skills in the commercial world*

**Breakout 3: Cellular Neuroscience short talks**
*Chair: Rachel Harris (University of Bristol)*

13.15-13.30  Haiyan An (MSc, Cardiff University)
*Modelling of cellular pathology caused by ALS-associated mutations in FUS gene by targeted genome modifications in cultured human cells*

13.30-13.45  Emily Clark (PhD, Cardiff University)
*Lysosomal involvement in the pathogenesis of Huntington’s disease*
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<th>Time</th>
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<tr>
<td>13.45-14.00</td>
<td>Dr Pamela Sarkar (Clinical Research Fellow, University of Bristol)</td>
<td>Neuroglial protective effects of multipotent mesenchymal stromal cells derived from patients with multiple sclerosis</td>
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<tr>
<td>14.00-14.15</td>
<td>Julia Vlachaki Walker (MPhil, University of Exeter)</td>
<td>The role of AMP-activated protein kinase in astrocytes in response to hypoglycaemia</td>
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<td>14.15-14.30</td>
<td>Cezar Tigaret (Research Associate, University of Bristol)</td>
<td>Hebbian Spike Timing-Dependent Plasticity at mature hippocampal Schaffer collateral synapses requires co-ordinated activation of distinct Ca²⁺ sources and metabotropic glutamate receptors</td>
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<td>14.30-14.45</td>
<td>Katy Barwick (PhD, University of Exeter)</td>
<td>Varied neurological phenotypes and modes of inheritance associated with mutation of the essential choline transporter</td>
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**Breakout 4: Cognitive Neuroscience short talks**  
*Chair: Clara Humpston (Cardiff University)*

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<td>Michael Dalili (PhD, University of Bristol)</td>
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<td>13.30-13.45</td>
<td>Clara Humpston (PhD, Cardiff University)</td>
<td>Dimensions of schizotypy in relation to different types of predictive processing and source-monitoring</td>
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<td>Nick Clifton (PhD, Cardiff University)</td>
<td>The enrichment of extinction-related genes in schizophrenia copy number variants</td>
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<td>14.00-14.15</td>
<td>Bethany Coad (PhD, Cardiff University)</td>
<td>Emotional connections need structural connections: interindividual variation in uncinate fasciculus microstructure is related to facial emotion processing</td>
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<td>14.15-14.30</td>
<td>Bonni Crawford (PhD, Cardiff University)</td>
<td>Expectancies of social pain and pleasure are reflected in brain structure</td>
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<td><strong>Parallel Breakout Sessions (2)</strong></td>
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**Breakout 1: Public Engagement**
*Chair: Rachel Harris (University of Bristol)*

15.45-16.15 John Meredith (Understanding Animal Research)  
*The “A” word: Speaking up about animal research*

16.15-16.45 Ellie Cripps (Graphic Science)  
*Outreach in Schools: STEM Ambassadors*

**Breakout 2: Academic Career**
*Chair: Dr Lydia Staniaszek (University of Exeter)*

15.45-16.05 Dr Nichola Brydges (Research Fellow, Cardiff University)  
*An academic career: From Undergraduate to Research Fellow*

16.05-16.25 Dr Talitha Kerrigan (Research Fellow and Associate Lecturer, University of Exeter)  
*Perspectives of a Post-doc*

16.25-16.45 Dr Jacqui Oakley (Programme Manager, MRC)  
*MRC funding and top tips for successful applications*

**Breakout 3: Behavioural Neuroscience**
*Chair: Hannah Smithers (University of Exeter)*

15.45-16.00 Stefan Hirschberg (PhD, University of Bristol)  
*A viral approach for chemogenetic activation of noradrenergic neurons in health and disease*

16.00-16.15 Emma Yhnell (PhD, Cardiff University)  
*Using cognitive training as a therapeutic intervention in a knock-in mouse model of Huntington’s disease*

16.15-16.30 Gráinne McNamara (Research Associate, Cardiff University)  
*A role for increased dosage of the imprinted Cdkn1c gene in linking early life adversity and later life behavioural disorders*

16.30-16.45 Charles Evans (PhD, Cardiff University)  
*Evaluating 2B3, a novel immunotherapy, in a preclinical model of amyloid pathology*
Breakout 4: Developmental Neuroscience
Chair: Kira Rienecker (Cardiff University)

15.45-16.00 Hayley Moulding (PhD, Cardiff University)
Sleep problems in children and adolescents with 22q11.2 deletion syndrome

16.00-16.15 Stavros Dimitriadis (Research Associate, Cardiff University)
Gender and age differences of intra-frequency and phase-to-amplitude coupling (PAC) based on EEG resting-state networks

16.15-16.30 Adam Cunningham (PhD, Cardiff University)
Developmental co-ordination disorder, psychopathology and cognition in 22q11.2 deletion syndrome

16.30-16.45 Vafa Alakbarzade (PhD, University College London)
A partially inactivating mutation in the sodium-dependent lysophosphatidylcholine transporter MFSD2A causes a non-lethal microcephaly syndrome

17.00–17.45 Plenary talk:
Professor Anne Rosser (Professor of Clinical Neuroscience and Honorary Consultant Neurologist at the University Hospital of Wales, Cardiff)

17.45–18.00 Prizes and Round-Up
Prof Nishan Canagarajah (Pro Vice-Chancellor for Research, University of Bristol)

18.00–20.00 Drinks and basket food Reception
Useful Information

Committee members - We are here to help!

Volunteers and committee members will be available throughout the day if you have any questions – we will do our very best to answer them. Many will have backgrounds in neuroscience so, as well as practicalities for the day (like how to get to the train station), we welcome questions and conversation about starting out in neuroscience (and if you catch someone without the appropriate knowledge, we can point out the people who do!).

You will be able to recognise volunteers and committee members by their yellow name badges. There will also be manned welcome desk throughout the day.

Poster sessions

Posters are arranged alphabetically according to presenting author, with each poster allocated a board number. Lists of numbers and authors can be found further on in this booklet. The full list of poster abstracts, also listed alphabetically, can be downloaded from the ECND website, http://gw4.ac.uk/all-events/gw4-early-career-neuroscientist-day/.

There are two poster sessions, one in the morning between 10:30-11:30, and one in the afternoon between 14:45-15:45. **Presenters must attend their poster for at least half the duration of their session.** Remember there are prizes to be won!!

Please ensure you put your poster up **BEFORE 9:30** if you are presenting during the morning session; poster boards will be rotated during the lunch break. Afternoon presenters please put your poster up **BEFORE 13:00**. You **MUST TAKE YOUR POSTER AWAY** with you at the end of the day (or you will be charged a clearance fee and the poster will be disposed of).

Further comments or questions
We would be delighted to receive your comments and feedback on the day- please email b-n@bristol.ac.uk. You should also email with any queries following the event.

The Venue

At-Bristol, Anchor Road, Harbourside, Bristol, BS1 5DB

Travel

**Bike:** At-Bristol is located close to the National Cycle Network; there is ample cycle parking and a permanent bike pump (for both types of tyre valve) just outside the main entrance

**Train:** Bristol Temple Meads is 20-min walk, 5-min taxi, 17-min ferry, 10-min bus

**Bus:** First Bus number 8 or 9 to College Green from Bristol Temple Meads station. Most buses stop in the city centre; from there it is a 7-min walk
**Ferry:** Bristol Ferry Boat Company and Number Seven Boat Trips run timetabled ferries. The closest stops are City Centre and Cannons Marsh

**Park and Ride:** Secure parking at Brislington (A4) or Long Ashton (A370) then a bus ride to the city centre

**Road:** Sat Nav Reference: BS1 5LL. Millennium Square underground car park is adjacent; this is open 24 hrs/day with on-site security
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**Biography: Professor Adrian Harwood** PhD FSB
Technical Director of the Neuroscience and Mental Health Research Institute, Cardiff University

Prof Harwood is co-founder of the Cardiff University's Neuroscience and Mental Health Research Institute (NMHRI). He is a cell biologist with extensive experience in molecular signalling systems and cell analysis in neuronal and model cell systems. His current work focuses on the molecular and cellular interactions that underlie genetic risk for psychiatric conditions and epilepsy. As a world leader in the emerging field of cellular psychopharmacology, he is also studying the interaction of psychotropic drugs in the cellular context. His investigations into phospho-inositide signalling and the protein kinase GSK-3 function, the two major lithium targets, resulted in the recent discovery that lithium suppresses PIP3 signalling.

**Biography: Professor Anne Rosser**
Professor of Clinical Neuroscience and Honorary Consultant Neurologist, University Hospital of Wales

Professor Anne Rosser is joint Director of the Brain Repair Group at the University Hospital of Wales, Cardiff. Anne leads the South Wales Huntington's disease clinical service and chairs the UK HD Network, the English-speaking sector of the European HD Network and the EHDN Scientific and Bioethical Advisory Committee. Her research is focused on cell replacement therapies and the potential of stem cells for neural transplantation. She is joint co-ordinator of a UK pilot trial of neural transplantation in HD.
Modelling of Cellular Pathology Caused by ALS-associated Mutations in FUS Gene by Targeted Genome Modifications in Cultured Human Cells

An H, Dimasi P, Shelkovnikova T, Buchman V

**Background:** Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease selectively affecting motor neurons in the central nervous system. About 10% of ALS cases are familial (fALS), and around 5% of them carry mutations in Fused in Sarcoma (FUS) gene. In cultured cells with over-expressed FUS variants lacking Nuclear Localization Signal (NLS), they mislocalize and accumulate in the cytoplasm. When cells are under stress, cytoplasmic FUS enters stress granules which are thought to protect the protein from irreversible aggregation. However, over-expressed FUS with compromised RNA binding capacity escapes this protective mechanism and forms pathological cytoplasmic aggregates. Our study aimed to introduce specific deletions into the FUS gene that will result in production of endogenous FUS protein with different C-terminal modifications, in human neuroblastoma SH-SY5Y cells, using CRISPR/Cas9 system.

**Methods:** Two guide RNAs (gRNAs) targeting both ends of the FUS gene regions to be deleted were cloned into pX330 vector. Plasmids encoding upstream and downstream gRNAs as well as Cas9 enzyme were delivered into SH-SY5Y cells through lipofection. Editing specificity of CRISPR/Cas9 system and the phenotype of transfected cells were characterized in these transiently transfected cells. Single cell-derived clones were obtained and the clones with desired deletions were identified by PCR, expanded and characterised.

**Results:** Stable SH-SY5Y cell lines that produce physiological levels of FUS protein lacking NLS as well as a cell line in which the FUS gene is completely inactivated, have been established. In these, FUS protein lacking NLS, in contrast to normal FUS, becomes redistributed to the cytoplasm and forms stress granules under stress. In some of the lines established, mislocalized FUS spontaneously forms cytoplasmic RNA granules distinct from stress granules.

**Conclusion:** Cellular models of ALS-FUS with physiological levels of FUS protein have been successfully generated. In these cell lines, mislocalized FUS protein is prone to forming cytoplasmic RNA granules.

**References:**


Keywords: Amyotrophic Lateral Sclerosis (ALS); FUS/TLS gene (Fused in Sarcoma); Cellular model; CRISPR/Cas9; Stress granule
Lysosomal involvement in the pathogenesis of Huntington’s disease


**Background:** Huntington’s disease (HD) is a fatal inherited neurodegenerative disorder caused by expansion of a polyglutamine tract in the huntingtin protein, and characterised clinically by motor, cognitive and psychiatric deficits. The cellular pathology, and the mechanisms by which polyglutamine expansion in huntingtin leads to disease, are complex and poorly understood. We have identified a defect in trafficking and function of the lysosomal transmembrane protein NPC1 in HD. This protein plays a role in endocytic lipid trafficking and Ca2+ homeostasis, and mutations in this protein lead to Niemann-Pick type C disease (NPC), a rare and fatal neurodegenerative disease characterised by lysosomal storage of lipids.

**Results:** Mislocalisation of NPC1 and a deficit in lysosomal function are observed in HD, potentially due to a direct interaction between NPC1 and huntingtin. The existence of this protein defect in HD is supported by the presence of lysosomal dysfunction matching that seen in NPC. Storage of characteristic lipids including cholesterol and sphingolipids, lysosomal Ca2+ signalling defects, and a block in endocytic trafficking and autophagic vacuole clearance are present in multiple models of HD. One licensed disease-modifying therapy is currently available for NPC, the glycosphingolipid-biosynthesis inhibitor miglustat. This drug partially restores lysosomal Ca2+ signalling and endocytic trafficking and slows clinical progression in NPC. Treatment of Huntington’s disease cellular models, including patient iPSC-derived neurons, with miglustat reduced lysosomal defects, improved cellular trafficking, and was protective against excitotoxic cell death.

**Conclusion:** This novel finding contributes to understanding of HD pathogenesis, and may help to unravel the mixed reports of altered lipid homeostasis in HD. Correct lysosomal function is vital to the cell, and the defects we have observed may explain some of the known problems in HD, for example in cellular trafficking and Ca2+ homeostasis. Our work has also highlighted an approved small molecule as a novel therapeutic strategy for HD.

**References:**
Lloyd-Evans E, et al. (2008). Niemann-Pick disease type C1 is a sphingosine storage disease that causes deregulation of lysosomal calcium. *Nat Med* 14: 1247-1255


The HD iPSC Consortium (2012). Induced Pluripotent Stem Cells from Patients with Huntington’s Disease Show CAG-Repeat-Expansion-Associated Phenotypes. *Cell Stem Cell* 11: 264-278

Castiglioni V, et al. (2012). Induced pluripotent stem cell lines from Huntington's disease mice undergo neuronal differentiation while showing alterations in the lysosomal pathway. *Neurobiology of Disease* 46: 30-40

**Keywords:** Huntingtin; NPC1; Lipid; Lysosome
Neuroglial protective effects of multipotent mesenchymal stromal cells derived from patients with multiple sclerosis

Sarkar P, Redondo J, Wilkins A, Scolding NJ and Rice CM

**Background:** Multiple sclerosis (MS) is the commonest cause of non-traumatic disability in the UK; over 80% of patients develop progressive disease for which there is no proven treatment. The potential of multipotent mesenchymal stromal cells (MSCs) for repair in MS has been extensively examined in vitro. Clinical trials are now in progress (Rice, Kemp et al. 2013). We, and others, have demonstrated (Wilkins, Kemp et al. 2009, Kemp, Hares et al. 2010, Redondo, Hares et al. 2015) and that MSCs have similar baseline characteristics irrespective of whether they are derived from the bone marrow of normal controls or patients with MS (Mallam, Kemp et al. 2010, de Oliveira, de Lima et al. 2015). However, the capacity of these cells for neuroglial protection in vitro has not been examined.

**Methods:** MSCs were isolated from the bone marrow of participants in the ongoing clinical trial ‘Assessment of bone marrow-derived Cellular Therapy in progressive Multiple Sclerosis (ACTiMuS; NCT01815632)’. Using in vitro models of neuroglial toxicity, we have compared the protective properties of MSC-conditioned medium derived from cultures isolated from patients with MS and from normal controls.

**Results:** The neuroglial protective effects of MSC conditioned medium decline with expansion in vitro. In addition, MSC conditioned medium has differential protective effects depending on whether MSCs are derived from MS patients or control subjects. This effect is most pronounced in models of neurotoxicity. It cannot be fully accounted for by variables such as age but negatively correlates with duration of disease progression.

**Conclusions:** These findings have important implication for those developing cellular therapy as a treatment for MS. They suggest that the reparative capacity of MSCs to protect neurons and glia is affected by expansion ex vivo and with duration of progressive disease. Future work will employ proteomic techniques to explore the mechanisms underlying our observations.

**References:**


Keywords: Multiple sclerosis; Mesenchymal stromal cells; Neuroprotection; Glial protection; Cellular therapies
The role of AMP-activated protein kinase in astrocytes in response to hypoglycemia

Vlachaki Walker J, Ashford MLJ, McCrimmon RJ, Beall C

Background: Hypoglycaemia remains a serious side-effect of intensive insulin treatment in patients with diabetes. Following recurrent hypoglycaemic episodes, patients may develop a defective counter-regulatory response (CRR) to hypoglycaemia. One enzyme postulated to be involved in the CRR is AMP-activated protein kinase (AMPK). This enzyme plays an important role in glucosensing neurones in the hypothalamus, but its significance in astrocytes has not been studied.

Methods: Human U373MG astrocytoma cells, neonatal mouse primary cortical and hypothalamic astrocytes were used. Cells were serum-starved for two hours before treatment with normal (2.5mM) or low (0.1mM) glucose DMEM for 30 mins then lysates and media were collected for analysis. Cells were also treated with 100 uM A769662 in 2.5 mM glucose DMEM for 30 mins or 2.5 mM or 0.1mM glucose ± 50 uM noradrenaline for 15 mins, or with 50 uM noradrenaline ± 50uM A769662 for 30 mins in 2.5mM glucose.

Results: Low glucose increased AMPK phosphorylation, accompanied by an increase in extracellular ATP. Reducing glucose availability led to a ~50-60% reduction in lactate release, despite a 25 fold reduction in glucose availability. AMPK activation using A769662 resulted in increased AMPK phosphorylation, ATP release and lactate release. A769662-induced ATP release was attenuated by Compound C pre-treatment. Noradrenaline increased lactate release at both euglycaemic and hypoglycaemic glucose levels. Co-application of A769662 and noradrenaline had an additive effect on lactate release.

Conclusion: These data indicate that low glucose increases AMPK phosphorylation and ATP release which is replicated by direct AMPK activation and can be attenuated by Compound C pretreatment, indicating ATP release is AMPK-mediated. Low glucose may result in enhanced glycogenolysis, indicated by increased lactate release per mole of glucose available, which is further enhanced by noradrenaline treatment. A769662 and noradrenaline produced an additive effect on lactate release, indicating that these drugs may be acting through distinctive pathways.

References:
Keywords: Astrocytes; Hypothalamus; Purinergic system; Hypoglycaemia; AMPK
Induction of spike timing-dependent plasticity (STDP) at mature Schaffer collateral (S/C) synapses onto CA1 hippocampal pyramidal neurons requires synaptic input time-correlated with postsynaptic spikes to generate postsynaptic NMDA receptor (NMDARs) – dependent Ca2+ transients (EPSCaTs) in dendritic spines. The Ca2+ hypothesis for synaptic plasticity proposes that the size of spine EPSCaTs determines the magnitude and direction of synaptic plasticity, and predicts that the strongest spine Ca2+ signals are evoked by stimuli that induce spike timing-dependent long-term potentiation (STD-LTP) as opposed to stimuli that induce long-term depression (STD-LTD). However, this prediction has not been directly tested in the mature hippocampus. We evaluated the rules for NMDAR-dependent STDP induction at S/C – CA1 synapses in acute hippocampal slices from adult rats, by pairing pre-synaptic stimuli in stratum radiatum with somatically-evoked postsynaptic spikes. Using two-photon Ca2+ fluorescence imaging we show that the amplitude of EPSCaTs induced by STDP stimuli does not match the observed plasticity induction rule. Recordings were performed in whole-cell current clamp, at 36°C, under GABAA receptor inhibition (50 µM picrotoxin). In contrast, induction of NMDA receptor-dependent LTP by time-correlated pre- and post-synaptic spikes requires the sequential activation of NMDARs followed by voltage-sensitive Ca2+ channels within dendritic spines. Furthermore LTP requires mGlu1-dependent inhibition of SK channels to promote NMDAR activation. We conclude that induction of LTP by time-correlated pre- and post-synaptic activity requires the activation of distinct sources of Ca2+ and the recruitment of an mGluR1-dependent inhibition of a negative feedback loop that targets the activation of NMDARs.

**Keywords:** Synaptic plasticity; Two-photon imaging; Hippocampus
Varied neurological phenotypes and modes of inheritance associated with mutation of the essential choline transporter


Background: The neuromuscular junction (NMJ) is a specialised synapse with a complex molecular architecture that provides for reliable transmission between the nerve terminal and muscle fibre. Previously, we identified a mutation in SLC5A7, encoding the presynaptic choline transporter (CHT) critical for normal NMJ signalling, as the cause of a dominantly inherited motor neurone disease (dHMN-VII). We established that the mutation responsible resulted in the dominant-negative interference with the wild type choline transporter resulting in significantly reduced, although not completely abolished, transporter activity. Here, as well as confirming that truncating C-terminal mutation underlies autosomal dominant motor neuropathy in other individuals with this presentation, we also show that N-terminal missense mutation of SLC5A7 underlies autosomal recessive severe neurological disease.

Methods: We used whole genome SNP genotyping to undertake gene mapping in autosomal recessive families assuming that a founder mutation was responsible, and whole exome as well as dideoxy sequencing to identify and confirm the causative mutation. Transporter assays in HEK-293T cells transiently transfected with SLC5A7cDNAs containing each of the four mutations were also undertaken to evaluate the outcome of gene mutation on CHT function.

Results: We have identified a second family with phenotypic overlap with dHMN-VII caused by a distinct mutation resulting in heterozygous elimination of the SLC5A7 C-terminus. We have also identified two families in which missense mutations nearer the N-terminal of SLC5A7 which likely lead to a further reduction in choline uptake activity compared to the truncating mutations, resulting in a severe congenital neuromuscular phenotype.

Conclusion: Our findings lead us to hypothesise that dominant-negative mutation arising from heterozygous SLC5A7 C-terminal mutations lead to greatly reduced although not completely abolished CHT function and AD motor neurone phenotypes, while N-terminal missense loss of function mutations alterations result in AR severe congenital neuropathy. These studies provide further important insight into the role of aberrant choline transporter function in neurological disease.

References:
Keywords: Distal hereditary motor neuropathy; Severe congenital neuropathy; High affinity choline transporter; Cholinergic signalling; Neuromuscular junction
Emotion Recognition Training Increases Neural Response to Happy Faces in Individuals with High Levels of Depressive Symptoms


Background: Emotion recognition training (ERT) has shown promise in modifying cognitive biases associated with low mood (Penton-Voak et al., 2012) and can be easily delivered via computer or smartphone applications. Using a novel paradigm we conducted a randomised controlled trial of the effects of ERT on amygdala response to facial expressions of emotion, in order to explore the neural mechanism of action of this intervention in a sample of individuals with depressive symptoms.

Methods: We randomised 36 adults from the general population who reported high levels of depressive symptoms (≥ 14 on the Beck Depression Inventory-II) to five consecutive daily sessions of the ERT intervention or control procedure, followed by an fMRI scan on the final training day.

Results: Region of interest analysis demonstrated significant group differences in the neural response to happy vs. sad stimuli in the left amygdala, with activation greater in the trained versus control groups. This effect was driven by amygdala responses to happy faces, with an 8% increase in amygdala activation in the trained group relative to a 4% reduction in the control group relative to resting state.

Conclusion: Our findings suggest that computerised training (ERT) using a novel cognitive bias modification technique targeting emotional processing in depression resulted in greater neural activation to positive faces relative to negative faces. This effect is similar to those of antidepressants in depressed individuals, raising the possibility that ERT may be a valuable and cost-effective adjunctive treatment for depression.

References:

Keywords: Psychology; Emotion recognition; Cognitive bias modification; fMRI; Training
Dimensions of schizotypy in relation to different types of predictive processing and source-monitoring

Humpston C, Evans L, Teufel C, Ingram J, Wolpert D, Linden D

Background: Schizotypy could be defined in two ways: one confers subclinical risk-state/liability to schizophrenia and the other refers to a personality trait fully dimensional with normal experiences. Adopting an individual-differences approach and a dimensional conceptualisation of psychosis, the current study investigates the relationships between schizotypy, different types of predictive processing, and source-monitoring.

Methods: 115 healthy volunteers (25 males, mean age 22.23 years) recruited from across Cardiff University participated in a battery of five behavioural tasks: force-matching (sensory prediction), Kamin blocking (cognitive prediction), reversal learning (motivational prediction) and source-monitoring of both actions and words. Performance in these tasks was correlated to three questionnaires that measure different dimensions of schizotypy: the 21-item Peters et al. Delusions Inventory (PDI-21), the Cardiff Anomalous Perceptions Scale (CAPS) and the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE). The a priori hypotheses were that only positive schizotypy dimensions (i.e. delusion-like ideation and hallucinatory experiences) would be related to disrupted predictive processing and reality monitoring errors.

Results: A significant positive correlation was found between the O-LIFE unusual experiences subscale, the PDI-21 and sensory prediction as measured by the force-matching task in contrast to previous research. Hyper- instead of hypo-blocking was demonstrated in participant with high positive schizotypy, which was again a failure of replication. However, high positive schizotypes (as measured by PDI-21) performed significantly worse in the reversal learning task with a slower learning rate and more randomness, and made significantly more reality monitoring (external-internal) source memory errors in the action source-monitoring task but not the verbal one.

Conclusion: The current study demonstrates specific differences in high positive schizotypes, in particular those who are most prone to delusion-like ideas, when performing the reversal learning and action source-monitoring tasks. Hence motivational/reward predictive processing and reality monitoring of actions could be most affected in individuals with high but nonclinical delusional ideation.
References:

**Keywords:** Prediction error; Source-monitoring; Schizotypy
The enrichment of extinction-related genes in schizophrenia copy number variants

Clifton NE, Pocklington AJ, Thomas KL, Hall J

Background: Converging evidence from recent human genetic studies into schizophrenia support the notion that pathways involved in synaptic plasticity are central to the disorder’s etiology. In particular, plasticity pathways required for associative learning have been associated with schizophrenia through studies of copy number variants (CNVs, Pocklington et al., 2015). The present study aimed to deduce whether genes involved in a particular phase of associative learning are enriched in schizophrenia CNVs.

Methods: Microarray gene expression data was obtained from hippocampal CA1 of adult Lister Hooded rats that had undergone either contextual fear conditioning (CFC), CFC with a retrieval test (2min, 48 hours later) or CFC with extinction (10 min, 48 hours later). The data was ranked by the significance of gene expression change vs control and human gene homologs were identified. Human CNV data was obtained from three European studies: ISC, MGS and ClozUK. CNVs less than 100kb or with less than 15 probes were filtered out. Logistic regression analysis was performed to determine the enrichment of the top 125% plasticity genes in schizophrenia CNVs.

Results: The top 5% plasticity-related genes were used in a primary analysis. Extinction-related genes were heavily enriched in case CNVs (P = 9.37*10^-5, Bonferroni-corrected), whilst consolidation- or retrieval-related genes were not (P = 0.23; P = 0.55). A subsequent analysis regressed the top 1-25% plasticity-related genes on schizophrenia CNVs with permutation-correction. Only the top 1-5% extinction-related genes were enriched in schizophrenia CNVs. The contribution of the top extinction-related genes to this enrichment was assessed. It was found that several of these genes overlap with past Schizophrenia-associated loci.

Conclusion: These results imply that plasticity pathways involved in the generation of extinction learning may be selectively disrupted by CNVs in schizophrenia. This is in keeping with past studies that have demonstrated the failure of extinction learning in schizophrenic patients and an impairment of other inhibitory learning processes such as latent inhibition.
References:

Keywords: Schizophrenia; Extinction learning; Synaptic plasticity; Contextual fear conditioning; Copy number variants
Emotional connections need structural connections: interindividual variation in uncinate fasciculus microstructure is related to facial emotion processing

Coad BM, Postans M, Graham KS, Lawrence AD

Background: The Uncinate Fasciculus (UF) is a long-range association fibre tract connecting regions in the frontal and temporal lobes, and is thought to be important for social cognition. However, few studies have directly investigated the microstructural properties of the UF in relation to social-emotional functioning in healthy adults. This study addressed this gap by studying the relationship between microstructural characteristics of the UF and performance on measures of social cognition. In Study 1 the presence of a relationship between UF microstructural properties and social cognition was established. In Study 2 the nature of this relationship was further explored with a battery social cognition tests to elucidate the underlying process driving the relationship observed in Study 1.

Methods: A total of 85 individuals took part across 2 studies. Diffusion-MRI measures of white matter microstructure (fractional anisotropy (FA)) were extracted for all participants, from the left and right UF from tracts reconstructed using deterministic tractography. In Study 1 participants completed the Mind in the Eyes task (MITE), a commonly used measure of cognitive empathy as well as a control odd-one-out (“oddity”) task of facial identity processing. In Study 2 participants completed a facial emotion perception (“emotion matching”) task and the short story task, a measure of mental state attribution.

Results: In Study 1, FA of the right, but not the left, UF was significantly correlated with performance on the MITE task, but not the face oddity task. In Study 2 FA in right UF was significantly correlated with performance on the emotion matching but not the short story task.

Conclusion: Results indicate an important role for the UF in social cognition but more specifically in facial emotion perception. Findings fit well with existing evidence suggesting the presence of different neural networks underlying emotion perception and mental state attribution.

References:

Keywords: Uncinate Fasciculus; Empathy; Emotion; Perception; Tractography
Expectations of social pain and pleasure are reflected in brain structure

Crawford B, Muhlert N, Macdonald G, Lawrence AD

Expectations of reward and punishment are pivotal in motivating approach and avoidance behaviour. Little is known, however, of the neural substrates of generalized expectations of social punishment and reward. We have developed a measure of expectations of social reward and punishment, the Levels Of Dispositional Expectancies for Social Threat and Reward Scale (LODESTARS). Data from 848 adults demonstrate that the scales have excellent psychometric properties.

To investigate the brain structure correlates of social expectations, grey matter volume (GMvol) of 100 healthy individuals (26 males; mean age 24.3 years) was assessed. High-resolution anatomical magnetic resonance images were acquired and analysed using voxel-based morphometry (VBM). Age, gender and total brain volumes were accounted for in all statistical models.

Higher expectancies of social reward were associated with greater GMvol in left dorsomedial prefrontal cortex (dmPFC). This region is engaged during savouring – a form of cognitive rumination, by which individuals can up-regulate the expected emotional impact of positive events.

Higher social threat expectancies were associated with greater GMvol in brain regions involved in social attention and perception, including right posterior middle temporal gyrus (pMTG). This may reflect hypervigilance towards potential threat signals in the social environment.

Lower expectancies of social threat were associated with greater GMvol in brain regions implicated in emotion regulation, particularly right ventromedial PFC (vmPFC). Our results suggest that the minimisation of social threat expectancies – and/or the maintenance of low threat expectancies – may be implemented in the brain in a similar manner to the reduction of fear in other emotion regulation scenarios.

Our findings indicate that, at the macro-structural brain level, individual differences in generalized social pain and pleasure expectancies are most prominently associated with differences in brain regions involved in emotion regulation. Our study may have implications for understanding brain structural dispositions to mood disorder, including social anxiety and depression.
Keywords: Social Neuroscience; Emotion regulation; Brain structure; Self-fulfilling expectancies
A viral approach for chemogenetic activation of noradrenergic neurons in health and disease

Hirschberg S, Li Y, Randall A, Pickering AE

Background: The Locus coeruleus (LC) is the principle noradrenergic nucleus in the brain. By means of its extensive projections the LC plays a diverse role in autonomic functions and behaviour. Malfunction of the noradrenergic system has been associated with pathologies such as major depression, Alzheimer’s disease and neuropathic pain. We have therefore been interested in developing means to activate the noradrenergic system and subpopulations of noradrenergic neurons.

Methods: We developed a lenti-viral vector (lenti-PRS-EGFP2aPSAM) with catecholaminergic promotor (PRS) that co-expresses PSAM and EGFP. PSAM is an engineered excitatory receptor-ionophore and is specifically activatable by the PSEM308 (Magnus et al. 2011).

Results: EGFP immunofluorescence was restricted to neurons that were positive for the noradrenergic marker dopamine beta hydroxylase (98%). In patch clamp recordings from pontine slices transduced and untransduced neurons showed no difference in electrophysiological properties, suggesting that transduction was well tolerated. In vivo extracellular recordings were made with multi-barrelled electrodes allowing simultaneous localised drug delivery in an anaesthetised preparation. 12 of 26 identified LC units were time locked and dose dependently excited by PSEM308, reflecting putatively transduced neurons.

Conditioned place aversion protocols were used to assay for adverse effects from tonic activation of noradrenergic neurons. Lenti-PRS-EGFP2aPSAM (N=7) or EGFP control vectors (N=5) were delivered into the LC. We developed the retrogradly transported CAV2-PRS-EGFP2aPSAM and delivered it into the spinal cord (N=8). This vector exclusively transduces noradrenergic neurons that synapse at the injection site. Conditioning with 10mg/Kg caused aversion of the drug paired chamber LC injected rats. The same dose however had no effect on rats expressing PSAM in the spinally projecting subpopulation or controls.

Conclusion: Here we present a novel chemogenetic approach for specific in vitro and in vivo activation of noradrenergic neurons. Our findings support that the hypothesis that subpopulations of noradrenergic neurons are heterogeneous in projection targets and physiological function.
References:

Keywords: Locus coeruleus; Noradrenaline; Chemogenetic; Viral vectors; Conditioned place aversion
Using cognitive training as a therapeutic intervention in a knock-in mouse model of Huntington’s disease

Yhnell E, Brooks SP, Dunnett SB

Background: Huntington’s disease (HD) is a rare, incurable neurodegenerative disorder caused by a CAG trinucleotide expansion with the first exon of the huntingtin gene. HD causes a range of motor, cognitive and psychiatric disturbances. Cognitive training interventions, have been used successfully to improve symptoms in other neurological diseases such as Alzheimer’s disease ¹ and Parkinson’s disease ². Cognitive training interventions therefore present an exciting non-pharmacological treatment possibility for HD.

Methods: To test this hypothesis the HdhQ111 knock-in mouse model of HD was given an intensive session of cognitive training in the 5-choice serial reaction time task (5-CSRTT), an attentional task, for 20 days at 4 months of age. In addition to the group that had attentional training, two age matched control groups were used. One control group received training in a similar task with no attentional component for a comparable number of days, and the other group were cage controls. All animals were then tested in the 5CSRTT at 12 months of age.

Results: Results revealed that all types of cognitive training had a positive effect on task performance in comparison to cage controls. Attentional cognitive training, generally improved attentional performance in all animals and specifically improved motor performance in HD animals. In the control group who received comparable training in a non-attentional task, a general positive effect of training was seen, although, this type of training did not confer any specific advantage to the HD animals in comparison to wildtype animals.

Conclusion: The results demonstrate that attentional cognitive training implemented at a young age improves attentional performance at an older age in both wildtype and HD mice. Attentional training also specifically improved motor performance in HD mice. This leads to the exciting possibility that specific cognitive training can improve HD disease symptoms later in life.

References:

**Keywords:** Huntington’s disease; Cognitive training; Operant testing; Mouse models; Executive function
A role for increased dosage of the imprinted Cdkn1c gene in linking early life adversity and later life behavioural disorders

McNamara GI, Dwyer DM, Humby T, Dalley JW, Xia J, John RM, Isles AR

Exposure to early life adversities such as poor maternal nutrition or suboptimal maternal care is associated with abnormal behavioural outcomes in offspring. Prenatal low protein diet and altered maternal care have both previously been shown to increase the expression of epigenetically regulated gene Cdkn1c in the brains of rodent exposed offspring. Using a transgenic model (Cdkn1cBACx1) recapitulating this alteration, we show that increased expression of Cdkn1c in the brain gives rise to neurobiological changes reminiscent of those seen in animals exposed to early life adversity. Cdkn1cBACX1 mice had altered expression of dopamine (DA) system related genes, increased tyrosine hydroxylase staining and increased tissue content of DA in the striatum. In addition, transgenic animals were hypersensitive to amphetamine as revealed by c-fos expression in the nucleus accumbens. Cdkn1cBACX1 mice also had significant changes in a number of DA-related behaviours, including prepulse inhibition (PPI) of startle response, and reward-related behaviours such as motivation for, and hedonic reaction to, palatable foodstuffs. These data demonstrate, for the first time, the consequence of elevated Cdkn1c expression on behaviour further highlighting the importance of correct dosage of imprinted gene expression in the brain. This work suggests that increased expression of Cdkn1c is a causative factor driving some of the neural and behavioural phenotypes observed in the offspring exposed to early life adversity.

Keywords: Epigenetics; Reward; Dopamine; Early life adversity; Imprinted genes
Evaluating 2B3, a novel immunotherapy, in a preclinical model of amyloid pathology

Evans CE, Thomas RS, Kidd EJ, Good MA

Background: Currently Alzheimer’s disease (AD) has no effective treatment. βamyloid (Aβ) is a major pathological hallmark of AD, metabolised from the amyloid precursor protein (APP) by enzymes β- and γ-secretase. We developed a novel monoclonal antibody, 2B3, which binds at the β-secretase cleavage site of APP, inhibiting production of Aβ in vitro. These effects are yet to be determined in vivo. The aims of this study were: 1) characterise object-in-place memory in PDAPP mice, 2) assess whether 2B3 can alleviate cognitive deficits observed following intracerebroventricular (ICV) administration, and 3) investigate the ability of 2B3 to affect APP processing ex vivo in PDAPP mice.

Methods: To characterise object-in-place memory, PDAPP mice and wild type (Wt) controls were tested at a range of ages, in an open arena with a variety of objects. Following behavioural assessment, PDAPP mice were treated with 2B3 or vehicle. Wt mice were treated with vehicle or no treatment. Treatments lasted for 14-days; delivered into the lateral ventricle via ICV administration using osmotic mini-pumps. Object-in-place memory was assessed at days 13 and 14. Following behavioural testing, mice were sacrificed and brain regions dissected. Levels of APP and metabolites were analysed by enzyme-linked immunosorbent assay (ELISA) and western blot.

Results: An age-dependent deficit in object-in-place memory was observed in PDAPP mice. Following ICV administration of 2B3 for 14 days, PDAPP mice showed a full recovery of object-in-place memory. Ex vivo tissue analysis of 2B3 treated PDAPP mice revealed a significant reduction in total levels of the β C-terminal fragment (β-CTF) of APP, with no significant effect on Aβ-42 or APP.

Conclusions: Our findings show a novel age-dependent deficit in object-in-place memory. This deficit was reversed following treatment with 2B3. Significant reduction in β-CTF implies that 2B3 inhibited APP processing in vivo without affecting APP. These results support the hypothesis that inhibition of APP processing can improve memory function in PDAPP mice.

Keywords: Alzheimer’s; Behaviour; Immunotherapy; Biochemistry; Animal Models
Sleep problems in children and adolescents with 22q11.2 deletion syndrome

Moulding HA, van den Bree M

Background: To study the prevalence of reported sleep problems encountered by individuals with 22q11.2 deletion syndrome. 22q11.2 deletion syndrome individuals alongside their unaffected siblings, and further unaffected siblings of other copy number variants (CNVs), were questioned about their sleep problems. All of these individuals participated in the Experiences of CHildren with cOp (Konofal and Cortese, 2005) y number variants (ECHO) study aged 6-18 years old. Psychiatric and neurodevelopment symptoms and diagnoses were taken into account and assessed in relation to reported sleep problems. Sleep problem assessment was governed by the subscales in the sleep section of the Child and Adolescent Psychiatric Assessment (CAPA) Questionnaire.

Methods: Quantitative and qualitative data was obtained from the CAPA specifically regarding sleep disturbances in both 22q11.2 deletion syndrome individuals and unaffected siblings. Quantitative analysis was undertaken using regression analysis and factor analysis in Stata (v13.).

Results: 58.6% (n=111) 22q11.2 deletion syndrome individuals reported at least one sleep problem, with the preponderance of restless sleep reported by 34.2% (n=38/111) of individuals compared to 12.2% (n=10/72) of siblings. After controlling for gender and age there was a 3.64 increased likelihood of restless sleep in 22q compared to unaffected siblings of CNVs (OR, 3.64 95%CI, 1.67-7.98 p, 0.001). Controlling for ADHD diagnosis saw a 3.29 increased risk of restless sleep for 22q11.2 deletion syndrome with ADHD and 5.97 increased risk with 22q11.2 deletion syndrome with a positive combined subtype of ADHD (OR, 3.29 95%CI, 1.53-7.06 p, 0.002; OR, 3.92 95%CI, 1.87-19.1 p, 0.003).

Conclusion: There is an increased likelihood and risk of development of sleep problems in 22q11.2 deletion syndrome when compared to unaffected siblings of copy number variant individuals. Individuals with 22q11.2 deletion syndrome and a positive ADHD diagnosis show significant associations with restless over other sleep problems.

References:


**Keywords:** 22q11.2 deletion syndrome; Sleep; Copy number variants (CNVs); Children and adolescents; Attention-deficit hyperactivity disorder (ADHD); Schizophrenia
Gender and age differences of intra-frequency and phase-to-amplitude coupling (PAC) based on EEG resting-state networks

Dimitriadis SI, Sallis C, Tsalikakis D, Perry G, Singh K, Linden D

Background: Cognitive performance and spontaneous brain activity show significant changes over the life-span, but the interrelations between age, resting-state brain oscillations and cognition in terms of functional connectivity is not well explored yet. Our first goal was to characterize connectivity patterns of age and sex-related alterations in resting-state functional networks across the lifespan.

Methods: Here, we estimated resting-state EEG networks based on both intra-frequency and phase-to-amplitude coupling (PAC) from 102 healthy adults 1,2 (60 females from 20 to 58 years old and 42 males from 19 to 67 years old). To investigate the prediction of age at each gender and in both eyes-open (EO) and eyes-closed (EC) conditions, we estimated a probability distribution (PD) of prominent intra-frequency and PAC estimates from the whole brain network of each individual 3,4. Our analysis focused in the frequency range of 1-75 Hz.

Results: Based on PD and followed a leave-one-out cross-validation (LOOCV) scheme, we succeeded to predict the age of males with 82.42 % (SD:2.5) for EC and 90.54% (SD:3.5) for EO condition. In contrast, the prediction of age in females was 67.68 % (SD:4.2) for EC and 74.46% (SD:5.1) for EO. Prediction of age based on the strength of the combined intra-frequency and PAC resting-state brain networks was higher for females (81.45 % (SD:3.9) for EC and 90.54% (SD:5.9) for EO condition) compared to men ( 9.86 % (SD:4.5) for EC and 13.75% (SD:4.9) for EO condition).

Conclusions: The spatial distribution of intra-frequency and PAC connections and their strength contributed differently to gender. These findings substantiate further the important role of studying brain networks at resting-state under the notion of both intra-frequency and PAC cross-frequency interactions during healthy development. The type of prominent interactions at intrinsic networks reflect possible gender and age-related cognitive differences 5. This study can guide future research for finding sex-related connectomic biomarkers for neurological disorders.

References:
1 http://www.physionet.org/pn4/eegmmidb/


Keywords: Phase-to-amplitude coupling; Resting-state; EEG; Brain networks; Developmental cognitive neuroscience
Developmental Coordination Disorder, Psychopathology and Cognition in 22q11.2 Deletion Syndrome

Cunningham A, Linden D, Owen M, van den Bree M

**Background:** The 22q11.2 Deletion Syndrome (22q11.2DS) is associated with a range of neurodevelopmental, psychiatric and motor problems. This study investigates the prevalence of Developmental Co-ordination Disorder (DCD) in 22q11.2 Deletion Syndrome, the relationship between co-ordination difficulties and cognitive ability, and the link between co-ordination and psychopathology.

**Methods:** We compared children with 22q11.2 DS (n=61 mean age 12.75 years, SD 2.47) their unaffected siblings (n=24 mean age 13.21 years, SD 2.13). Motor co-ordination difficulties were established using the Developmental Co-ordination Disorder Questionnaire (DCDQ). The Social Communication Questionnaire (SCQ) was used to establish autism spectrum disorder (ASD) symptoms. Attention deficit hyperactivity disorder (ADHD) symptoms were assessed using the hyperactivity and inattention sections of the Child and Adolescent Psychiatric Assessment (CAPA). IQ was tested using the Weschler Abbreviated Scale of Intelligence.

**Results:** 85% of children with 22q11.2 DS met criteria for indicative Developmental Co-ordination Disorder, compared to 8% of their unaffected siblings (p<0.001). In children with 22q11.2 DS, DCDQ total score was correlated with ADHD hyperactive (rho=-0.46, p<0.001) and inattentive (rho=-0.55, p<0.001) subtype symptom scales as well as the ASD SCQ behaviour subscore (r= -0.35, p=0.006; assessing repetitive and stereotypic behaviours). Developmental co-ordination difficulties were not related to IQ.

**Conclusion:** There is a high prevalence of co-ordination difficulties in children with 22q11.2 DS, which are not related to cognitive ability. This has wider implications for diagnosing DCD in populations with a low IQ. The association between coordination difficulties and ADHD and ASD symptomatology may be indicative of an underlying common deficit.

**References:**


Murphy KC, Jones LA, Owen MJ (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry* 56(10):940-945

**Keywords:** Co-ordination; Genetics; Motor Difficulties; Neurodevelopment; Copy Number Variants
A partially inactivating mutation in the sodium-dependent lysophosphatidylcholine transporter MFSD2A causes a non-lethal microcephaly syndrome


Background: The major pathway by which the brain obtains essential omega-3 fatty acids such as docosahexaenoic acid (DHA) from the circulation is through a sodium-dependent lysophosphatidylcholine (LPC) transporter (MFSD2A), expressed in the endothelium of the blood-brain barrier, which is essential for normal brain growth and cognitive function. Here, we investigated an extensive Pakistani pedigree with multiple interlinking nuclear families with individuals affected by an autosomal recessive progressive neurological condition involving microcephaly, intellectual disability, spasticity, absent speech and dysmorphic features, which we show is associated with mutation in MFSD2A.

Methods/Results: A whole genome SNP scan was performed using DNA samples of family members which identified a single notable homozygous region peculiar to all affected family members on chromosome 1p34.2. Whole exome sequencing identified a single likely deleterious sequence variant located within the disease locus, in the MFSD2A gene (chr1:40433304C>T), affecting a highly conserved amino acid residue (p.Ser339Leu). The variant co-segregated with the disease phenotype and was absent in online genomic databases and regional controls. While immunofluorescence localisation studies determined that the p.Ser339Leu alteration does not affect protein or cell surface expression of MFSD2A, patient plasma lipidomic analysis demonstrated that the mutation significantly reduces, although not completely abolishes, transporter activity. Notably, affected individuals displayed significantly increased plasma concentrations of LPCs containing mono- and polyunsaturated fatty acyl chains, indicative of reduced brain uptake, confirming the specificity of MFSD2A for LPCs having mono- and polyunsaturated fatty acyl chains.

Conclusion: Our findings provide the first description of disease associated with aberrant brain LPC transport in humans and establish an essential role for LPCs in human brain development and function.

References:
Keywords: MFSD2A; Microcephaly; Developmental delay; Lysophosphatidylcholine
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