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Plenary Presentations

Recent advances toward high-performance prosthetic performance

Professor Andrew Schwartz

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A better understanding of neural population function would be an important advance in systems neuroscience. The change in emphasis from the single neuron to the neural ensemble has made it possible to extract high-fidelity information about movements that will occur in the near future. The realization that useful information is embedded in the population has spawned the current success of brain-controlled interfaces. Since multiple movement parameters are encoded simultaneously in the same population of neurons, we have been gradually increasing the degrees of freedom (DOF) that a subject can control through the interface. Currently, monkeys in our laboratory are using this interface to control a very realistic, prosthetic arm with a wrist and hand to grasp objects in different locations and orientations. This technology has now been extended to a paralyzed patient who cannot move any part of her body below her neck. Using a high-performance “modular prosthetic limb” she has been able to control 10 degrees-of-freedom simultaneously. The control of this artificial limb is intuitive and the movements are coordinated, graceful, and closely resemble natural arm and hand movement. This subject has been able to perform tasks of daily living- reaching to, grasping and manipulating objects as well as performing spontaneous acts such as self-feeding.
Hypothalamic CRH neurons control behavioural choice following stress

Professor Jaideep Bains

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The activation of hypothalamic CRH neurons is obligatory for the neuroendocrine response to stress. These cells, however, may extend axon collaterals to regions of the lateral hypothalamus, but whether they play any role in controlling stress-responsive behaviours is not known. Here we used an approach that combines behavioural assessments, optogenetics and electrophysiology to probe for a potential role for hypothalamic CRH neurons as behavioural controllers. We saw that these stress command cells play a key role in balancing opposing behaviours following stress. This is accomplished through a non-canonical, glucocorticoid independent excitatory pathway to a subset of neurons in the lateral hypothalamus. These surprising findings add to our current understanding of how the brain makes behavioural choices during stress and are consistent with an emerging theme of a ‘bottom-up’ circuit motif in which hypothalamic circuits control complex behaviours beyond those required for need based or homeostatic functions.
Caught in the net: Perineuronal nets and addiction

Professor Barbara Sorg

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In addiction research, attention has recently shifted from targets located on pre- and post-synaptic cells and astrocytes to targets located in the extracellular matrix within brain regions important for drug-taking behavior and drug-related memories. This shift has contributed to the advancement from a tripartite to a tetrapartite synapse theory. The studies in our lab focus on the medial prefrontal cortex (mPFC), which contributes to cocaine-seeking behavior in humans and rodents. Exposure to cocaine and cocaine-associated cues increases the activity of pyramidal output neurons from the mPFC. The activity of these neurons is significantly modulated by GABAergic, parvalbumin (PV)-containing, fast-spiking interneurons. The majority of these interneurons are enveloped by unique structures of extracellular matrix called perineuronal nets (PNNs) that are integral to the maintenance of many types of plasticity. Using conditioned place preference (CPP), we have shown that removal of PNNs within the mPFC of rats impairs the acquisition and reconsolidation of a cocaine-induced CPP memory. This impairment is accompanied by a decrease in the number of c-Fos-positive cells surrounded by PNNs. Consistent with these findings, repeated cocaine increases PV and PNN intensity in the mPFC, which may be associated with the formation of strong cocaine-induced memories. Together, our findings indicate that cocaine-induced plasticity is impaired by removal of PNNs in the mPFC and that repeated cocaine exposure may reduce plasticity of PV+/PNN+ interneurons in the mPFC. Our studies suggest that PNNs may be a therapeutic target for disruption of cocaine CPP memories.
Proton magnetic resonance (MR) imaging has revealed much about human neuroscience with localization of function-structural relationships and insight into higher cognitive processes. Higher magnetic fields have not only improved resolution of proton imaging but also enabled metabolic MR imaging of other elements of the periodic table including sodium, oxygen, phosphorus and potassium. Lower sensitivity has always compromised imaging of these nuclei compared to protons. Proton imaging of brain water can now achieve exquisite anatomical images in a few minutes, albeit in qualitative terms of image contrast based on nuclear relaxation properties rather than biochemistry. Metabolic MR imaging, being orders of magnitude less sensitive, must aim to provide new biochemical information beyond that available from protons. The quantitative bioscale of the tissue sodium concentration (TSC), measured by 23-sodium MRI and reflecting tissue ion homeostasis, has been found to be constant with normal ageing, allowing speculation that age-related brain volume loss follows a mechanism of adjusting the volume of extracellular matrix with neuron volume with age. The bioscale of cerebral metabolic rate of oxygen consumption (CMRO2), measured by 17-oxygen MRI during inhalation of 17-oxygen enriched oxygen gas, has provided a spatially resolved quantitative measure of cerebral function. Together, these and other quantitative metabolic parameters offer the potential for generating mathematical models that may add new insight into human cognition in health and illness.
Developing non-invasive tactile feedback from artificial sensors using a biomimetic code

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Background: The current generation of commercially-available hand prostheses offer some limited motor control, but none incorporate tactile feedback. Our novel method of providing tactile feedback sends the outputs of artificial tactile sensors to algorithms that convert them into physiologically-plausible action potential (spike) trains. The spike trains are delivered to intact peripheral afferents using non-invasive stimulation.

Methods: All protocols were approved by the UNSW Human Research Ethics Committee. Four virtual neurons were built using a noisy leaky integrate and fire model and trained on non-human primate data obtained from fingertip afferents (two FA1 and two SA1). Sensor signals driven by mechanical stimuli that moved in either a proximal or distal direction were input to virtual neurons and their spiking output pattern recorded. Twelve healthy young-adult subjects had these spike patterns delivered to their upper arm by a pair of stimulators (electrical or mechanical) to determine their ability discriminate the direction of movement. A ten minute training session combined skin stimulation with a visual representation of the movement. In the subsequent testing, subjects had no visual cue, and were presented novel spike patterns as well as ones from the training set.

Results: More than half the subjects were able to discern movement direction with greater than 90% accuracy with electrical or pulsatile mechanical stimulation. There was no significant difference between novel and non-novel stimuli, indicating subjects could generalise stimulus sensations across specific instances of firing patterns.

Conclusions: This approach offers a promising way to return tactile sensation to amputees.
Providing force feedback to controllers from signals recorded from the median nerve

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Assistive devices such as prosthetic limbs, functional electrical stimulation systems and exoskeletons can be considered neuroprosthetics when they offer an interface with the nervous system. A closed-loop neuroprosthetic system has a controller that responds to feedback, improving the performance of the system. We have utilised microneurography to record multiunit somatosensory activity from the median nerve of healthy human participants, and utilised machine learning methods to decode a signal relating the multiunit activity to the force of stimuli applied to the finger. This signal may be suitable for use as a sensor signal in a neuroprosthetic.
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Encoding of grip safety by tactile afferents for manipulation of objects with varying friction

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Adjustments to frictional forces are crucial to maintain a safe grip during precision object handling in natural human manipulation, prostheses and robotic manipulators. The aim of this work was to investigate whether a population of human tactile afferents can provide information about the current tangential/normal force ratio expressed as the percentage of the critical load capacity – the tangential/normal force ratio at which the object would slip. A smooth stimulation surface was tested on the fingertip under three frictional conditions, with a 4 N normal force and a tangential force generated by motion in the ulnar or distal direction at a fixed speed. During stimulation, the responses of 29 afferents (12 SA-I, 2 SA-II, 12 FA-I, 3 FA-II) were recorded. A multiple regression model was trained and tested using cross-validation to estimate the percentage of the critical load capacity in real-time as the tangential force increased. The features for the model were the number of spikes from each afferent in windows of fixed length (50, 100 or 200 ms) around points spanning the range from 50% to 100% of the critical load capacity, in 5% increments. The mean regression estimate error was less than 1% of the critical load capacity with a standard deviation between 5% and 10%. A larger number of afferents is expected to improve the estimate error. This work is important for understanding the tactile input that facilitates human dexterous manipulation and for inspiring improvements in prostheses and robotic grippers.
The effects of cervical trans-spinal direct current stimulation on motor pathways supplying the upper limb

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Background: Cervical trans-spinal direct current stimulation (tsDCS) is a relatively new technique that reportedly modifies muscle responses to motor cortical stimulation\(^1,2\); however it is not known whether neural changes occur within the spinal cord. Here we tested H-reflexes as well as muscle responses to subcortical cervicomedullary stimulation to identify spinal level effects of cervical tsDCS.

Methods: Participants (Study 1: n=12; Study 2: n=12) received 20min of 3mA tsDCS or sham (1min of tsDCS) stimulation on separate days through electrodes placed anteriorly under the chin (anode), and posteriorly over the 7\(^{\text{th}}\) cervical vertebra (cathode). In Study 1, muscle responses to cervicomedullary stimulation (cervicomedullary motor evoked potentials, CMEPs) and transcranial magnetic stimulation (motor evoked potentials, MEPs) were recorded from biceps brachii, flexor carpi radialis (FCR) and first dorsal interosseous (FDI) muscles before and after tsDCS. In Study 2, median nerve stimulation elicited FCR M waves and H reflexes. H-reflex recruitment curves were recorded and post-activation depression (PAD) of the H reflex was measured before and after tsDCS.

Results: Two-way repeated measures ANOVAs revealed no differences between tsDCS and sham stimulation in CMEPs or MEPs in any muscle, nor were there differences between tsDCS and sham in H-reflex recruitment curve parameters or PAD.

Conclusions: TsDCS did not alter evoked motor responses. In contrast to previous studies, cervical tsDCS did not modify MEPs or CMEPs. Consistent with previous work H-reflex recruitment curve data also showed no difference between tsDCS and sham stimulation. Moreover, unlike thoracic tsDCS, cervical tsDCS did not modify H-reflex PAD.
Development of complex neural cell culture systems for preclinical assessment of biomaterials

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Background: Conventional metals such as platinum (Pt) have limited cell interactions due to their mechanical stiffness and smooth surface. The poor integration in vivo leads to fibrous encapsulation and limits Pt efficacy and safety when used for implantable electrodes. Conductive polymers (CPs) have been investigated for use as coatings for stimulating tissue in implantable devices. While CPs can improve the electrical properties of bioelectrodes, and cell studies using classical in vitro cell based assays indicate improved compatibility. These in vitro improvements translate poorly to tissue and cell integration of CPs in vivo. This study aimed to develop in vitro cell models that provide more translatable data regarding the potential in vivo tissue and cell integration of biomaterials.

Methods: Astrocyte enriched glial cultures were derived from neonatal murine forebrains, and grown for 7 days. Cells were seeded onto poly-l-lysine (PLL) coated samples. At 14 days, mixed glial and neuron precursor cells were derived from fetal mouse spinal cords. These cells were co-cultured directly on top of the astrocyte enriched cultures for a further 21 days. Samples were fixed and stained for immunofluorescence microscopy. The CP poly(3,4ethylene dioxythiophene) (PEDOT) was used as a model CP. Pt and glass were used as control materials.

Conclusions: Astrocyte cultures on the various materials have minimal differences at 7 and 14 days in vitro. Neurons and myelin similarly require greater than 14 days to provide clear image of cell/material interactions. This complex model of the CNS provides a valuable preclinical evaluation tool for neural interfacing electrode materials.
High quality RNA isolation from rat spinal cord motor neurons using Laser Capture Microdissection

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Background: Spinal cord motor neurons play a central role in bridging the connection between the brain and the skeletal muscles. Information regarding the fate of motor neurons below a spinal cord injury (SCI) is thus essential to understand the pathophysiology of SCI. As motor neurons represent less than 10% of the total cell population in the spinal cord, the transcriptional profile of motor neurons below a transection cannot be characterized from spinal cord homogenates. A laser capture microdissection (LCM) system is thus ideal for analyzing the mRNA profile in these neurons.

Methods: The rats were anesthetized, perfused and segments C2-C3/C4-C5 of the spinal cord were sectioned on RNase-free slides. The tissue sections were stained with Azure B and LCM system was used to capture the stained motor neurons. RNA was isolated and RNA integrity (RIN) was determined on Agilent Bioanlyser 2100. Anti-ChAT antibody staining was performed to identify and confirm that the collected cells were motor neurons. We performed an RT-PCR analysis to confirm the presence of microdissected transcripts as an additional RNA quality control.

Results: The procedure described above produced good quality RNA with RIN above 7 and the motor neurons isolated by LCM produce amplified cDNA from as little as 5 ng of RNA.

Conclusion: We conclude that LCM is an ideal system for the identification and isolation of motor neurons to generate intact and high quality RNA and will provide valuable information to advance our understanding of the molecular mechanisms in SCI.
Assessment of Facial Expressions of Emotion Using Optical Flow Analysis

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Background: Investigation of emotion manifested through facial expression has valuable application for predictive behavioural studies. We believe that facial expressions are valid reflections of a person's mental state and allow us to predict future behaviours. The objectives of this research is to examine whether emotional expression derived from the whole, half or profile views of the face can be used to determine differences in 3 emotions: Amusement, Fear and Sadness.

Methods: Still facial images representative of neutral expressions and peak of emotional expressions were obtained from 102 subjects who were videotaped while watching 3 emotion-inducing short films. Method of analysis included optical flow to extract activity of facial movements, and the nine-point Likert scale (self-reported emotional assessment) which allowed participants to independently evaluate the emotion they believe they felt.

Results: Statistical analysis of the data using t-test performed on profile views during neutral and peak emotional expression states showed differences in facial movement for the emotion of fear, having a p-value <0.05. No significant difference was found for amusement and sadness. Further analysis will be performed to compare the differences across the emotions from whole and half-view facial images.

Conclusions: Optical flow analysis could potentially be used in the discrimination of emotional facial expressions. However, further research is required to assess the link between emotion and behaviour and to understand the neural pathways that encode facial expression. In addition, coupling the use of galvanic skin response (GSR) to observe sympathetic nervous activity would confirm the emotion obtained through facial expression.
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Beauty in the Eye of the Beholder: The Relativity of Visual Experience

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**Background:** The edges of a straight road across a flat plane are seen to converge to a point at a finite distance. However, visual experience forms merely the ventral aspect of an encompassing 3-dimensional virtual reality, within which the road edges must also converge to a point on the horizon behind the subject. What are experienced as straight lines correspond to shortest paths or geodesics through a positively curved ‘subjective space’.

**Methods/Results:** We describe a metric for a 2-dimensional curved subjective subspace, and a projection onto it from a corresponding objective plane, which together model distortions of the apparent fronto-parallel plane, of the apparent equidistant circle and of apparent distance bisection in normal subjects. If there is an attentional spatial filter that biases the distribution of event probability in the subject’s local environment, we argue that such a representation maximizes the entropy of events in subjective space.

**Conclusions:** The deviation of the virtual world of subjective space and time (the latter presented at the last Inter-university Conference) from objective reality resembles the divergence of objective reality from Newtonian laws of mechanics and gravity, characterized a century ago by Einstein as General Relativity. Our model reveals how the common spatial distortions of neglect and unilateral vestibular failure might be considered a neurologic ‘equivalence principle’. We propose that just as gravity is the curvature of objective spacetime by mass, so is attention the curvature of subjective spacetime by information.
Systemic delivery of a connexin43 hemichannel blocking mimetic peptide in rats improves hindlimb locomotor function following spinal cord injury

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A major challenge in the management of spinal cord injury is the development of effective treatments that can be delivered to patients in a timely manner following a traumatic accident. In a rat model of spinal cord injury a mimetic peptide, Peptide5 (P5), against the gap junction protein connexin43, has been previously shown to reduce tissue damage and improve functional outcomes when delivered directly to the lesion. In this study we asked whether acute systemic delivery of peptide5 at connexin43 hemichannel blocking doses is protective. Intraperitoneal injections of P5 or control scrambled peptide (SP) were given immediately after a mild contusion injury in rats using the NYU impactor, with injections repeated at 2 and 4 hours post-injury. Rats were euthanised at 8 hours (n=8), 2 weeks (n=32) or 6 weeks (n=32) post-injury. Open field and error ladder tests showed an improvement in hindlimb locomotor function in P5 treated rats between 3 and 6 weeks post-injury (p<0.05). Immunohistochemistry results on longitudinal tissue samples showed that P5 treatment reduced connexin43 and increased phosphorylated connexin43 at 8 hours compared to SP (p<0.05). At 2 weeks, lesion size, and the astrocytic (GFAP), macrophage and microglial (ED1/IBA1) response were decreased in P5 animals (p<0.05). In addition, neuronal (NeuN) numbers were also higher in the P5 treated animals compared to the SP rats (p<0.05) at 2 weeks. These results suggest that Peptide5, administered systemically to block the pathological opening of connexin43 hemichannels, has a positive effect in ameliorating the damage resulting from spinal cord injury.
Comparison of the injury and innate immune cell response over a 6 week period after spinal cord injury in neonates, juvenile and adult rats

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Background: Spinal Cord Injury (SCI) is a complex pathology with a high impact. There exists a trend for a better functional recovery in younger patients, compared to adults, which is also reported for animal studies, however the reasons for this and potential impact on therapies are yet to be elucidated. Inflammation has been shown to play a significant role in central nervous system (CNS) pathologies, and SCI is no exception.

Methods: Using a mild contusion injury model from a NYU impactor adult (9wk), juvenile (5wk) and infant (P7) Spague-Dawley rats were compared at 24hrs, 1wk, 2wks and 6wks post-injury (n=108). To examine the injury progression the lesion area and the prevalence of swollen axons were measured and compared between groups. The innate cells in the inflammatory response were examined using neutrophil counts and ED1/IBA1 double labelling for microglia/macrophages.

Results: This study found a decreased inflammatory response in the neonates, compared to the mature animals. This was demonstrated by decreased neutrophil infiltration, macrophage and microglial activation in the neonate groups compared to the adult and juvenile groups at all 4 time points. There were also greater proportions of ramified microglia visible in the neonates.

Conclusions: These results point to significant differences in the inflammatory response between infants and adults, which may contribute to the observed better recovery in young patients. This highlights a therapeutic potential if we are able to mirror and manipulate this response in patients of all ages; however much greater exploration in this area is required.
The response of endogenous neural progenitor cells throughout the neuroaxis after a rat spinal cord contusion injury

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Background: Spinal cord injury (SCI) leads to the destruction of neuronal and glial cells causing motor function deficit within an individual. There is currently no cure for SCI. It’s been reported that there is a niche of ependymal cells at the neuroaxis called tanycytes exhibiting endogenous neural progenitor cell (eNPC) qualities where eNPC have been shown to proliferate and differentiate during the acute stages of SCI. Little is known about the extent of the eNPC response following traumatic SCI.

Methods: 25 Sprague-Dawley rats underwent a T10 spinal cord contusion injury and spinal cords were dissected at 24-hours to examine eNPC response. Frozen sections of the third ventricle, cervical, 3 regions of the thoracic injury and lumbar segments were cut at 15μm. Astrocytic and eNPC response were determined using immunohistochemistry using antibodies against glial fibrillary acidic protein (GFAP) and nestin respectively.

Results: GFAP reactivity was significantly high only at the SCI site (ANOVA; P<0.001) indicating a localised astrocytic response. In contrast, nestin reactivity at the ependymal layer was high throughout the spinal cord in the injured group indicating a systemic eNPC response. No significant difference in nestin reactivity were found at the third ventricle between the injured and control groups (Bonferroni post-hoc; P<0.05), although this was high in both groups.

Conclusion: The response of eNPC should be further investigated in other regions lining the neuroaxis such as the aqueduct, fourth ventricle, and brain stem. Determining the extent of eNPC response is important in considering eNPC manipulation in SCI repair and regeneration.
Treatment with connexin-43 mimetic peptide, Peptide5, reduces pain hypersensitivity in a mouse model of neuropathic pain

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Neuropathic pain is a debilitating condition often caused by nervous system damage, such as peripheral nerve injury. Spinal astrogliosis, implicated in neuropathic pain, is associated with the opening of undocked hemichannels and the efflux of small excitatory molecules that contribute to neuroinflammation, neuronal excitability and central sensitisation. Astrocytes primarily form hemichannels using the protein connexin-43 (Cx43), thus blockade of Cx43 using a mimetic peptide, Peptide5, is a promising target for the inhibition of neuropathic pain. Mice (n=4/group) were subjected to a chronic constriction injury (CCI) of the sciatic nerve (a model of neuropathic pain) and Cx43 expression in the nervous system was examined. Another group of mice were tested for mechanical pain sensitivity using vonFrey filaments. Ten days following injury, mice (n=6/group) received a single spinal (intrathecal) injection of Peptide5 (20µM), a scrambled peptide (20µM) or saline control, followed by pain hypersensitivity tests at 8 and 24hours post-injection. We found that CCI mice had a 2-fold increase in Cx43 protein expression in the spinal cord (p<0.05). Pain behavioural analysis confirmed that neuropathic pain was established at day 7 (p<0.05). Mice treated with Peptide5 had significantly reduced mechanical pain hypersensitivity at 8hours post-injection compared to control CCI mice (p<0.05), with an average 5-fold reduction in total number of responses to vonFrey filaments, compared to saline controls (p<0.05). Our findings demonstrate that spinal delivery of Peptide5 is effective in reducing mechanical pain hypersensitivity following nerve injury and suggest that the reduction in neuropathic pain results from the specific closing of Cx43 hemichannels.
Exploring the structure activity relationships of different halogen containing piperazine and diazepane compounds targeting the α4β2 subtype of nicotinic acetylcholine receptors

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Background: The α4β2 subtype of the nicotinic acetylcholine receptor (nAChR) has been pursued as a drug target for treatment of psychiatric and neurodegenerative disorders, smoking cessation aids for decades and more recently, it has been studied in the area of neuropathic pain. The aim of my Master of Philosophy Research project is to find an agonist, moreover a superagonist for the α4β2 subtype of the nicotinic acetylcholine receptor and also, to explore the structure activity relationships between the halogen containing compounds and the two different stoichiometries of the α4β2 subtype of the nAChR.

Methods: Using two-electrode voltage-clamp electrophysiology in - previously α4β2 nAChR RNA injected - Xenopus laevis oocytes

Results: The results are shown on the diagrams made with GraphPad Prism 6. The results are the recorded data compared to the maximal efficacy of the acetylchol in the oocytes.

Conclusions: The electrophysiology results of the explored compounds, their effects on the low and high sensitivity sites of the α4β2 nAChR, and the structure activity relationships between the halogen containing piperazine/diazepane compounds and the receptor. Activation of the cholinergic pathways elicits antinociceptive effects, which means finding a successful agonist or a superagonist would lead to a new type of analgesic dealing with chronic pain.
The effect of varying ratios of α4, β2, and δ cRNA subunits on the GABAA receptor stoichiometry

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Background: δ-containing γ-aminobutyric acid type-A receptors (GABAAR) are exclusively expressed on extrasynaptic sites and mediate tonic inhibition. These receptors are important targets for neurosteroid, alcohol, and anesthetics and have been associated with numerous neurodegenerative and psychiatric disorders. Thus, δ-containing GABAAR are potential therapeutic targets for drug development. However, significant variation in the pharmacology of these receptors is often reported in recombinant systems. We hypothesize that differences in pharmacology of δ-containing receptors are due to variability in receptor stoichiometries.

Methods: Two-electrode voltage clamp was used to study the influence of varying the amount of α4, β2, and δ cRNA injected to Xenopus oocytes. Concentration-response curves (CRC) to GABA were measured along with the modulation and direct activation by δ-selective compound 2 (DS2).

Results: GABA CRC at oocytes injected with α4+β2+δ cRNA in ratios of 1:1:1, 1:1:5, 5:5:1, 1:5:1, and 1:5:5 had EC50 values ranging from 140 to 720 nM. 300 nM DS2 elicited large inward currents of 68-103% of the maximum GABA-elicited currents at these ratios. CRC of GABA at oocytes that were injected with 5:1:1 and 5:1:5 ratio of α4+β2+δ had higher EC50 values of 1.6 μM. The activation of DS2 on the 5:1:5 and 5:1:1 ratios were significantly lower than other ratios (P < 0.05, one-way ANOVA).

Conclusions: At least two stoichiometries were expressed and each of the expressed stoichiometry responded differently to GABA and DS2. Under our conditions, varying the amount of α4 and β2 but not δ has a substantial role in the stoichiometry.
The pharmacological characterisation of kavain at GABA<sub>A</sub> receptors

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The pepper plant kava (Piper methysticum) has been an integral part of the Pacific Islander culture, but is also a popular alternative medicine to treat insomnia and anxiety in western societies. The clinical effects of kava are mediated by a group of chemicals called kavalactones, and GABA<sub>A</sub> receptors (GABA<sub>A</sub>Rs) have been proposed to be a possible target. In this study, we evaluated the activity of kavain, one of the major kavalactones at human recombinant α1β2, β2γ2L, αxβ2γ2L (x = 1, 2, 3 and 5), α1βxγ2L (x = 1, 2 and 3) and α4β2δ GABA<sub>A</sub>Rs expressed in Xenopus oocytes using the two-electrode voltage clamp technique. We found that kavain positively modulates all receptors regardless of the subunit composition. Using α1β2γ2L and α4β2δ as the representative isoforms of synaptic and extrasynaptic GABA<sub>A</sub>Rs respectively, we found that kavain only enhances α1β2γ2L GABA<sub>A</sub>Rs at GABA concentrations below EC<sub>45</sub>, but enhances maximal GABA responses at α4β2δ GABA<sub>A</sub>Rs. To understand the pharmacodynamic interaction of kavain with other GABA<sub>A</sub>R ligands, we co-applied GABA, kavain and other positive modulators such as diazepam, allopregnanolone, DS2, etomidate and propofol, and found that the combinations resulted in infra-additive enhancement. Mutational studies showed that while α1M236W, β2M286W and β3N265M mutations affected general anaesthetics’ sensitivity, kavain’s modulation was only reduced at β3N265M. This finding suggests that kavain may share similar mechanisms with general anaesthetics, but may differ in their molecular determinants. Previous work implicating the role of GABA<sub>A</sub>Rs in kavalactones’ actions was inconclusive, but our study demonstrates for the first time that a kavalactone is able to directly modulate GABA<sub>A</sub>Rs.
PTSD, stress and anxiety

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Stress and the New South Wales Police Force: The prevalence of various coping mechanisms

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Background: Policing is romanticised as a stressful occupation, wherein officers abuse alcohol and drugs to ‘cope’. There is a higher incidence of physical and mental disorders within policing attributable to stress; however, contention exists as to which coping strategies police are employing. Hence, the aim of this project is to identify the prevalence of coping mechanisms in police officers and its relationship to their perception of stress.

Methods: Data was obtained from 235 general duties police officers (164 males; 31.20 ± 8.53 years) after attending ten local area commands across New South Wales (NSW). Subjects were asked to complete a questionnaire battery which included the Revised Ways of Coping Questionnaire (WCQR) and the Lifestyle Appraisal Questionnaire (LAQ). Salivary samples were collected before and after shift, to be analysed for cortisol via high-performance liquid chromatography mass spectrometry (HPLC-MS).

Results: Preliminary exploratory analysis identified 33% of subjects reporting perceptions of stress which were worse than normal ranges (values drawn from the LAQ). The most prevalent coping mechanisms (WCQR) were planful-problem solving (60.13%) and seeking social support (52.92%), while confrontive coping (44.83%) and escape-avoidance (41.41%) were the least frequently employed. Further, lower planful-problem solving (r=-0.23, p<0.01) and higher escape-avoidance (r=0.48, p<0.001) coping strategies were significantly correlated with greater perceptions of stress. Salivary cortisol HPLC-MS is currently being conducted.

Conclusions: Based on preliminary findings, the majority of police officers’ perceptions of stress are equal to or better than the general public, and this is likely due to the higher prevalence of approach-based behavioural coping strategies. However, further research is required to determine whether these positive coping mechanisms are inherent or learned. The outcomes of this study have the potential to improve stress management and reduce the disease burden attributable to stress, thereby directly benefiting the NSW Police Force and subsequently the wider community.
Childhood interpersonal trauma exposure is associated with enhanced electrophysiological responses to threat faces in adults with PTSD

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Background: Interpersonal trauma exposure occurring early in life predicts significantly increased risks of adult psychopathology, including posttraumatic stress disorder (PTSD). Children and adults with interpersonal trauma exposure or anxiety disorders also display enhanced neural responses to threat faces. Given PTSD is associated with enhanced neural response to threat cues, we expected childhood interpersonal compared to non-interpersonal or adult trauma exposure to predict relatively greater neural response to threat faces versus non-threat faces in adults with PTSD.

Methods: N170 peak amplitude differences between threat (Fear/Angry) versus non-threat (Happy/Neutral) faces at temporo-occipital sites (T5, T6) during nonconscious and conscious conditions were calculated in 69 adults (aged 18-64 years, 61% women, 75% right-handed) with syndromal or subsyndromal PTSD. N170 peak amplitudes for threat versus non-threat faces were then subjected to hierarchical multiple regression analysis. Severity of childhood interpersonal and non-interpersonal trauma exposure, as well as adult trauma, were entered as predictors of interest after controlling for PTSD symptoms severity and socio-demographic factors.

Results: Greater severity of childhood interpersonal trauma exposure was associated with greater N170 peak amplitudes for nonconscious Fear versus Happy/Neutral faces and conscious Angry versus Neutral faces at T5. The converse effect was observed for childhood non-interpersonal trauma exposure.

Conclusion: Exposure to childhood interpersonal trauma potentiates early neural processing of threat faces, even in the absence of awareness. Enhanced automatic processing of threat faces is a likely contributor to the increased risks of PTSD in adults exposed to childhood interpersonal trauma.
Predicted vs. random chronic stress, effects on cell morphology and learning and decision based behaviour.

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**Background:** Chronic stress has been shown to dramatically affect the brain on a molecular and cellular level, changing dendritic morphology in the prefrontal and sub-cortices to a degree that changes in grey matter volume become evident. Recent evidence has revealed that neurons go through region specific atrophy and proliferation under stress. These regions are specifically involved in the circuitry of learning and decision based behaviour. Further evidence has indicated that control of an acute stressor removes all negative effect of said stressor on the animal.

**Methods:** To replicate this in a chronic stress paradigm we have used prediction as a form of control. We investigated the effects predicted and random chronic restraint stress had on rat dendritic and spine morphology within a large battery of regions, and how any changes within these regions may relate to any changes in performance in learning and decision based behavioural tasks.

**Results:** These results support previous evidence that chronic stress changes dendrite and spine morphology and performance in learning and decision based tasks. Predicted stress animals showed fewer affected regions of interest, as well as less dendritic change in those regions still effected. Further predicted stress animals showed almost no deleterious effects of stress on behavioural measures.

**Conclusions:** Prediction of a stressor appears to offer the same protective effects control of a stressor does; removing almost all the harmful effects stress has on the brain and mind. Further the protective effects appear to carry across into chronic levels of stress.
Inhibition of the α9α10-nACh receptor: Good pain relief or a side effect liability?

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Background: The α9α10 subtype of nicotinic acetylcholine receptors (nAChRs) is being pursued as a novel target for pharmacological analgesic agents. However, evidence to support the involvement of this receptor in pain perception and analgesia is mostly indirect, coming from pharmacological studies that use inhibitors of varying specificity. There is now evidence that α9α10-nAChR-inhibition does not account for the analgesic effects of those pharmacological agents. Conversely, inhibition of α9α10-nAChRs may affect the regulation of affective responses to stress, which potentially represents a previously overlooked side effect of α9α10-nAChR-inhibiting analgesics.

Methods:
In order to determine the importance of the α9α10-nAChR in affective regulation, mouse models of stress, depression-like and anxiety-like behaviour were used to compare wildtype (WT) mice with animals with a germline deletion of the α9α10-nACh (knockout (KO) mice). Home-cage (IntelliCage) activity was also observed to determine broader consequences of deletion (or, by extension, inhibition) of the receptor.

Results: In naïve, non-stressed animals, behavioural and physiological (corticosterone) indices were largely comparable between the WT and KO mice, with the only divergence being in the circadian rhythms. After stress (restraint or cognitive challenge), significant depression-like and anxiety-like behaviour emerged in the KO animals, while the physiological responses showed significant dysregulation in the KO mice.

Conclusions: The present findings emphasise the need for caution in the reliance on pharmacological agents to characterise the function of in vivo proteins. Inhibition of the α9α10-nAChR by pharmacological agents (analgesic or otherwise) may cause hitherto unforeseen side effects by altering the affective response to stress.
Impaired fear extinction retention following consumption of high fat high sugar diet during adolescence

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Adolescence is a period of increased vulnerability to the development of anxiety and mental health disorders, and is a window of heightened neuroplasticity, particularly in the maturing prefrontal cortex (PFC). During adolescence the neural circuits driving behaviour may be especially sensitive to environmental influences. Adolescents are the highest consumers of junk foods, but little is known about the effects of over-consumption of palatable high fat high sugar “junk” foods on emotional memories and PFC maturation. We examined the impact of 2 hours consumption of a high fat high sugar (HFHS) food per day during adolescence on fear inhibition in young adult rats. Adult rats exposed to the HFHS diet in adolescence exhibited impaired retention of fear extinction, but showed no differences in the rate of fear acquisition or extinction learning compared to rats fed a standard diet. We also examined the effect of a HFHS diet on 1) GABAergic parvalbumin-expressing inhibitory interneurons neurons which functionally mature in the PFC during adolescence, and 2) ΔFosB, a stable transcription factor marker which accumulates in the PFC in response to chronic stimuli. Immunohistochemical analysis of the medial PFC revealed that animals fed the HFHS diet had fewer parvalbumin-expressing interneurons and increased levels of FosB/ΔFosB expression in the infralimbic PFC, a region implicated in fear inhibition. These findings demonstrate that a HFHS diet during adolescence is associated with reductions of prefrontal parvalbumin neurons and impaired fear inhibition in adulthood, and may indicate diet-induced alterations in excitatory/inhibitory balance and gene expression in the PFC.
For whom the fear returns: Individual differences in relapse

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Background: The World Health Organisation estimates anxiety and depression will be the second most burdensome disease in the world by 2020. As such, effective treatment options for mental illness are needed. While treatments for psychopathology are improving, relapse remains a major issue in regards to long-term maintenance of treatment gains. An important consideration that has not yet been examined is whether some individuals are more susceptible to relapse than others. Using Pavlovian fear conditioning, an animal model of anxiety, I explored individual differences in relapse of fear.

Methods: Animals were trained to fear a white-noise by pairing it with foot-shock. Animals then underwent extinction training; the number of white-noise presentations required for the animal to stop showing fear was used to classify animals as either “fast” or “slow” extinguishers. Animals were then tested for renewal (Experiment 1) or spontaneous recovery of fear (Experiment 2).

Results: In Experiment 1 “slow” but not “fast” extinguishers showed ABC renewal, and both “slow” and “fast” extinguishers showed ABA renewal. In Experiment 2, “slow” but not “fast” extinguishers showed spontaneous recovery with an 8 day retention interval, however both “fast” and “slow” extinguishers showed spontaneous recovery with a 29 day retention interval.

Conclusions: Our research shows that while both “fast” and “slow” extinguishers show relapse of fear under some conditions (i.e., ABA renewal or a long retention interval), “slow” extinguishers are more susceptible to relapse (over time and in altered contexts). These findings have implications for identifying those most at risk for relapse following treatment.
Cortical perineuronal nets, parvalbumin neurons, and fear inhibition in adolescent rats

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Perineuronal nets (PNNs) are extracellular matrix structures that preferentially surround and protect mature GABAergic neurons expressing parvalbumin (PV). PV neurons functionally mature in the prefrontal cortex during adolescence, a time when PNN expression increases. Aberrant PNN and PV neuronal maturation in humans may contribute to psychological disorders, many of which often emerge during childhood and adolescence. We examined the behavioural effect of impairing the maturation of prefrontal PV neurons through repeated exposure to an NMDA receptor antagonist in early adolescence. Adolescent rats received daily injections of MK801 (0.1 mg/kg), or saline, for 5 days from P27-P31. Rats were trained to fear a white-noise CS, given two days of extinction training, and tested on consecutive days (from P34). Saline-treated rats showed good retention of extinction after two days of extinction training. In contrast, exposure to MK801 in early adolescence caused impaired fear inhibition despite extensive extinction training. That is, MK801-treated rats exhibited poorer extinction learning on day 2 which contributed to higher fear at test. MK801 exposure reduced the number of PV neurons, but not PNNs, in the infralimbic cortex, a region implicated in fear inhibition. The effects of exposure to MK801 in early adolescence persisted into adulthood. These findings suggest that adolescence is an important time for the maturation of prefrontal PV inhibitory neurons and that reductions of prefrontal PV neurons during this stage of development leads to impaired fear inhibition.
Mobile phone-assisted psychological wellbeing for the prevention of coronary heart disease – randomized clinical trial

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Background: Psychological factors, like depression and anxiety are among the major contributing modifiable risk factors for the development of coronary artery disease (CAD). Text messaging may be a preventive tool in reducing psychological distress among CHD patients and healthy care givers. This study aimed to explore the effectiveness of a text messaging intervention for improving the mental and physical health of patients with CHD.

Methods: A prospective, randomized, clinical trial was conducted in 3 cardiac specific tertiary care hospitals in Karachi, Pakistan. Participants were patients who had their first cardiac events and their respective nominated care-givers. Patients and their care-givers were randomized into two groups, intervention (IG) or usual care group without intervention (NIG). Research assistants, recruiting the subjects were blinded to the IG or NIG. Validated Urdu version of PHQ9 and GAD7 was implemented at baseline and at every subsequent follow-ups. Positive psychological wellbeing motivational text messages were sent twice weekly to the intervention group.

Results: Analysis revealed that motivational psychological wellbeing SMS messages through mobile phone does not have any significant effect in reducing depression and anxiety among intervention group as compared to non-intervention group. Although female were more depressed and anxious in both group, but trend remain the same till the end of study.

Conclusions: SMS text messaging alone to improve psychological wellbeing was not effective. Keeping in view of the experiences gained from this study, future study with short term face to face motivational sessions with support of long term SMS text messaging is recommended.
Learning and Memory

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Learning and choice in a complex and dynamic world

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Background: Goal-Directed Learning and Executive Functions allow organisms to develop, apply, maintain and alter appropriate patterns of behaviour in a dynamic world. Much is still unknown about the mechanisms that control complex and integrative higher order functions in the brain. Developing robust and species-relevant behavioural tests is essential for improving our understanding of healthy and disordered neural systems.

Methods: We have developed novel and fully automated methods for investigating the cognitive functions of mus musculus in the IntelliCage which enables testing in a more complex and naturalistic social setting for this species. Group housed adult male C57BL/6 mice were required to learn one of either two discriminatory choice tasks to gain access to water in this home cage setting: a Visual cue-Dependent [VD] task or a Response-Dependent [RD] task. Once an animal reached acquisition criterion the task contingencies were changed in one of either two ways: an Extradimensional Shift [EDS; between-modality] or a Rule Reversal [RR; within-modality].

Results: Robust learning was observed in both discriminatory choice tests, though animals required significantly fewer sessions to acquire the RD task compared to the VD task. Performance disturbances after EDS and RR were consistent with expected performances after such task changes. Close inspection of individual performance profiles revealed step-like transitions in behaviour as animals adapted to the altered task contingencies.

Conclusions: This automated approach in a more naturalistic setting allows for a novel and highly detailed examination of the evolution of choice behaviour during all phases of learning and adaptation to contingency changes.
Upregulation of cortico-cerebellar functional connectivity after motor learning

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Background: Interactions between the cerebellum and primary motor cortex are crucial for the acquisition of new motor skills. Recent neuroimaging studies indicate that learning motor skills is associated with subsequent modulation of resting-state functional connectivity in the cerebellar and cerebral cortices. The neuronal processes underlying the motor-learning induced plasticity are not well understood.

Methods: We investigate changes in functional connectivity in twenty young adults using electroencephalography (EEG) recorded after the performance of a single session of a dynamic motor task. Source activity was reconstructed in 90 anatomically defined regions of interest in the cortex and cerebellum. Functional connectivity between all 90 regions was estimated using coherence analysis. Significant changes in resting-state connectivity were assessed using partial least squares.

Results: We found that subjects adapted their motor performance and showed improved accuracy but slower movement times. Several connections were significantly upregulated after motor training, in particular connections within the cerebellum and between the cerebellum and motor cortex. Increased connectivity was confined to specific frequency ranges in the alpha and beta frequency bands. The phase spectra of the cortico-cerebellar connections revealed greater phase difference after training, indicative of a longer delay from the cortex to the cerebellum.

Conclusions: These findings show a reorganization of intrinsic cortico-cerebellar connectivity related to motor adaption and demonstrate the potential of EEG connectivity analysis in source-space to reveal the neuronal processes that underpin neural plasticity. This approach has great potential to assess neural plasticity induced by other interventions such as brain stimulation.
Using peripheral electrical stimulation to increase brain excitability and enhance the rate of motor learning

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Background: Peripheral electrical stimulation (PES) is used extensively in rehabilitation for pain management and recovery of muscle function. Recent studies demonstrate changes to motor cortex (M1) excitability following application of PES. Specifically, motor stimulation increases M1 excitability while sensory stimulation decreases M1 excitability. Interestingly, research also suggests that raised M1 excitability facilitates motor learning while reductions in excitability impair motor learning. Here for the first time, we examined whether PES-induced increases and decreases in M1 excitability influence motor learning.

Methods: Two PES interventions were delivered to the first dorsal interosseous (FDI) in 14 participants, one intervention increased excitability (motor stimulation) and the other decreased excitability (sensory stimulation). Motor evoked potential amplitudes were recorded from FDI before and after each intervention to monitor changes in M1 excitability. Following PES, participants were asked to learn a visuomotor rotation task. This required participants to learn how to accurately move a cursor (on a computer screen) towards virtual targets by performing index finger movements when the screen was rotated 30 degrees left.

Results: A power fit analysis of the form $y=ax^b$ revealed that the rate of learning a visuomotor rotation task was significantly faster following PES-induced increases in M1 excitability compared to PES-induced decreases in excitability ($p=0.038$).

Conclusion: Increased M1 excitability, induced by PES, enhanced the rate of visuomotor learning when compared with PES-induced decreases in M1 excitability. This investigation has implications for the use of PES in the rehabilitation of neurological and musculoskeletal conditions where learning, or re-learning, of movement skills is impaired.
Timing in taste aversion learning: When is interference most effective?

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Background: As Revusky (1971) first demonstrated, giving a rat an additional taste during the interval between a target taste and an injection of lithium chloride can strongly interfere with acquisition of an aversion to the target taste. This set of experiments examined the question of when interference would be most effective in overshadowing the acquisition of long delay taste aversion learning. The general aim was to understand the mechanisms responsible for 1-trial serial overshadowing in other preparations where manipulation of the timing of the interfering event occurs is less easy to control.

Methods and Results: In Experiment 1, rats drank sucrose, the target solution, followed by a hydrochloric acid (HCl) solution before lithium injection some time later; HCl was presented either early or late in the interval. The late condition was found to produce greater overshadowing than the early condition. Experiment 2 found that even placement in a different context—a event that normally produces little overshadowing of a CTA—produced one-trial overshadowing of a sucrose aversion as long as the context was novel and exposure to it occurred immediately before lithium injection.

Conclusions: No current account of one-trial overshadowing predicts that a late event produces more overshadowing than an early event. This result can, however, be accommodated within a modified version of the Rescorla-Wagner model (1972) with the assumption that a sickness episode consists of a succession of bouts and the assumption that context-event associations are important in long-delay CTA.
Deconstructing episodic memory processes in the dementias

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Background: Episodic memory impairment represents one of the hallmark clinical features of Alzheimer’s disease (AD) attributable to the degeneration of medial temporal and parietal regions of the brain. In contrast, a somewhat paradoxical profile of relatively intact episodic memory, particularly for non-verbal material, is observed in semantic dementia (SD), despite marked atrophy of a crucial memory structure – the hippocampus.

Methods: We investigated the neural substrates of episodic memory retrieval across verbal and non-verbal domains in 20 patients with a diagnosis of SD and 21 disease-matched cases of AD and compared their performance to that of 35 age- and education-matched healthy older Controls. Participants underwent T₁-weighted imaging for structural neuroimaging analyses.

Results: AD patients showed characteristic memory deficits irrespective of modality. In contrast, memory deficits in SD were modality-specific occurring exclusively on the verbal task. Voxel-based morphometry analyses revealed significant overlap in the neural correlates of verbal episodic memory in AD and SD involving predominantly anteromedial regions, including the bilateral hippocampi. Controlling for semantic processing served to ameliorate these deficits in SD. Memory impairments, however, persisted in AD reflecting the breakdown of a distributed network of frontal, medial temporal, and parietal regions.

Conclusions: Episodic memory deficits in SD arise largely as a consequence of the verbal loading of traditional tasks. Despite significant hippocampal atrophy, the functional integrity of frontal and parietal regions likely enables new learning to occur in SD. Our findings underscore the inherent complexity of the episodic memory circuitry and the importance of regions beyond the medial temporal lobes.
Use of a maze test to evaluate disease progression in Merino sheep with neuronal ceroid lipofuscinosis.

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Background: Neuronal ceroid lipofuscinoses (NCL) are the most common inherited childhood onset neurodegenerative disorders and are characterised by the accumulation of autofluorescent lysosomal storage material, progressive blindness and neurodegeneration. The disease mechanism is poorly understood and there is no cure. Ovine models for NCL have been pivotal in the investigation of the disease and we describe the use of a behavioural (maze) test for sheep affected with a natural occurring recessive CLN6 (c.184C>T) variant, with the aim to provide a non-invasive method to evaluate disease progression in therapeutic trials.

Methods: 29 Merino ewes (7 affected, 10 heterozygote, 12 normal) were assessed in a maze test previously developed for sheep to assess cognitive function (spatial memory and learning). After an initial learning phase over 3 consecutive days at an age of approximately 4.5 months (before onset of clinical signs), sheep were assessed monthly to a current age of 9.5 months.

Results: No significant differences were observed for all groups during the first three days of the trial and all groups showed improved cognitive performance in negotiating the maze at day three. In the following three months no significant differences were observed between groups. At approximately 8.5 months of age the group of affected sheep had a significant lower maze performance when compared with controls.

Conclusions: The maze test allows objective assessment of disease progression in NCL affected sheep with decrease in maze performance occurring around the same time as previously described onset of behavioural changes in affected sheep.
Differential associations between quantitative electroencephalogram markers and memory performance in mild cognitive impairment: influence of obstructive sleep apnea.

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Introduction: Both mild cognitive impairment (MCI) and obstructive sleep apnoea (OSA) place older adults at risk of dementia, however not all experience further cognitive decline. Analysis of brain activity during sleep (such as quantitative electroencephalography; qEEG) has been associated with cognitive function during the day, and may be important in understanding the pathophysiology underpinning the role of OSA in neurodegenerative diseases and memory decline.

Methods: 15 older adults (>50 years) with both moderate OSA and MCI (MCI+), 21 older adults with MCI only (MCI-), and 19 aged-matched controls completed neuropsychological and medical assessments, and overnight sleep studies. Power spectral analysis (PSA) of the EEG (C3 derivation) was performed after previously validated automatic artefact removal, in 30-second epochs for sigma frequency (12-15Hz; a surrogate measure of sleep spindle activity).

Results: There were no significant differences in EEG measures across the three groups. There were differences in memory performance between MCI- and controls, and MCI+ and controls, but not between MCI- and MCI+ groups. Spectral power in the sigma frequency band was significantly correlated with tests of verbal memory in the MCI+ group (r range -0.55-0.58, p < 0.05), but not in the MCI- or control groups.

Discussion: These preliminary findings indicate that there is a difference in the relationship between brain activity during sleep and daytime memory in older adults depending on the presence of OSA. Further studies looking at longitudinal qEEG measurements and cognitive functioning should help to further characterise any relationships.
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Understanding the gain of function ADNFLE mutations in heteromeric α4β2 neuronal nicotinic receptors

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Autosomal Dominant Frontal Lobe Epilepsy (ADNFLE) is partial epilepsy often arising during stage 2 of sleep, and is characterized by clusters of complex hyperkinetic seizures. Long term effects like memory impairment and neuropsychological disturbances have been reported in ADNFLE patients. ADNFLE mutations have been detected in neuronal nicotinic receptors (nAChRs), Na+ gated K+ channel (KCNT1), Corticotropin-release hormone and DEPD5 protein. nAChRs are pentameric ion channel permeable to cations and are activated by the endogenous agonist Acetylcholine (ACh). They play an important role in brain functions including cognition and memory. ADNFLE mutations that increase the sensitivity of the receptor to ACh have been identified in the α4 and β2 nAChR subunits. These subunits form the α4β2 subtype, the most prevalent nAChR subtype found in the brain that exists in two stoichiometries, (α4)2(β2)3 and (α4)3(β2)2, with distinct pharmacological properties driven by the presence of two distinct ACh-binding interfaces, α4-α4 and α4-β2, on α4β2 nAChRs. The partial agonists’ sazetidine-A and TC-2559 activate the receptor by binding only at the α4-β2 interface.

Using two-electrode electrophysiology in Xenopus oocyte system, my work involved characterizing the functional effects of ADNFLE mutations in α4 & β2 subunits. Using ACh and ligands that selectively bind at α4-β2 and α4-α4 binding interfaces, my work is aimed to understand the mechanism of gain of function in (α4)3(β2)2 nAChR. There was an increase in the efficacy of Sazatidine-A and TC-2559 in mutant receptors when compared to wild-type. This study signifies understanding of the gain of function ADNFLE mutations in heteromeric α4β2 nAChR and sheds light on possible ways to treat the underlying disease.
Addiction

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Does Food Addiction exist in children and relationship with diet, weight status and parental feeding style

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**Background:** With increases in obesity and the changing food environment, food addiction research has become increasingly popular both among researchers and lay public. The most commonly used definition for food addiction is derived from mapping the Diagnostic Statistics Manual (DSM) criteria for substance dependence to eating behaviours. Food addiction criteria include: tolerance, withdrawal persistent desire, reduction in social activities, increased time and attention to seek food. The primary aim of this study is to investigate the relationship between parents and children’s food addiction scores. A secondary aim is to determine the association between child food addiction scores, diet, weight status and parental feeding style.

**Methods:** Parents/primary caregivers, of 5 to 12 year-old children, were recruited through Amazon Mechanical Turk. The Food Addiction Survey used in this study consisted of 137 items relating to participant’s demographics, dietary intake, parental feeding practices and addictive eating behaviours (The Yale Food Addiction Survey).

**Results:** Eighteen parents (12.0%; 5 male, 13 female) and 34 children (22.7%; 18 male, 16 female) were classified as food addicted (FAD). Of the 18 parents, meeting the criteria for food addiction, six had children that met the criteria also. Parents of non food addicted children reported a significantly greater Perceived feeding responsibility ($p = <0.01$), whereas parents of food addicted children scored higher for the Restriction ($p = <0.01$) and Pressure to eat ($p = 0.01$) feeding practices.

**Conclusion:** A relationship exists in food addiction between parents and children and relationships with weight and child feeding practices exist.
Limited daily exposure to high fat diet in young rats alters patterns of social behaviour

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Excessive consumption of palatable high energy foods is known to disrupt cognitive function and cause enduring changes to behaviour. Adolescence is a period of neuroplasticity in which the regions of the brain including the prefrontal cortex mature, potentially predisposing a vulnerability to environmental factors such as poor diet. In developed countries, adolescents are the largest consumers of high fat and high sugar “junk” foods. In this study we sought to investigate the impact of high fat diet (HFD) consumption on social interaction in adolescent and young adult rats. Social play is a rewarding behaviour and one of the earliest and most distinctive forms of non-mother-directed social interaction. Social play typically declines across adolescence as the mature behaviour of social investigation becomes dominant. Diet access commenced at postnatal day 28 (P28), rats in the HFD diet condition (N=12) were provided with 2 hours daily access to semi-pure HFD pellets (18.4 kJ/g; 20% fat, 39% sucrose) in addition to chow and water access. Control rats (N=12) had constant access to chow and water. Social interaction behaviours with a novel control rat were studied in adolescence (P42) and in early adulthood (P58) in both HFD and control rats. HFD exposed rats were tested for social behaviours 1-hr and 25-hr following diet access. Overall frequency of social interaction behaviours did not differ between diet groups at either age. However, it was observed that HFD fed rats engaged in significantly higher frequencies of social play as young adults. This observation is indicative of alterations in development of a mature form of social interaction behaviour in HFD consuming rats compared to controls.
Differential effects of acute exposure to a fat plus sugar or liquid sugar diet on central and peripheral inflammation and memory

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High-energy diets impair cognition however, the rapidity of these deficits and the relative contributions of fat and sugar remain unclear. We have previously shown selective hippocampal-dependent memory deficits after 1 to 3 weeks on a cafeteria diet plus 10% sucrose solution (Caf+Sugar), or a regular diet supplemented with 10% sucrose (Sugar). At 1 month, these deficits were strongly correlated with hippocampal inflammation.

To determine whether inflammation was present when the deficits first emerged, here we killed a similar cohort at 2 weeks (n=12/group). The Sugar and Caf+Sugar rats again showed selective hippocampal-dependent memory deficits. However, the Sugar rats had higher hippocampal expression of a number of inflammatory markers including TNF-α and SOCS-3, than the Caf+Sugar rats. White adipose tissue showed the same pattern, Sugar rats had 50-75% higher TNF-α and IL-1β mRNA expression than Caf+Sugar rats. There was a parallel increase in adipose and hippocampal inflammation. No evidence of inflammation was observed in the perirhinal cortex or hypothalamus.

The Sugar rats drank three times more liquid sugar than the Caf+Sugar rats and had higher blood glucose concentrations which were correlated with hippocampal inflammation markers (e.g., TNF-α $r=0.55$, $p=0.004$). Drinking large quantities of liquid sugar would lead to a faster gastric transition, a higher glycaemic response and reduced satiety, which would then promote further consumption. In contrast, the Caf+Sugar rats derived more energy from solid sources of sugar and fat, which would slow gastric transition and produce greater feelings of satiety. Greater fluctuations in blood sugar are known to promote inflammation.
The role of variety and contrast in the magnitude and selectivity of cue-potentiated feeding

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Background: Cue-potentiated feeding (CPF) describes the stimulation of food consumption by initially neutral environmental cues. Determining the selectivity of this effect is important in light of its relevance to overeating and obesity. Few studies of CPF have utilised hyperpalatable ‘junk foods’ (JF) during training, and none have compared the effects of pairing multiple versus a single JF with cues.

Methods: Our CPF paradigm manipulates the number of JF paired with contextual cues. In 4 experiments, adult female rats (N = 102) received intermixed daily exposures (30-min) to a “Plus” context that contained 1 (Single condition) or 3 (Many condition) JF or regular chow (Control), and to a “Minus” context that contained no food (Experiments 1-3) or chow (Experiment 4).

Results: In Experiments 1 and 2, when testing consumption of a non-novel JF not used in training (Froot Loops), only the Many group overate in the Plus relative to the Minus context. In Experiment 3 both Single and Many conditions showed this CPF effect with Froot Loops. To examine contrast effects, Experiment 4 addressed how CPF was affected when chow was provided in the Minus context. CPF effects were not associated with rats’ ‘binge-status’ (pre-training Froot Loop intake) or with body weight in any experiment.

Conclusions: These results indicate that CPF is not always selective to the food/s paired with that cue.
Effect of adenosine 2A receptor knockdown in the nucleus accumbens shell on conditioned reward for methamphetamine

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Background: Addiction to methamphetamine (METH) is a global health problem for which there are no approved pharmacotherapies. The adenosine 2A receptor (A₂A) provides an interesting therapeutic avenue, this receptor modulates reward behaviour for METH (Chesworth et al. 2015. Addiction Biology). Of critical interest was the neural locus where A₂A mediates reward behaviour for METH.

Methods: To address this question, we employed viral-mediated knockdown of A₂A, by injecting the adeno-associated virus Cre-recombinase (AAV-Cre) into the nucleus accumbens shell (NAcc shell) of A₂AloxP/loxP mice. This region was selected due to high A₂A expression and the strong implication of the NAcc shell in reward processing. Following a 3 week transduction period, A₂AloxP/loxP mice injected with AAV-Cre or mCherry (a fluorophore control, n = 10-13 per treatment group) were tested for METH conditioned reward behaviour using conditioned place preference (CPP). Site validation and knockdown quantification was conducted following behavioural assessments.

Results: Our injections resulted in Cre recombinase expression in ~70% of the NAcc shell. Viral mediated knockdown of A₂A had no effect on the development or expression of METH CPP, nor the development or expression of psychomotor sensitization.

Conclusions: These results suggest the NAcc shell may not be the sole locus where A₂A modulates conditioned reward or psychomotor behaviour for METH.
Micro-RNA (miR)-137 and miR-212 expression profiles are altered by cocaine taking in the dorsomedial striatum (DMS) of Sprague Dawley rats screened for addiction behaviours

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Background: We have previously shown that the expression of key synaptic plasticity genes, are significantly decreased, in the dorsomedial striatum (DMS) of addiction/relapse vulnerable animals. Interestingly, miRNA directly involved in the post-transcriptional regulation of these genes were increased in DMS. Here we assessed whether these miRNA::mRNA interactions are dysregulated prior to relapse and extinction training.

Methods: Animals were trained to self-administer cocaine (0.25mg/infusion, n=63) or received yoked saline infusions (n=8), and subsequently completed behavioural tests assessing addiction relevant behaviours, including responding during drug unavailable (NDA) periods and progressive ratio (PR) breakpoint. A computational model was used to identify ‘addiction’ resilient (n=8) or vulnerable (n=8) animals. qPCR was performed to assess mRNA and miRNA expression between cocaine, saline groups and resilient versus vulnerable groups.

Results: We found significant decreases in Arc and Drd1 expression in the DMS of cocaine animals, with no change between vulnerable and resilient groups. Further, we found that miR-137 expression was altered in the DMS in cocaine versus saline animals, while miR-212 was increased in the DMS of addiction vulnerable versus resilient groups.

Conclusion: Given the importance of the DMS in goal-directed behaviour our findings are consistent with the hypothesis that impairments in the ability to evoke plasticity in this brain area may lead to the development of addiction-like habits. Presumably however, as most changes were observed in all cocaine-exposed animals; only addiction vulnerable animals display persistent plasticity associated gene expression deficits.
Rats selectively choose high doses of nicotine in compensation for and anticipation of restricted access to nicotine

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Background: People adapt to restrictions on when and where they can smoke by adjust their smoking patterns: they increase their rate of nicotine intake both before and after a period when they cannot smoke. The present study used an animal model, nicotine intravenous self-administration in rats, to investigate the factors that underpin the shift towards greater nicotine intake under restricted access conditions.

Methods: In Experiment 1, rats were trained to choose between three doses of nicotine (15, 30 or 60 µg/kg/infusion). Restricted access was modelled by progressively increasing the post-infusion time-out interval from 20 s (free access) to 300 s (restricted access). Experiment 2 used a procedure in which a signalled time-out interval varied within each self-administration session.

Results: Rats equally sampled all doses of nicotine under free access conditions, but exhibited a preference for the highest dose (60 µg) as access was restricted across sessions. This preference was immune to treatment with a partial nicotine receptor agonist, Varenicline, but decreased when the response requirement for the highest dose increased and when rats were returned to conditions of free access. Experiment 2 showed that rats can use a signal of future access conditions to regulate their current dose selection.

Conclusions: Together these results indicate that rats, like people, seek higher doses of nicotine under restricted access conditions. Critically, the preference for a higher dose is not simply a consequence of extended nicotine exposure, but instead, reflects both compensation for and anticipation of a restricted access period.
Effects of chemogenetic and optogenetic manipulation of the striatopallidal pathway on the renewal and reacquisition of extinguished alcohol seeking

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The ventral pallidum (VP) is a key component of the neural circuitry mediating relapse to drug seeking. Using designer receptor exclusively activated by a designer drug (DREADD), we bi-directionally manipulated the VP. We transduced VP with an adeno-associated virus expressing hM3Dq (excitatory) and hM4Di (inhibitory) DREADD. Rats were trained to self-administer alcoholic beer in one context (A), extinguished in a second context (B), tested in the extinction (ABB), in context (A) for renewal and reacquisition. VP contributed to relapse and reacquisition of alcohol seeking. We further studied the role of the nucleus accumbens core (AcbC) to the VP pathway in ABA renewal and reacquisition of alcohol seeking. Rats received application of adenoviral vectors encoding eYFP, ChR2(H134R), or eNpHR3.0 to AcbC and implantation of fibre optic cannulae into VP to permit photostimulation of AcbC terminals there. There was evidence for ABA renewal of alcohol seeking but neither optogenetic excitation nor inhibition of the AcbC-VP pathway affected this renewal. In contrast, optogenetic inhibition of the AcbC-VP striatopallidal pathway did reduce reacquisition of alcohol seeking - as measured either by the number of active nosepokes emitted or by the number of alcohol rewards earned and consumed. Moreover, optogenetic excitation of the AcbC-VP striatopallidal pathway increased the number of magazine entries during reacquisition test. This finding shows the importance of the AcbC-VP pathway in controlling relapse when the drug reinforcer is present on test and is consistent with a role for the AcbC-VP pathway in regulating the hedonic or incentive motivational properties of drug reinforcers.
Neurodegenerative Disorders

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Biological role of ABCA7 in Alzheimer’s disease brain

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Background: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by dementia and abnormal deposits of aggregated amyloid-β in the brain. Recent genome-wide association studies revealed that ABCA7 strongly associates with AD (Nature Genetics 43:429, meta $P = 5.0 \times 10^{-21}$). In vitro evidence suggests that the role of ABCA7 is related to phagocytic activity. Deletion of ABCA7 in a mouse model of AD exacerbates cerebral amyloid-β plaque load, indicating a pathological link between ABCA7 and amyloid-β plaque load. However, the biological role of ABCA7 in the brain in the context of AD is unknown.

Methods: Microglia and macrophages were prepared from ABCA7 knockout (Abca7$^{-/-}$) and wild type mice (n=10) and were tested for their capacity to phagocytose amyloid-β oligomers. In a second study, Abca7$^{-/-}$ and wild type mice were injected intracranially into the hippocampus with a dose of 200 pmol of amyloid-β oligomers. After six days, the mice were euthanized and brain sections prepared for immunohistochemical analysis.

Results: We found that the phagocytic clearance of amyloid-β was significantly reduced ($P < 0.01$) in both microglia and macrophages from Abca7$^{-/-}$ mice compared to wild type mice. Consistent with these results, in vivo phagocytic clearance of amyloid-β oligomers in the hippocampus was substantially reduced in Abca7$^{-/-}$ mice.

Conclusions: These results indicate that ABCA7 mediates phagocytic clearance of amyloid-β in the brain, and reveal, for the first time, a mechanism by which loss of function of ABCA7 increases the susceptibility to AD.
A role for the Alzheimer’s disease-related BACE1 enzyme in regenerating neurons

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Alzheimer’s disease (AD) is a devastating neurodegenerative disease that is pathologically characterized by the deposition of amyloid-beta (Aβ) as extracellular plaques in the brain. BACE1, a transmembrane aspartyl protease, catalyzes the generation of Aβ by producing the initial cleavage of the amyloid precursor protein (APP). We and others have shown that BACE1 protein and activity levels are increased in the AD brain. To date, little is known regarding the physiological role of BACE1 in the human brain. The enzyme is expressed in all tissue with highest expression in the brain. BACE1 plays a role in the myelination of both peripheral and central nervous system axons. The ablation of BACE1 leads to a hypomyelination phenotype. In an attempt to further elucidate the role of BACE1 in the brain, we examined its expression following facial nerve transection. We employed the facial nerve axotomy (FNAx) paradigm in which we axotomized the right facial nerve after its exit through the stylomastoid foramen. This lesion triggers a response (retrograde changes) in the facial nucleus that can be monitored over time. The FNAx model has been extensively investigated and the time course has been documented. We have observed a rapid and sustained up regulation of BACE1 protein expression in activated microglia. In addition, we also observed an increase in BACE1 protein expression in injured neurons in the facial nucleus up to 21 days (longest time-point evaluated) following axotomy. The in vivo expression of BACE1 in activated microglia and motor neurons are novel. This up regulation may constitute a mechanism whereby activated microglial cells aid in clean up and repair processes and neurons react to injury, highlighting novel physiological roles for BACE1 in the CNS.
The effect of exercise on individuals with Dementia with Lewy Bodies: A systematic review

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Background: Individuals with dementia with Lewy bodies (DLB) experience functional decline through Parkinsonism and sedentariness exacerbated by motor, psychiatric and cognitive symptoms. Exercise may improve functional outcomes in Parkinson’s disease (PD), and Alzheimer’s disease (AD). However, the multi-domain nature of DLB symptom cluster results in vulnerable individuals often being excluded from exercise studies evaluating physical function in PD or cognitive function in dementia to avoid confounding results. This review evaluated existing literature reporting the effects of exercise interventions or physical activity (PA) exposure on cluster symptoms in DLB.

Methods: A high-sensitivity search was executed across 19 databases. Peer-reviewed articles of any language and quality, published or unpublished, that analysed effects of isolated exercise/PA on indicative DLB or PD-dementia cohorts were evaluated.

Results: 111,485 articles were initially retrieved; 275 full articles were reviewed and 87.2% subsequently deemed ineligible due to exclusion of participants with coexistence of dementia and Parkinsonism. Five low-quality articles were deemed eligible enrolling 16 participants (14 exercise, 2 control). Interventions were diverse and outcome homogeneity was low. Notably, in exercise participants (n=13) habitual gait speed increased (0.18m/s, 95% CI -0.02, 0.38m/s), exceeding minimal detectable change (0.09m/s) for AD cohorts. Other outcomes appeared to improve modestly in most participants.

Conclusions: Scarce research exists surrounding exercise in DLB. This review confirms high-quality exercise studies for PD, and dementia cohorts consistently exclude DLB participants. Small, uncontrolled samples of participants analysed indicate exercise may improve LBD symptoms. Larger, more robust study designs are needed to explore exercise efficacy, feasibility and clinical relevance.
MAPT mutations and frontotemporal tauopathies: lost in translation?

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Background: Many advances in our understanding of the pathogenesis of neurodegenerative disorders have arisen from studying familial and genetic forms of these diseases. In contrast to other neurodegenerative diseases, patients with frontotemporal lobar degeneration (FTLD) harbouring mutations in the microtubule associated protein tau (MAPT) gene are considered independently to sporadic FTLD in neuropathological diagnostic criteria. Pathologically there are four main subtypes of FTLD: Pick’s disease (PiD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and globular glial tauopathy (GGT). Cases with MAPT mutations show considerable heterogeneity in the biochemistry and neuropathological features observed, making diagnosis more challenging.

Methods: All FTLD cases with a MAPT mutation in the Sydney-Cambridge cohorts were screened for differentiating features used to diagnose FTLD-tau subtypes to determine whether categorical separation of MAPT mutations from FTLD-tau is valid. The type and distribution of tau-immunoreactive neuropathological features were compared between 11 cases with a MAPT mutation (including 3 siblings with a S305S mutation) and 16 FTLD-tau cases (PiD=4, CBD=4, PSP=4, GGT=4).

Results: The neuropathological phenotype associated with MAPT mutations varied between and within families with the same mutation. Each case had similar neuropathological features to one of the FTLD-tau subtypes and could be classified into a comparable diagnostic subtype: PiD (Lys257Thr), CBD (S305S, IVS10+16, R406W), PSP (S305S), GGT (P301L, IVS10+16).

Conclusions: This study demonstrates similarities in neuropathology between genetic and sporadic FTLD-tau indicating that cases with a MAPT mutation should be considered as familial forms of FTLD-tau and on a disease continuum with sporadic FTLD-tau, simplifying neuropathological criteria.
TDP-43 in the hypoglossal nucleus identifies amyotrophic lateral sclerosis in behavioral variant frontotemporal dementia

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The pathological TAR DNA-binding protein 43 (TDP-43) characterizes the distinct clinical syndromes of amyotrophic lateral sclerosis (ALS) and behavioural variant frontotemporal dementia (bvFTD), suggesting that the regional concentration of TDP-43 pathology has most relevance to specific clinical phenotypes. Our recent analysis in 92 patients identified the hypoglossal nucleus as a key brain region in which the presence of TDP-43 could accurately discriminate TDP-43 proteinopathy cases with clinical ALS. The present study set out to validate this association in a further bvFTD cohort. Following institutional approvals, tissue blocks of the hypoglossal nucleus from patients with neuropathological FTLD-TDP and clinical bvFTD (n=29) from the Sydney Brain Bank were sectioned at 10 μm and immunostained with anti-phospho TDP-43 antibody. TDP-43 was identified in the hypoglossal nucleus of 100% (n=12) patients with a dual diagnosis of bvFTD-ALS at presentation, and in 35% (n=6) patients that presented with bvFTD only. A review of the final clinical assessments performed outside of ALS specialist clinics revealed evidence of possible or probable ALS towards the end of disease in 5 of the 6 pure bvFTD cases with hypoglossal TDP-43 (83%), but not in any case without hypoglossal TDP-43 (n=11). In summary, the present study validates grading the presence of TDP-43 in the hypoglossal nucleus for the pathological identification of TDP-43 proteinopathy cases with a clinical ALS diagnosis, extending this to include cases with possible ALS. We suggest the inclusion of simple measures of hypoglossal function in longitudinal studies of patients with bvFTD to identify potential markers of early ALS.
Investigating deficits in motor initiation and cessation in patients with Parkinson’s disease and freezing of gait using a virtual reality paradigm.

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Background: Freezing of gait is a common and disabling symptom in patients with Parkinson’s disease that is associated with deficits in gait initiation and cessation. To date, our understanding of the neurobiological mechanisms underlying these phenomena has been limited by difficulties in reliably eliciting and objectively characterizing such gait phenomena in the research setting. However, recent work has suggested that virtual reality techniques might offer this potential.

Methods: This study utilized a virtual reality (VR) paradigm to explore start hesitation and stop failure in Parkinson’s disease patients both with (Freezers, n = 16) and without (Non-Freezers, n = 16) freezing of gait, as well as healthy, age-matched Controls (n = 12).

Results: We found that Freezers experienced significantly greater start hesitation with more frequent footstep initiation failure during performance of the VR paradigm compared to Non-Freezers. We also found that Freezers experienced a significantly greater proportion of impaired responses to stop cues during the paradigm compared to Non-Freezers. This relative impairment in stopping was restricted to stop cues that required additional cognitive processing.

Conclusions: Our results suggest that virtual reality may provide a useful, safe and objective method for the characterization and investigation of start hesitation and stopping failure in Parkinson’s disease patients with freezing of gait. Future work continuing to combine such virtual reality paradigms with neuroimaging techniques may increase our understanding of these phenomena and promote the development of novel technologies and therapeutic approaches.
Freezing of gait and its associations in the early and advanced clinical motor stages of Parkinson’s disease: a cross-sectional study

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Background: Parkinson’s disease (PD) is a common neurodegenerative disease affecting 1-2\% of the population. Freezing of gait is a common disabling symptom of PD with limited treatment options. It is characterised by brief episodes of inability to step forward. The pathophysiological mechanisms of freezing behaviour are still contentious. The aim of the current study is to investigate the prevalence of freezing of gait and its associations with increasing disease severity to gain a better understanding of the underlying pathophysiology.

Methods: This exploratory study included 389 idiopathic PD patients, divided into four groups; early and advanced PD with freezing of gait, and early and advanced PD without freezing of gait. Motor, cognitive and affective symptoms, REM sleep behaviour disorder and autonomic function were assessed. Kruskal Wallis tests were used to determine differences between the four groups.

Results: Regardless of disease stage, patients with freezing of gait had more severe motor symptoms and a predominant non-tremor phenotype. In the early stages, freezers had a selective impairment in executive function and had more marked REM sleep behaviour disorder. Autonomic disturbances were not associated with freezing of gait across early or advanced disease stages.

Conclusion: These findings support the notion that impairments across the frontostriatal pathways are intricately linked to the pathophysiology underlying freezing of gait across all stages of PD. Features of REM sleep behaviour disorder suggest a contribution to freezing from brainstem pathology but this does not extend to more general autonomic dysfunction.
Ovine neuronal ceroid lipofuscinoses

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Neuronal ceroid lipofuscinoses (NCL, Batten disease) are the most common inherited childhood onset neurodegenerative disorders and this group of diseases is characterised by the accumulation of autofluorescent lysosomal storage material, progressive blindness and neurodegeneration. Mutations in 13 different genes are described to lead to different variants of the disease. The disease mechanism is poorly understood and there is no cure, however, clinical trials have commenced for some variants of the disease.

Studies on naturally occurring ovine models of NCL have been central to our current understanding of many aspects of the disease and we summarise research conducted over the past decades using three Australasian ovine models: the CLN6 New Zealand South Hampshire and CLN6 Australian Merino sheep and the CLN5 New Zealand Borderdale sheep.

Highlights include determining the nature of the so-called “lipofuscin like” storage material as subunit C of mitochondrial ATP synthase, identification of the disease causing mutations for all three ovine models, determining the regional nature of cortical atrophy and its close association with neuroinflammation, developing neuron culture cell biology studies, and trialing therapeutic approaches.
Chronic neuroinflammation as a therapeutic target – from cell based screening assays to animal models of chronic neuroinflammation

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Inflammation in the central nervous system contributes to the pathogenesis of multiple neuro-degenerative disorders, including Alzheimer’s disease. Cytokine-suppressive anti-inflammatory drugs (CSAIDs), which include inhibitors of NFκB signaling, have been suggested as a novel type of anti-inflammatory drugs with a broader range than conventional NSAIDs. In order to identify such drugs from natural sources, we have started to screen polyphenolic compounds with purported anti-inflammatory activity in N11 microglia and RAW 264 macrophage cells using LPS+IFN-γ as activators and NO and TNF-α as readouts, and have identified apigenin (from parsley and celery) as the most potent compound with an IC50 value of approx. 10 µM. We have also screened various plant extracts for novel and more potent compounds and identified betulinic acid derivatives from the leaves of the Australian rainforest tree Alphitonia petriei (Rhamnaceae) as novel anti-inflammatory drugs with superior potency (IC50 < 2 µM). To test the anti-inflammatory and neuroprotective activity of such compounds in vivo, are using a transgenic animal model of chronic neuroinflammation (“GFAP-IL6 mouse”), in which interleukin-6 is overexpressed under the GFAP promoter resulting in chronic, low-grade neuroinflammation. GFAP-IL6 mice display chronic microglial and astroglial activation, accompanied by neurodegeneration, and a decline of motor and cognitive skills starting from 3-6 months of age. We believe that by using this model, the therapeutic efficiency of many brain-permeable cytokine suppressive anti-inflammatory drugs can be tested in vivo.
Sensory dysfunction following stroke: somatotopic mismatch of hand representation. Is there anything we can and should do?

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Background: Recovery of the hand dexterity after stroke cannot be achieved in absence of the tactile sensory information, but the interpretation of this input requires that somatotopic representation of hand’s skin has to be preserved. Unfortunately, this is not necessarily the case after substantial reorganization of neural connectivity following stroke. The aim of current study was to demonstrate the evidence of such pathological condition using easy accessible testing procedures.

Methods: The order of somatotopic representation of the hand was assessed by testing mismatch between the test site where the point-type stimuli were applied and location on the skin where stimuli were perceived by the patient. Twenty-five predefined sites on the glabrous skin of each hand were tested.

Results: Out of 20 patients tested, five patients were identified to show three forms of somatotopic mismatch: (1) scrambled somatotopic representation, high detection thresholds; (2) orderly distorted somatotopic representation, close to normal detection thresholds; and (3) labile, changing somatotopic representation. None of the patients were aware of this pathology prior to our testing. While mismatch in somatotopic representation is reported to be present many years after stroke we retested one patient 9, 21 and 60 month after stroke and observed that normalisation of somatotopic maps is possible.

Conclusions: Whether there is a critical time period for intervention and whether somatotopic representation order may be achieved in some, but not other patients is not known. This indicates the need for new targeted rehabilitation strategies and clinical tests to diagnose such patients during routine clinical examination.
A role for EphA7 in the development of the ipsilateral retinal projection

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Background: EphA7, a receptor tyrosine kinase known to mediate axonal guidance, is expressed in a number of brain areas during development. Recently, the expression of EphA7 was shown to decrease in knockout (KO) mice which lack the gene encoding the transmembrane protein tenerurin-m3 (Ten-m3). Ten-m3 has been shown to play an important role in the formation of ipsilateral retinal ganglion cell (RGC) projections to central targets. This indicates that EphA7 might have functional associations with Ten-m3, and could play an important role in regulating the formation of the ipsilateral retinal pathway.

Method: Bulk-fill tracing of retinal projections was also performed using cholera-toxin B conjugated to fluorescent dyes. For focal injections, Dil (a long-chain dialkylcarbocyanine) was injected into mouse retinas at post-natal day 13 (P13). Three structures from the early visual pathway (retina, dorsal lateral geniculate nucleus (dLGN) and superior colliculus (SC)) were dissected and analyzed.

Results: Bulk-fill labeling showed a decrease in the size of the ipsilateral retinal projections to the dLGN in EphA7 KO mice ($p<0.01$), especially in the caudal portion. Focal injections revealed a point-point projection that the ipsilateral patches were significantly elongated in the rostral end of the dLGN in the EphA7 KO mice ($p=0.016$), but not in the more caudal portion. Analysis on SC did not reveal any significant difference.

Conclusions: The results suggest that EphA7 alone can influence the ipsilateral retinal projection pathway, which is consistent with a functional relationship with Ten-m3.
Proteomic MALDI-TOF/TOF-IMS examination of peptide expression in formalin fixed brainstem and changes in the Sudden Infant Death Syndrome

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Matrix assisted laser desorption/ionisation imaging mass spectrometry (MALDI IMS) has not previously been utilised to examine Sudden Infant Death Syndrome (SIDS). This study aimed to optimise MALDI IMS for use on archived formalin-fixed-paraffin-embedded human infant medulla tissue (n=6); to evaluate any differences between multiple nuclei of the medulla by using high resolution IMS and; subsequently compare the profile between SIDS and controls. MALDI identified 132 proteins based on 568 peptides across all samples; 286 peaks were found using IMS, corresponding to 55 proteins that were directly compared between controls and SIDS. Comparisons between control nuclei demonstrated common peptides for neuronal/non-neuronal structures allowing for the identification of medullary regions. In SIDS, abnormal expression patterns of 41 peptides were observed (p≤0.05) corresponding to nine proteins. These abnormalities varied between nuclei; the majority of variations occurred in the raphe nuclei, hypoglossal and pyramids. The changes in expression observed were confirmed with immunohistochemistry. The abnormal proteins are not related to a previously identified neurological disease pathway; instead consist of developmental neuronal/glial/axonal growth, metabolism and cyto-architecture and apoptosis components. This suggests that SIDS infants have abnormal neurological development in the raphe nuclei and pyramids of the brainstem which may contribute to the pathogenesis of SIDS.
Induced Oxidative Stress in the Senescence-Accelerated Mice

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Background: Aging is associated with a number of neurodegenerative disorders, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), etc. Senescence accelerated mouse prone 8 (SAMP8) is often employed to study the pathogenic process during brain aging. Oxidative stress and its mediated neural inflammation and neurotoxicity have been highlighted as pathogenesis of human brain aging. However, how these changes are developed over time has not been clearly demonstrated.

Methods: 18 SAMP8 mice were randomly separated into three groups (n=6) and cultivated till 4-month, 8-month and 12-month respectively. The hippocampus from each mouse was dissected for RNA and protein extraction. The gene expression of Nrf2, HO-1 and NF-κB were tested using Real-time PCR. The total protein amount of HO-1, NF-κB and Aβ, as well as the levels of nuclear and cytoplasmic Nrf2 in the hippocampus was tested using western blots. Student t test and linear repeated measures were used to analyze the oxidative indices among different time points.

Results: The most significant change is the accumulation of Aβ1-42 in the hippocampus of mice from 4-month to 8-month. During aging process, the expression levels of Nrf2, HO-1, and NF-κB genes are upregulated, consistent with the increased protein levels of Nrf2, HO-1 and NF-κB, in accordance with the upregulation of Aβ1-42 peptide. There was an increase in nuclear translocation of Nrf2 observed at 8-month mice and exacerbated as the mice were at 12 month old.

Conclusions: The deleterious effects of oxidation and inflammation induced by Aβ1-42 are likely contributing to aging.
Age-related changes in TrkB-TK mRNA expression in the human subependymal zone

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Background: Neurogenesis continues well into adult life in the human subependymal zone (SEZ) lining the lateral ventricles. Brain-derived neurotrophic factor/tyrosine kinase receptor B (TrkB-TK) signalling is critical for neuronal differentiation, maturation and survival; however, it is unknown how TrkB-TK expression is altered with age in the human SEZ.

Methods: In this study, we used \textit{in situ} hybridisation to determine full-length (TrkB-TK+) and truncated (TrKB-TK-) TrkB-TK transcript levels in the SEZ and caudate from infancy to middle age (n=28, 2 months-43 years). We further measured expression of TrkB-TK isoforms in the human SEZ from young adulthood into aging (n=50, 21-103 years) using quantitative PCR and related mRNA levels to expression of neurogenic markers.

Results: Both TrkB-TK mRNAs were detected in the SEZ and caudate during human development, although in starkly contrasting amounts. TrkB-TK+ mRNA showed higher expression levels in the caudate, whereas TrkB-TK- mRNA was higher in the SEZ across all age groups. The SEZ TrkB-TK- transcript was significantly diminished from infancy to middle age. In contrast, TrkB-TK- expression was significantly increased in the adult SEZ over the nine decades of human lifespan, while TrkB-TK+ mRNA levels remained stable. Expression of TrkB-TK isoforms did not relate to cell proliferation; however, TrkB-TK+ mRNA was positively correlated with neuronal markers, while TrkB-TK- mRNA showed a negative relationship with neuronal markers.

Conclusion: Our findings indicate that TrkB-TK isoforms show region-specific expression patterns during human development. We provide evidence that TrkB-TK expression does not appear to become limited in the aging SEZ and suggest that these two distinct TrkB-TK isoforms may modulate neuronal determination in complementary ways.
Background: We previously reported that it is specific macronutrient intake rather than caloric restriction that facilitates lifespan extension in ad-libitum fed mice. The hypothalamus plays a key role in mediating the effects of diet on the body, since it is not only involved in food intake, but also in the neuroendocrine interactions that mediate functions such as growth, reproduction and metabolism. This study therefore investigated the effects of varying protein-to-carbohydrate-to-fat (P:C:F) ratios on mouse hypothalamic gene expression with a focus on the cellular growth pathways.

Methods: Three-week old C57BL/6 mice were assigned one of 25 diets varying in P:C:F ratio. Food intake was measured weekly for 6 months, and monthly until 15 months. Mice were sacrificed, and RNA from the hypothalamus was extracted for transcriptome analysis by microarray. Data was analysed using the geometric framework, a 3-dimensional state-space modelling tool, which allows investigation of the impact of individual macronutrients on gene expression.

Results: Overall, the results indicate that several genes involved in cellular growth and metabolism were altered by diet. The key findings in terms of the growth pathways were: carbohydrate intake significantly influenced expression of Slc6a3, Igf1 and Sirt2; protein intake significantly influenced Npy, Akt3, Sirt1; and P:C ratio significantly influenced Sirt5, Rps6a4/5, Igf2r, Igf1r and Sirt3.

Conclusions: Taken together, these findings suggest that diet plays a significant role in hypothalamic gene regulation, and differential activation of cellular growth pathways such as Akt, IGF and sirtuins may mediate the beneficial effects of diet on ageing.
Structural neuroimaging of the long term effects of childhood maltreatment

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Background: Increased psychiatric vulnerability following childhood maltreatment is proposed to arise from altered developmental trajectories of brain regions involved in emotion and stress. Reduced adult hippocampal and amygdala volume have previously been reported to be associated with childhood trauma. To date, however, no longitudinal studies have been conducted in adolescents with a history of maltreatment. Cortical thickness and white matter, despite being highly vulnerable to function-induced alterations, have also rarely been studied in the context of childhood trauma.

Methods: Using structural magnetic resonance imaging, we explored the relationship of childhood maltreatment with hippocampal volume, amygdala volume, cortical thickness and white matter fractional anisotropy (FA) in a cohort of young adults exhibiting an admixture of psychiatric symptoms. Additionally, we examined whether longitudinal changes in hippocampal and amygdala volumes differed depending on childhood maltreatment history.

Results: Childhood physical abuse was found to be associated with right isthmus cingulate thickness, whilst childhood neglect was associated with reduced uncinate fasciculus FA and greater corpus callosal FA. Hippocampal and amygdala abnormalities were not evident at baseline in individuals with a history of childhood trauma. However, longitudinal analyses revealed a difference in left amygdala and left hippocampal volume changes over time between individuals with a history of childhood maltreatment and those without.

Conclusions: This is the first longitudinal evidence of aberrant hippocampal and amygdala volume loss in young adults with a history of childhood maltreatment. These findings, alongside cross-sectional results, can aid our understanding of how childhood trauma increases the risk of adulthood psychopathology and possible sites of intervention.
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Abnormal glutathione pathway in postmortem dorsolateral prefrontal cortex from people with schizophrenia

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Background: Our group has previously identified a subgroup of people with schizophrenia with increased expression of inflammatory cytokines which may be related to oxidative stress responses. Glutathione (GSH) is a major antioxidant in the human brain. There are two different states of GSH: reduced GSH (GSHₐ) or oxidized GSH (GSSG). GSH is synthesized by the rate-limiting enzyme glutamyl-cysteine ligase (GCL). GSH detoxifies reactive oxygen species via GSH peroxidase (GPx). It is hypothesised that people with schizophrenia have brain oxidative stress with reduced levels of GSHₐ and total GSH.

Methods: Dorsolateral prefrontal cortex (DLPFC) from 37 schizophrenia cases and 37 matched controls were studied. Western and dot blot analyses were used to examine the catalytic subunit of GCL (GCLC) and GPx protein levels. The levels of GSHₐ and total GSH were determined by spectrophotometry.

Results: There were no significant differences in the levels of GCLC [t(72)=1.007, p=0.285] or GPx [t(72)=-0.060, p=0.952] between people with schizophrenia and controls. GSHₐ [t(66)=3.001, p=0.004] and total GSH [t(66)=2.467, p=0.016] levels from people with schizophrenia were significantly less than in controls. In the schizophrenia group, both GSHₐ (r=-0.496, p=0.005) and total GSH (r=-0.412, p=0.021) levels were negatively correlated with interleukin-1β (IL1β) mRNA levels.

Conclusion: In this study, the schizophrenia group had significantly less mean GSHₐ and total GSH than the control group, indicating impaired antioxidant capacity in the prefrontal cortex in schizophrenia. Our findings suggest that abnormal cytokines levels may affect the GSH pathway, or alternatively that increased oxidative stress may increase cytokines’ expression.
Decreased hippocampal and amygdala volumes in psychotic disorders are independent of childhood trauma exposure

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Background: Reduced volumes of the hippocampus, amygdala and anterior cingulate cortex (ACC) have been widely reported in schizophrenia (SCZ), schizoaffective disorder (SZA) and bipolar-I disorder (BD). Converging evidence suggests these specific structural brain abnormalities might be potentiated by childhood trauma exposure. We therefore examined whether hippocampal, amygdala and ACC reductions in these clinical groups were influenced by childhood trauma exposure.

Methods: High-resolution MPRAGE T1 structural brain scans were acquired for 154 participants, including 53 SCZ/SZA cases, 46 BD cases and 55 healthy controls (HC). Of these, 34 SCZ/SZA, 28 BD and 21 HC reported moderate-high levels of childhood trauma on the Childhood Trauma Questionnaire (CTQ), while 19 SCZ/SZA, 18 BD and 34 HC did not. Following standard Voxel-Based Morphometry pre-processing (VBM8 toolbox), bilateral hippocampal, amygdala and ACC volumes were extracted for use as dependent variables in a series of MANCOVAs to test the effects of trauma (exposed, non-exposed) and clinical group (SCZ/SZA, BD, HC) on regional brain volumes, with age and sex as covariates.

Results: A significant main effect of group, but not childhood trauma, was evident for hippocampal and amygdala volumes only. Post-hoc t-tests showed that these effects were due to a significant reduction in amygdala volume in SCZ/SZA cases relative to HC, and reduction of hippocampal volume in both SCZ/SZA and BD cases relative to HC. Conclusions: This study provides evidence that decreased hippocampal volumes in BD and SCZ/SZA are independent of childhood trauma exposure.
Negative mental states, their association to frontal lobe brain activity and the effect of coping strategies on these relationships

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Background: Negative mental states like depression, anxiety and stress, can have a detrimental impact on the mental and physical well-being of an individual. More specifically, limited research has shown the presence of these mental states can lead to changes underlying architecture and brain activity. Individuals deploy various strategies and mechanisms that are used in attempts to counter these mental states. The present study examined how negative mental states affect brain activity and how coping alters these associations.

Methods: Twenty-one healthy adult participants were assessed for the presence of symptoms associated with negative mental states using the Depression, Anxiety, Stress scale. Individual coping was assessed using the revised Ways of Coping Checklist. Finally, a 32 channel electroencephalogram was recorded for a resting baseline and an active phase, involving a cognitive task (the Stroop test).

Results: The analysis indicated that depression, stress and anxiety were independently associated to the change in beta and gamma activity between baseline and active phase, as well as active phase beta and gamma activity at various frontal lobe regions (p<0.05). Additional analysis indicated that controlling for various coping types like avoidance may alter these initial relationships.

Conclusions: The inter-relationship between negative mental states, brain activity and coping strategies is a series of complex interactions which seem to revolve around task effort and potential neuroplastic recruitment; as brain activity increased with greater levels of negative mental states. Controlling for coping, unsurprisingly, alters these relationships. Finally, brain activity changes may enable dynamic and potential prediction of negative mental states.
A psycho-educational intervention for people with a family history of depression for use in general practice: Results from pilot testing

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Background: No psycho-educational interventions are currently available that specifically target people with a family history of depression. We developed and pilot-tested an online psycho-educational intervention (‘LINKS’). LINKS provides genetic risk information and evidence-rated information on preventive strategies for depression and incorporates a risk assessment tool and several videos using professional actors. Results from pilot-testing in the GP setting will be presented.

Methods: Sydney GP practices were broadly sampled to ensure heterogeneity and generalizability. The patient sample included people with a family history of at least one first-degree relative with manic depressive (MDD) or bipolar disorder (BD). Patients attending participating GP practices were invited to the study by letter by their GP. Patients were asked to self-identify as having a first-degree degree relative with MDD or BD and then invited to access LINKS. Participants who accessed LINKS completed purposively developed measures assessing satisfaction, relevance, emotional impact and perceived improvement of understanding.

Results: 22 patients completed all questionnaires. 100% patients reported they were satisfied or very satisfied with LINKS. 85% reported they would recommend LINKS to others with a family history of depression. 73% reported that LINKS met their expectations, and 23% that it exceeded their expectations.

Discussion: This novel psycho-educational intervention provides individuals with a family history of depression with information on evidence-based strategies for the prevention of depression. In a subsequent cluster randomised controlled trial we will test the hypothesis that LINKS will enable people to make appropriate lifestyle choices and implement behaviours designed to reduce their risk for depression. ECR
Oxytocin induced grey matter changes in an early psychosis population

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Background: Schizophrenia is a heterogenous disorder characterised by the presentation of positive, negative and disorganised symptoms. It typically emerges between ages 18 and 24 with the majority of the deterioration occurring in the 5 years following onset. Current treatments fail to improve the negative symptoms and social functioning. Therefore the neuropeptide and hormone oxytocin has garnered interest as a treatment option for schizophrenia. A single dose of oxytocin has been shown to improve performance on social performance measures, with longer-term oxytocin studies producing mixed results. Our study investigated oxytocin combined with social cognition training as treatment for those experiencing first episode psychosis.

Methods: Participants were recruited into a double-blind, placebo controlled trial at the Brain & Mind Centre at the University of Sydney. Participants received either oxytocin (24 IU) or placebo nasal spray, twice daily, for 6 weeks. An additional dose was given before the weekly social cognition training sessions. Twenty four participants completed the imaging subcomponent of the study.

Results: Two clusters of grey matter change were found within the somatosensory cortex (post-central gyrus). Within these clusters, increased grey matter was found post-treatment for those who received oxytocin, compared to those who received placebo.

Conclusion: This novel finding suggests neurological change as a result of treatment with oxytocin. Finding of the change within the somatosensory cortex is interesting given the link between somatosensory stimulation and oxytocin release. Neurobiological changes resulting from oxytocin administration may enhance the perception of social stimuli to facilitate processing of cues and social contexts.
X-ray fluorescence mapping of elemental distributions in brain stem sections from multiple sclerosis patients

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Background: Locus ceruleus (LC) neurons supply central nervous system cells with noradrenaline, and damage to the LC has been found in multiple sclerosis (MS) and in neurodegenerative diseases such as Alzheimer’s disease. LC neurons selectively accumulate heavy metal toxicants, which could play an important role in the pathogenesis of these diseases. Histochemical studies of brain tissue from MS patients suggest Hg as a potential toxin in the LC, but there may be other metal toxicants present in the LC that cannot be detected histochemically.

Method: We used the X-ray Fluorescence Microscopy (XFM) Beamline at the Australian Synchrotron to image the LC in cryo-fixed brain stem sections of MS patients. The 384-element BioMaia detector provided the elemental sensitivity and spatial resolution required to map the metal toxicants of interest (such as Hg, Pb, and Cr), as well as lighter elements (such as S and Se).

Results: Several different metal toxicants can be detected in the LC neurons of MS patients. Further, the co-localization of these heavy metals with lighter elements reinforces the physiological effects of these metals. The spatial resolution of the BioMaia detector also enabled us to differentiate and compare the distribution of toxicants in glial cells (such as oligodendrocytes, with average diameter 10 um), with that in the larger LC neurons (average diameter 40 um).
Divergent network patterns of Amyloid-β deposition in language and amnestic AD presentations

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Background: Despite divergent clinical features, language and amnestic presentations of Alzheimer’s disease (AD) appear to show comparable regional amyloid-β (Aβ) burden. By using a statistical network approach, we aimed to identify complex network patterns of Aβ deposition and explore the effect of Apolipoprotein E ε4 (APOE ε4) allele on cortical Aβ burden across AD presentations.

Methods: Sixteen amnestic AD participants and 18 cases with language AD presentation, also known as logopenic aphasia, were selected. A comprehensive clinical assessment, PET Aβ imaging, and APOE genotyping was performed. Statistical network analysis was undertaken based on the estimation of sparse partial correlations of Aβ burden between cortical regions. Global and regional network statistical parameters as well as the effect of APOE ε4 genotype on cortical Aβ were explored.

Results: Both groups showed equivalent distribution of cortical Aβ burden and frequency of APOE ε4 genotype. Statistical network analysis, however, demonstrated divergent connectivity properties. The language AD group demonstrated higher mean network degree and shorter characteristic path length than amnestic AD. Amnestic AD cases showed connectivity hubs confined to the mesial temporal and prefrontal lobes bilaterally, whereas language cases showed hubs scattered across the whole cortical mantle, including posterior regions. AD presentations and APOE ε4 genotype demonstrated an interaction effect on total cortical Aβ burden.

Conclusions: The network analysis reveals interregional network differences not evident using a simple comparison of Aβ burden. This suggests that regional neurotoxic effects may explain the phenotypical differences in AD presentation, and that these can be modulated by APOE genotype.
Open-Field-PET: Reproducibility of detecting transient changes in D2/D3 receptor occupancy during drug competition studies on freely moving animals

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Background: Positron Emission Tomography (PET) imaging offers an exceptional opportunity to advance our understanding of the underlying molecular mechanisms of brain function. We have developed and previously presented a novel methodology for imaging awake rats, which enables simultaneous measurements of brain function and animal behaviour during pharmacological or environmental stimulus. The objective here was to assess the developed methodology in terms of reproducibility of detecting transient changes in receptor occupancy induced by an administered dopamine D2/D3 receptor antagonist.

Methods: Eight adult male Sprague-Dawley rats were injected with 44.8±11.8MBq (0.84±0.16 nmol) of [11C]raclopride via an intravenous jugular catheter and imaged for 60 min. During imaging the animals were free to move within a small enclosure (20x12 cm²). 20 min after tracer injection 4 animals were administered with 2 mg/kg of unlabelled raclopride, while the other 4 received only the vehicle (baseline). The dynamic PET data from the striatum and cerebellum were analysed using the lpntPET method, which models temporal fluctuations in receptor occupancy by the radioligand.

Results: For those animals administered with unlabelled raclopride we were able to reproducibly measure the displacement of [11C]raclopride from D2/D3 receptors, both in terms of activation onset (td=21.25±2 min) and magnitude (k2a=1.9±0.1 times the baseline). Additionally, no significant displacement was detected for those animals that received a vehicle injection.

Conclusions: The developed methodology allows for reproducible measurements of exogenous drug-induced radioligand displacement from D2/D3 receptors. Work is in progress to extend the evaluation of this methodology to include measurement of endogenous dopamine release induced by amphetamine and its temporal correlation with behavioural changes.