

# SYMPOSIUMS

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## SYM-01-01

**AUTOPHAGY, A GUARDIAN AGAINST NEURODEGENERATION****Rubinsztein D.C.**

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Intracellular protein misfolding/aggregation are features of many currently incurable late-onset neurodegenerative diseases, like Alzheimer's disease, Parkinson's disease and polyglutamine expansion diseases like Huntington's disease (HD) and various spinocerebellar ataxias. The mutations causing many of these diseases confer novel toxic functions on the target proteins. We showed that the autophagy inducer, rapamycin, reduced the levels of mutant huntingtin and attenuated its toxicity in cells, and in *Drosophila* and mouse HD models. We have extended the range of intracellular proteinopathy substrates that are cleared by autophagy to other related neurodegenerative disease targets and have provided proof-of-principle in cells, *Drosophila* and mice. In order to induce autophagy long-term, we have been striving to identify safer alternatives to the mTOR inhibitor, rapamycin. To this end, we have been trying to discover novel components of the autophagy machinery and new signalling pathways and drugs that impact on autophagy. While autophagy induction is protective in models of various neurodegenerative diseases, certain other conditions, including lysosomal storage disorders, are associated with compromised autophagy. I will review these data and then describe how impaired autophagy compromises cellular processes, including the ubiquitin-proteasome system.

## SYM-01-03

**A ROLE FOR SMALL UBIQUITIN-LIKE MODIFIER (SUMO-1) IN THE AUTOPHAGIC RESPONSE TO PROTEIN AGGREGATES IN NEURODEGENERATION****Pountney D.L.**

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Many neurodegenerative diseases are characterised by microscopically-visible protein aggregates, or inclusion bodies, within neural cells. Initially found in intranuclear inclusions in hereditary ataxias and Huntington's disease, the ubiquitin homologue, SUMO-1, has now been shown in a range of neurodegenerative diseases in both nuclear and cytoplasmic inclusions, and marks sub-domains in Lewy bodies and in glial cytoplasmic  $\alpha$ -synuclein inclusions. Proteomic analysis of intranuclear inclusion bodies revealed that SUMO-1 was associated with proteins of the endomembrane system. In recent studies, we have found that SUMO-1 is associated with lysosomes both in neurodegenerative diseases and in rodent and cellular disease models. We examined brain tissue from cases of progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and normal controls and identified co-localisation of the lysosomal marker, cathepsin D, and SUMO-1 associated with both the tau-positive PSP inclusions and the  $\alpha$ -synuclein-positive MSA inclusions. Rat and mouse models of Parkinson's disease were investigated that employ unilateral injection of the mitochondrial complex 1 inhibitor, rotenone and revealed the association of SUMO-1 with lysosomes and  $\alpha$ -synuclein intracellular inclusion bodies in the lesioned brain tissue. The OLN oligodendrocyte cell model recapitulates PSP-like tau inclusions and showed associated SUMO-1-positive lysosomes. SUMO-1-positive lysosomes were also associated both with polyglutamine aggregates in Httexon1-Q74-eGFP transfected cells and with  $\alpha$ -synuclein aggregates in  $\alpha$ -synuclein over-expressing cells. Western analysis of purified lysosomes revealed an increase of SUMO-1 in the lysosomal fraction. These findings suggest a role for SUMO-1 in the autophagy pathway in neurodegeneration.

## SYM-01-02

**DIFFERENTIAL ACTIVATION OF AUTOPHAGY DURING NEURONAL CELL DEATH: INSTIGATOR OR COLLABORATOR OF NEURONAL DEMISE?****Higgins G.C.**

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Autophagic cell death (ACD) is activated in the absence of caspase activity (essential for apoptosis) as a secondary programmed cell death (PCD) pathway and is thought to be brought on by overstimulation of autophagic activity. What is the "trigger point" that stimulates autophagy from being a cytoprotective mechanism to acting as an alternative PCD process? Under conditions where the ubiquitin proteasome system (UPS), another protein degradation pathway, is rendered inoperable, compensatory autophagy has been shown by others to be stimulated to offset the accumulation of damaged proteins. Purpose: To determine whether inhibition of the UPS may be the initiator of ACD, under oxidative stress, where overstimulation of autophagy results in cell death. Methods: Primary cortical neurons from C57 Black 6J mice were exposed to various oxidative stress insults (including hydrogen peroxide and superoxide) and studied for ACD and involvement of UPS. Using a combination of immunocytochemistry/confocal microscopy and western immunoblotting, neurons subjected to siRNA transfection (e.g. siAtg7) and pharmacological inhibitors such as MG132 (UPS inhibitor) and 3-methyladenine or Bafilomycin A1 (autophagy inhibitors) were monitored. Results: ACD is a PCD mechanism under oxidative stress, as determined with siAtg7 and 3-MA. The protein p62 has been implicated in the cross-talk between UPS and autophagy and in neurons exposed to hydrogen peroxide the UPS was disrupted, as shown by labeling patterns of western immunoblots. Immunocytochemistry showed co-localization of p62 and LC3 in a time-dependent manner in treated neurons, indicating a potential role for p62 in ACD. Conclusion: The roles of p62 and the UPS are now the focus of current studies to determine if this protein is the switch between cytoprotective autophagy and ACD.

## SYM-01-04

**THE ROLE OF NEUROINFLAMMATION IN MEDIATING KEY PATHWAYS INVOLVED IN PARKINSON'S DISEASE PATHOGENESIS****Taylor J.M.<sup>1</sup>, Main B.S.<sup>1</sup>, Ayton S.<sup>2</sup>, Zhang M.<sup>1</sup>, Ates R.C.<sup>1</sup>, Finkelstein D.<sup>2</sup> and Crack P.J.<sup>1</sup>**<sup>1</sup>Department of Pharmacology, University of Melbourne, Parkville, Victoria. <sup>2</sup>Mental Health Research Institute, Parkville, Victoria.

Purpose: Recent evidence has implicated neuroinflammation in Parkinson's disease (PD) pathogenesis. A key regulator of the neuroinflammatory response are the type I interferons (IFNs) however, their role in PD is unknown. We propose that type I IFNs mediate pathways that contribute to neuronal cell death and autophagy in PD. Methods: Wildtype (WT) and IFNAR1<sup>-/-</sup> primary neurons were treated with the environmental toxin, rotenone (25nM) for 1, 2, 4 8, and 24 hours. Western blot and QPCR analysis was used to characterise type I IFN signalling, pro-inflammatory cytokines and levels of apoptosis and autophagy. WT (n=10) and IFNAR1<sup>-/-</sup> (n=8) mice were injected with MPTP (4 x 10mg/kg doses) and killed at 21 days for histological, biochemical, western blot and QPCR analysis. Post-mortem human brain samples from control (n=10) and PD patients (n=10) were analysed for type I IFN signalling. Results: Western blot analysis demonstrated increased Stat-3 activation in WT neurons treated with rotenone and in the substantia nigra of human PD brain. QPCR confirmed a significant 3-fold increase (p<0.05) in IFN $\alpha$  expression in PD patients. In response to rotenone, IFNAR1<sup>-/-</sup> neurons displayed reduced levels of the apoptosis marker, cleaved caspase-3 and the autophagy indicator, LC3. A 2-fold reduction in levels of the pro-inflammatory cytokine IL1- $\beta$  was identified in MPTP-treated IFNAR1<sup>-/-</sup> mice compared to MPTP-treated WT mice. Conclusion: This study has confirmed a role for type I IFN signalling in modulating pathways involved in neuronal cell death and autophagy and suggests therapies targeting IFNAR to reduce neuroinflammation may be beneficial in the treatment of PD.

## SYM-02-01

**CHOLINERGIC MODULATION OF GOAL-DIRECTED ACTION: INTERLACING NEW MEMORIES WITH OLD IN THE STRIATUM**

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Considerable evidence suggests that rats can encode the relationship between actions and their specific consequences or outcomes and that this learning and its retrieval depend on dorsomedial striatum (DMS). To remain adaptive, however, such goal-directed learning needs to remain flexible; animals need to remain sensitive to changes in the consequences that an action might produce and yet changes of this kind produce a significant problem: new learning has to be shielded from interference produced by old learning if it is to be accurately retrieved. There is some evidence that cholinergic activity in both the hippocampus and the cortex, although relevant to different functions, protects new learning from interference of this kind and so we sought to assess whether cholinergic activity played this role in striatum. The main source of acetylcholine in the striatum is from a sparsely distributed set of tonically active, giant, aspiny interneurons known collectively as cholinergic interneurons (ChI). We first developed a method to assess the biochemical state of ChI through detection of ribosomal activation, which paralleled their firing rate. We then lesioned their main input from parafascicular thalamus (Pf) and found that (i) both their biochemical state and firing rate were strongly attenuated and, more importantly, (ii) changes in the action-outcome contingency resulted in an inability to retrieve both new and old action-outcome associations. Disconnection of the Pf from DMS produced a similar behavioural effect as did intra-DMS infusion of the M2 agonist oxotremorine, which acts on the membrane to inhibit ChI firing and acetylcholine release. These data support the hypothesis that acetylcholine protects goal-directed learning in striatum from catastrophic interference.

## SYM-02-03

**PLACING PREDICTION INTO THE FEAR CIRCUIT**

**McNally G.P.**  
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Pavlovian fear conditioning depends on synaptic plasticity at amygdala neurons. Electrophysiological, molecular and behavioral evidence suggest the existence of a distributed neural circuitry regulating amygdala synaptic plasticity during fear learning. This circuitry, which involves projections from the midbrain periaqueductal gray region, can be linked to prediction error and expectation modulation of fear learning, as described by associative and computational learning models. It controls whether, and how much, fear learning occurs by signaling aversive events when they are unexpected. Functional neuroimaging and clinical studies indicate that this prediction circuit is recruited in humans during fear learning and contributes to exposure-based treatments for clinical anxiety. This aversive prediction error circuit might represent a conserved mechanism for regulating fear learning in mammals.

## SYM-02-02

**PROSPECTIVE MEMORY DURING DECISION-MAKING**

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**Purpose:** The function of memory is to shape our behaviour in the present and to allow us to predict the future. This latter faculty, present in humans as episodic prospection, appears to depend on the medial prefrontal cortex and the hippocampus. To examine the neural underpinnings of this process we hypothesised that increased communication would occur between these two brain regions in an animal model wherein rats had the opportunity to use prospective memory in a decision-making task. **Methods:** EEG was simultaneously recorded from the anterior cingulate subregion of prefrontal cortex and from the dorsal hippocampus while rats performed a cost-benefit decision task in a figure 8 maze. The task required a choice between a low reward/low effort and a high reward/high effort (HRHE) option where effort involved climbing a barrier. An amplitude envelope cross correlation procedure was used to determine the temporal relationship between prefrontal and hippocampal activity. **Results:** Data was obtained from 6 animals across 27 recording sessions. EEG amplitude envelopes in the theta frequency range were compared as the animal moved up the stem of the maze towards the decision point. There was a significant shift in the lead/lag relationship as the animal approached the choice point, with the prefrontal cortex gradually taking the lead ( $p < 0.05$ ). Furthermore, the mean prefrontal lead at the base of the stem was positively correlated with the animals behavioural preference for the HRHE option ( $r = 0.52$ ,  $p < 0.01$ ). A comparison of lead/lag after the choice point again indicated that prefrontal cortex EEG led the hippocampus when the animal chose the HRHE option but not otherwise ( $p < 0.05$ ). **Conclusion:** These data suggest that the prefrontal cortex influences activity in the hippocampus immediately prior to a choice and that this influence increases the probability that an animal will make a physical effort to achieve a reward. These data are consistent with human data suggesting that these two regions are involved in prospective memory and provide new evidence as to the directionality of the coupling.

## SYM-02-04

**IDENTIFICATION OF NEURONS INVOLVED IN LEARNING AND MEMORY**

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Fear conditioning is one of the leading experimental models for the study of how the brain acquires and stores memory. Some of the major areas of the brain which are necessary for fear conditioning have been determined, with the amygdala playing a central role in the process. However, the changes in the brain that are responsible for and encode fear conditioning memory have not been found. A central missing element is that the neurons that are directly involved in fear learning and memory have not been identified. To search for these neurons, we have used a genetic approach, the fos-tau-lacZ (FTL) mouse, to map functionally activated expression in neurons following contextual fear conditioning. We have identified discrete populations of neurons in the brain that are activated specifically following learning. We have begun to characterise these neurons and in this presentation I will present the results we have to date in these studies. Additionally, we have been developing procedures to quantify synaptic proteins and we have found clear changes in the levels of these proteins following fear learning. The activated neurons we have identified and the changes in synaptic proteins we have found may form part of an engram for fear conditioning.

## SYM-03-01

**DIVERGENT MIGRATORY BEHAVIOURS ESTABLISH LAMINATION OF INTERNEURONS DURING CORTICAL DEVELOPMENT**Ng H.X.<sup>1,2</sup>, Lee E.P.<sup>1</sup>, Tan S.-S.<sup>1,2</sup> and Britto J.M.<sup>1,2</sup><sup>1</sup>Florey Neuroscience Institutes. <sup>2</sup>Centre for Neuroscience, University of Melbourne, VIC, Australia.

Modulation of cortical activity by GABAergic interneurons is required for normal brain function and is achieved through the high level of heterogeneity within this neuronal population. In rodents, cortical interneurons are generated in the ganglionic eminence and undergo tangential migratory routes determined by the birthdate, such that the majority of early born interneurons migrate through the marginal zone and later born interneurons migrate through the subventricular zone. Once within the neocortex, interneurons migrate radially into the cortical plate and achieve 'inside-out' lamination with layer specification corresponding to their contemporaneously-born pyramidal neurons. The question remains of the temporal sequence of interneuron entry into the cortical plate and radial migratory behaviours during this process. To address this, we conducted a birth-dating study on GAD67-knockin-GFP mice at E12.5 (early-), E14.5 (mid-) and E16.5 (late-corticogenesis) determined the position of interneurons at various time-points during embryonic and postnatal development. Our analysis revealed that late-born interneurons are the first to enter the cortical plate and position into upper layers II/III, followed by early-born interneurons that reach the lower cortical layer V/VI by the end of the first postnatal week. Interestingly, mid-born interneuron position in the second post-natal week and are the last to reside within the cortical plate. By using heterochronic explant cultures we have observed marked differences between migratory behaviours when early- or late-born interneurons are exposed to ventricle or pial cortical structures. This study reveals that, unlike pyramidal neurons, the timing of interneuron positioning does not follow a birthdate and highlights the role of local factors in dictating the temporal arrangement of entry into the cortical plate.

## SYM-03-03

**POSTNATAL INTERNEURON DEVELOPMENT: SETTING THE CELLULAR STAGE FOR SCHIZOPHRENIA**Fung S.J.<sup>1,2,3</sup> and Shannon Weickert C.<sup>1,2,3</sup><sup>1</sup>Schizophrenia Research Institute. <sup>2</sup>Neuroscience Research Australia. <sup>3</sup>University of New South Wales.

**Purpose:** The onset of schizophrenia symptoms in late adolescence implies a neurodevelopmental trajectory for the disease and GABAergic deficits are widely replicated in post-mortem schizophrenia studies. However, the link between human GABAergic inhibitory neuron maturation and schizophrenia onset has not been made. **Methods:** Using quantitative PCR, we examined mRNA expression of several interneuron markers across postnatal human prefrontal cortex development and in schizophrenia. Additionally, we used immunohistochemistry for neuronal and migration markers to study white matter neurons in development and schizophrenia. **Results:** Dynamic expression trajectories of interneuron markers were seen across postnatal life with most dramatic changes in the first few years. The majority of interneuron marker mRNAs were decreased in schizophrenia, with the exception of calbindin, which was increased. We note the largest reduction in somatostatin mRNA (31%), expressed by dendrite-targeting subtype of interneurons. Interestingly, in our cohort of people with schizophrenia, we found an increase in the density of white matter neurons that was correlated with a decrease in somatostatin mRNA, suggesting a deficit in interneuron markers in grey matter may be related to increased density of neurons in white matter. Furthermore, we found neurons in the white matter to be positive for markers that implicate them as immature GABAergic inhibitory interneurons (Dlx1, GAD-65/67, PSA-NCAM). **Conclusions:** It appears that a heterogeneous population of interneurons is potentially dysfunctional in schizophrenia, including those with more dramatic early developmental changes and more delayed maturation. Our data suggest that altered neuronal migration of cortical inhibitory interneurons might contribute to the interneuron deficit in the grey matter found in people with schizophrenia.

## SYM-03-02

**MOLECULAR DEVELOPMENT OF PROJECTION NEURON TYPES AND BUILDING OF LOCAL MICROCIRCUITRY IN THE CEREBRAL CORTEX**

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The activity and function of the mammalian cerebral cortex rely on the integration of an extraordinary diversity of excitatory projection neurons and inhibitory interneurons into balanced local circuitry. The developmental events governing the proper interaction between excitatory projection neurons and inhibitory interneurons are poorly understood. Here, we have first investigated the function of the transcription factor *Fezf2* in controlling the fate-specification of corticofugal projection neurons (CFuPN) of the neocortex. We find that *Fezf2* acts as a powerful master gene that is sufficient to instruct the birth of CFuPN even from progenitors fated to become medium spiny neurons in the striatum. Secondly, we report that different subtypes of projection neurons uniquely and differentially determine the laminar distribution of cortical interneurons into cortical layers. We find that in *Fezf2*<sup>-/-</sup> cortex, the exclusive absence of subcerebral projection neurons and their replacement by callosal projection neurons cause distinctly abnormal lamination of interneurons. This results in physiological imbalance of excitation due to altered GABAergic inhibition. In addition, experimental generation of either corticofugal neurons or callosal neurons below the cortex is sufficient to recruit cortical interneurons to these ectopic locations. Strikingly, the identity of the projection neurons generated, rather than strictly their birthdate, determines the specific types of interneurons recruited. These data demonstrate that in the neocortex individual populations of projection neurons cell-extrinsically control the laminar fate of interneurons and the assembly of local inhibitory circuitry. **Keywords:** Cerebral cortex, Microcircuit development, Directed differentiation, Projection neurons.

## SYM-03-04

**EXPLORING THE ROLE OF GABAERGIC INTERNEURON DYSFUNCTION IN NEUROPSYCHIATRIC DISORDER-LIKE PHENOTYPES**Nakazawa K., Zsiros V., Kolata S. and Nakao K.  
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**Purpose:** A cortical excitation/inhibition (E/I) imbalance, following impaired GABAergic inhibition, has been theorized to be critical to the emergence of neuropsychiatric disorders. We addressed whether an E/I imbalance is sufficient to trigger psychiatric-like phenotypes in mice. **Methods:** We generated three conditional knockout mutant lines, each with a cortical and hippocampal E/I imbalance. These mutant lines, NMDA NR1 (*Grin1*) KO, *Gad1* KO, and *ErbB4* KO, were made by crossing respective floxed mouse lines to the *Ppp1r2-Cre* line, in which the *Cre* recombination is confined to a subset (~50%) of cortical and hippocampal GABAergic interneurons. Impaired cortical inhibition phenotypes were assessed by slice physiology and/or in vivo unit recording. Furthermore, these mutants were subjected to behavioural battery tests. **Results:** Both NR1 mutants and *ErbB4* mutants displayed a reduced GABA release as measured by mini-IPSC frequency in principal neurons and a rebound excitation of principal neurons as measured by increased mean firing rates, compared to the littermate controls (in each group, n>7). *Gad1* mutants exhibited reduced GABA levels in the cortex and eventually elicited epileptiform activity by in vivo recording (n>5). Despite the presence of similar magnitudes of cortical disinhibition, these three mutants exhibited distinct behavioural phenotypes (in each group, n>7). In the NR1 KO mutants, schizophrenia-like symptoms emerged in mutants after adolescence (Belforte et al., 2010). In contrast, *Gad1* KO mutants demonstrated a deficit in generating motivated and/or hedonic responses. In the *ErbB4* KO mutants we found no major behavioural deficits. **Conclusion:** E/I imbalance by itself is insufficient to precipitate the emergence of specific psychiatric disorder-like phenotypes. Exploration for possible reasons for the varied phenotypes displayed by the different mutant lines is underway.

## SYMPOSIUM 4 – AUTONOMIC AND SENSORY CHANGES IN SPINAL CORD INJURY: IMPACT AND PROSPECTS FOR TREATMENT

*Proudly sponsored by the Spinal Cord Injury Network*

SYM-04-01

### MODULATING THE PATHOPHYSIOLOGY OF AUTONOMIC DYSREFLEXIA AFTER SPINAL CORD INJURY

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**Purpose:** Spinal cord injury (SCI) above mid-thoracic levels can lead to a potentially life-threatening hypertensive condition termed autonomic dysreflexia (AD) that is often triggered by unperceived distension of pelvic viscera (bladder/bowel) that elicits massive discharge of disinhibited sympathetic preganglionic neurons (SPN). Such dysreflexic vasoconstriction is usually accompanied by baroreflex-mediated bradycardia, and AD is associated with aberrant sprouting of nociceptive afferent fibers thought to amplify activation of disinhibited SPN. Selectively impeding intraspinal C-fiber sprouting with intrathecal therapeutics or site-specific transgene delivery mitigates experimental AD evoked by noxious colorectal distension (CRD) after complete high thoracic SCI in rats. **Methods:** Accordingly, we have reported that acute administration of the neuropathic pain medication, gabapentin (GBP; Neurontin, 50mg/kg, i.p.), significantly attenuated both AD and muscle spasticity induced by CRD and tail pinch, respectively, several weeks after complete thoracic (T4) SCI (n=9-12/group). Thus, GBP alleviated both AD and spasticity by eliminating a critical physiological link between these aberrant reflexes; the neurotransmission of noxious stimuli. **Results:** We have since employed long-term telemetry to establish, firstly, that chronic daily GBP administration did not have a significant effect on blood pressure for 21 days post-injury; there were trends for elevated blood pressure compared to daily saline treatment (n=6/group). Secondly, irrespective of chronic regimen, only acute GBP at 1 hr prior to stimuli significantly abolished both induced AD and spasticity at 14 and 21 days post-injury. Moreover, chronic GBP reduced daily spontaneous AD events detected by a novel algorithm developed based on telemetry data. **Conclusion:** While the precise mechanism by which GBP manifests these cardiophysiological alterations is not implicit, the AD algorithm provides a powerful investigative tool for assessing autonomic function pre- and post-SCI, in conjunction with experimental pharmacotherapeutics.

SYM-04-03

### CHANGES IN SYMPATHETIC NEUROVASCULAR TRANSMISSION AFTER SPINAL CORD INJURY

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Severe spinal cord injury (SCI) damages the brainstem-derived inputs to sympathetic preganglionic neurons (SPNs) that control the vasculature and thus higher centres no longer influence the vasoconstrictor neurons located below the level of the lesion. As a consequence, people with cervical or high thoracic SCI typically have low resting blood pressures (BPs) and are prone to hypotensive episodes in response to a postural challenge. Although SCI severs bulbospinal inputs to SPNs, the spinal reflex pathways below the lesion remain intact and are unopposed by inhibitory inputs from the brainstem. In the absence of central modulation, reflexly evoked increases in BP that are elicited by distension of visceral organs are exaggerated, raising arterial BP from low resting levels (mean ~70 mmHg) to systolic levels in excess of 200 mmHg, provoking cerebral and coronary vascular damage that increase the risk of strokes and myocardial infarcts. We have identified that this exaggerated reflex vasoconstriction (termed autonomic dysreflexia (AD)) arises, in part, from an augmented nerve-evoked constriction of blood vessels below the lesion, and that the augmented response involves a greater than normal role of L-type Ca<sup>2+</sup> channels in arterial responses, together with hyper-reactivity to angiotensin II. The significance of our observation is that drugs that specifically target the increased responsiveness of the vasculature to neural stimuli have the potential to limit the intensity of these abnormal hypertensive episodes and/or to improve prophylactic pharmacological treatment where the trigger for AD is unknown and when manipulations are going to be performed that evoke AD.

SYM-04-02

### PLASTICITY OF NOCICEPTIVE CIRCUITS AFTER SPINAL CORD INJURY

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A common problem following spinal cord injury (SCI) is the development of persistent, neuropathic pain that is very difficult to treat. It has been proposed that a contributing factor is the development of regions of abnormal activity (pain "amplifiers" or "generators") within the spinal cord and brain. Understanding the basis of this activity may facilitate the development of new treatments to prevent or attenuate SCI pain. We have investigated possible sites and mechanisms that underpin abnormal spinal activity using rodent models of complete and severe incomplete SCI. Direct comparison of both models enabled us to control for effects of injury on locomotion and to identify behavioural changes linked to presence of spared pathways. In this presentation I will discuss the outcomes of our behavioural pharmacology and neuroanatomy studies that demonstrate potential sites of plasticity in the dorsal horn that may contribute to the development and maintenance of pain. These may lead to new approaches for developing treatments tailored to this particularly debilitating pain state. In this presentation I will also discuss the challenges associated with SCI pain research and the importance of considering pain outcomes when performing studies to improve neural regeneration.

SYM-04-04

### AUTONOMIC DYSFUNCTION AFTER SPINAL CORD INJURY: INTERVENTIONS TO REDUCE THEIR IMPACT ON QUALITY OF LIFE

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Spinal cord injury (SCI), depending on the level and extent of neural damage, causes various somatic and autonomic nervous system dysfunctions. The impact on quality of life of loss of autonomic functions, such as control of bladder, bowel and sexual function, are often reported to be more important than an inability to walk. Autonomic dysreflexia (AD) is a potentially life-threatening condition affecting individuals with SCI above the major splanchnic outflow (typically due to a lesion at or above the T6 neurological level). Widespread reflex activity of the sympathetic nervous system below the level of injury, triggered by an ascending sensory stimulus such as bladder distension, leads to a rapid, high rise in blood pressure which remains uncontrolled due to the spinal cord being isolated from normal brainstem regulation. Neural prostheses, such as the Brindley Sacral Anterior Root Stimulator, have proven effective clinically for restoring bladder and bowel control, but traditionally have required sacral S2-4 rhizotomies to control detrusor hyperreflexia, prevent incontinence during bladder filling and avoid AD. Improved understanding of normal neural circuitry, physiology of human sacral reflexes, and structural and neurochemical changes following SCI offers new opportunities for interventions like Functional Electrical Stimulation (FES) to better modulate afferent activity and control/potentially remodel aberrant segmental reflexes.

## SYM-05-01

**FUNCTIONAL INTERACTIONS WITHIN AND BETWEEN OSCILLATORY BRAIN NETWORKS IN ATTENTIONAL CONTROL****Srinivasan R.**

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A fundamental question in any neurophysiological study using sensory input is whether observed modulations of neural responses in sensory cortex by cognitive processes are the result of the action of a local network in sensory cortex or due to the interactions between these local networks and the rest of the brain in global networks. This conceptual framework of local and global networks interacting in cognitive processes is salient to the interpretation of physiological signals obtained from the brain with any technique – EEG, MEG, fMRI, LFPs, or unit activity and to models of the underlying cognitive processes. In the visual system, functional organization of local networks has been shown to give rise to oscillations at gamma band (> 30 Hz) frequencies. Simultaneously, it also known that the visual system interacts with multiple parietal and frontal cortex large-scale functional networks typically exhibiting oscillations at lower frequencies in the theta (4-7 Hz) and alpha (8-12 Hz) bands. One important function of these interactions is attentional control of visual perception. We present the results of several EEG and MEG experiments that investigate these large-scale networks and their relationship to goal-oriented and stimulus-driven attention. These experiments make use of the frequency-tagging experimental design to elicit stimulus-specific steady-state visually evoked potentials (SSVEP) and fields (SSVEF). We demonstrate how these large-scale networks interact with each other and with local networks in the visual cortex during vigilance tasks.

## SYM-05-03

**INTERACTING WITH HUMAN BRAIN OSCILLATIONS BY RHYTHMIC TMS TO CHANGE ATTENTION AND PERCEPTION****Thut G.**

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Neuronal elements functionally assemble through synchronization in distinct frequency bands, depending on the state of the brain and on the task that is currently being executed, giving rise to brain rhythms that can be measured by electroencephalography (EEG). Transcranial magnetic stimulation (TMS) can be used to stimulate neuronal elements in rhythmic pulse-trains, at frequencies that characterize EEG-signals. This raises an intriguing question: Could frequency-tuned TMS be used to transiently entrain brain oscillations, and would this result in behavioural consequences, in line with the proposed functional roles of oscillations in perception and cognition? My talk will first cover known oscillatory EEG-signatures of visual attention. The main focus will be on EEG-signatures in the parietal alpha-band (8-14Hz), modulated by endogenous attention control in anticipation of an upcoming lateralized visual target (location-based attention), and predicting the perceptual fate of the forthcoming visual event. I will then provide evidence that the periodic electromagnetic force that is generated during TMS can be used to promote natural oscillatory signatures in a controlled manner (by entrainment via frequency-tuned rhythmic TMS). Finally, I will present recent findings on the perceptual consequences of parietal TMS, when TMS is tuned to the EEG-frequency of attention signatures. This covers frequency-specific effects of parietal alpha-TMS on lateralized target detection (location-based perception) and frequency-specific consequences of parietal TMS (at non-alpha frequencies) on feature-based attention/perception. This indicates that oscillatory EEG-activity can be used to derive state markers of visual cortex receptivity (amenable to attention control), that these signatures can be transiently entrained by frequency-tuned rhythmic TMS, and that this can alter brain states and thus functions in desired directions. This is indicative of brain oscillations to play a causal role in aspects of perception and cognition, and has implications for understanding TMS actions.

## SYM-05-02

**UTILITY OF FREQUENCY TAGGING FOR MEASURING VISUAL SELECTIVE ATTENTION IN HEALTH AND DISEASE****Mattingley J.B.**

The University of Queensland.

Mechanisms of attention are crucial for prioritising sensory inputs that are currently relevant for guiding behaviour and for suppressing those that are irrelevant. Within the human visual system, attention may operate to select subsets of stimulus inputs based upon their locations, visual features or task relevance. To investigate these different types of attentional selection, and how they are affected by acquired visual pathologies, we have combined scalp-recorded electroencephalography (EEG) with visual displays in which multiple concurrent stimuli flicker at distinct temporal frequencies. We then measure changes in the amplitude and coherence of these frequency-tagged stimuli as participants search for targets defined by their spatial locations, elementary features (e.g., colour), and so on. In the first part of the talk I will present recent findings from a series of experiments in which we examined the influence of visual and auditory perceptual load on cortical responses to ignored stimuli in the visual periphery. I will also discuss findings from experiments in which we asked whether feature-based selection extends to visual stimuli outside the focus of attention. In the second part of the talk I will present findings from frequency tagging investigations of patients with visual pathology involving the association cortex or retina. Patients with unilateral lesions of the posterior parietal lobe show characteristic deficits in both spatial and feature-based attention. Individuals who have lost foveal vision due to macular degeneration exhibit striking abnormalities in feature-based selection within their "intact", peripheral visual field. The measurement of neural oscillations induced by frequency tagged stimuli is a powerful technique for determining the cortical basis for visual selective attention in health and disease.

## SYM-05-04

**MANIPULATING OSCILLATIONS AND ATTENTION IN THE INSECT BRAIN****van Swinderen B.**

Queensland Brain Institute.

There is increasing evidence that even simple creatures such as flies have a selective attention, although evidence for parallel processing of simultaneous cues remains difficult to demonstrate in these animals. Local field potential (LFP) activity in the fly brain is associated with stimulus selection and suppression, much like in other animals, suggesting that similar processes may be working to control attention in vastly different brains. To investigate selective attention to competing visual cues, we recorded brain activity from behaving flies while applying a method used in human attention studies: visual flicker, or frequency tags. Behavioural fixation in a closed-loop flight arena increased the response to visual flicker in the fly brain, and visual salience modulated responses to competing tags. To further explore these attention-like effects, the *Drosophila* Gal4/UAS gene expression system was used to manipulate neuronal function in flies. A multichannel recording preparation allowed sampling of LFPs across the fly brain while specific populations of neurons were transiently activated or silenced. This combined behavioural, genetic, and electrophysiological approach provides a novel strategy for understanding of how brains process competing visual stimuli in order to pay attention and learn.

**SYMPOSIUM 06 – SENSORY INPUTS AND SENSATION***Sponsored by Neuroscience Research Australia*

SYM-06-01

**OROFACIAL SOMATOSENSORY MECHANISMS****Sessle B.J.**

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This presentation dedicated to Mark Rowe initially reviews his significant contributions to our understanding of somatosensory processes, first noting those related to orofacial somatosensation as evident from our collaborative studies in the 1960s. It then focusses on the research advances in the orofacial somatosensory field made by Mark and others since 1970, including the extensive orofacial representation in CNS somatosensory pathways, the exquisite coding properties of mechanosensitive and thermosensitive neurones in these pathways, and somatosensory modulatory and neuroplastic processes as exemplified by the whisker barrel system. The presentation also reviews pain mechanisms in the orofacial region, including its unique tissues (eg tooth-pulp, cornea) and the array of ion channels, receptors and chemical mediators involved in orofacial nociceptor activation, modulation and peripheral sensitisation. Acute and chronic pain models have targeted the brainstem regions receiving and relaying afferent inputs from these nociceptors, and documented the integral role that trigeminal subnucleus caudalis (medullary dorsal horn) plays in CNS processing related to orofacial pain. CNS substrates contributing to the sensory/discriminative and affective/motivational dimensions of orofacial pain and related sensorimotor and other behavioural manifestations have been identified in animals, and correlated findings in humans have resulted from an extensive repertoire of sensory, motor and psychosocial measures of experimental and clinical orofacial pain. Also noteworthy has been the discovery of intrinsic brain pathways and associated neurochemical, non-neural and genetic substrates that modulate orofacial nociceptive transmission and its behavioural expression. This includes central sensitisation of trigeminal nociceptive pathways which appears to be a fundamental facilitatory neuroplastic process involved in acute and chronic pain. These findings, including those of Mark Rowe, have provided a critical underpinning for future research utilizing the unique features of the orofacial somatosensory system to explore mechanisms underlying pain and other somatosensory functions.

SYM-06-02

**ANATOMICAL AND PHYSIOLOGICAL ORGANISATION OF THE LATERAL GENICULATE NUCLEUS FOLLOWING LESIONS OF PRIMARY VISUAL CORTEX IN EARLY LIFE****Rosa M.G.P.<sup>1,2</sup>, Yu H.-H.<sup>1,2</sup>, Chaplin T.A.<sup>1,2</sup>, Verma R.<sup>1</sup>, Reser D.H.<sup>1</sup> and Worthy K.H.<sup>1</sup>**<sup>1</sup>Department of Physiology, Monash University. <sup>2</sup>Monash Vision Group.

**Purpose:** In primates, projections from the lateral geniculate nucleus (LGN) to the primary visual area (V1) are essential for conscious visual perception. Partial damage to V1 in adults leads to irreversible blindness in a defined region of the visual field (scotoma). In contrast, V1 lesions in infancy allow preservation of some visual capacities, possibly due to contributions of parallel thalamic projections to extrastriate areas. However, we don't know if these pathways involve the LGN, particularly since many projection neurones in this nucleus die, as a result of severe retrograde degeneration, following infant V1 lesions. **Methods:** We studied the physiological properties of LGN cells in marmoset monkeys that had unilateral ablation of the representation of central 30-40° of visual field in V1, under isoflurane anaesthesia, between 2 and 36 weeks of age. Following survival times of 1-2 years, to allow development into adulthood, single-unit activity was recorded in the LGN, under sufentanil (6 µg.kg<sup>-1</sup>.h<sup>-1</sup>) N2O anaesthesia. **Results:** We found that, despite massive cell loss, the sector of the LGN that sent projections to the lesioned part of V1 (lesion projection zone) contained neurones with clear visual responses. The receptive fields of these neurones were well-defined, and followed the expected patterns of topographic representation and eye dominance. However, in many instances these receptive fields were enlarged, relative to those of cells outside the lesion projection zone. **Conclusion:** These results demonstrate that the surviving LGN neurones are plausible candidates for mediators of the pathway that allows residual vision following V1 lesions in early life.

SYM-06-03

**PROPRIOCEPTION: NOVEL INPUTS AND PROCESSES****Gandevia S.C.**

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Proprioception is an enigmatic group of sensations which is critical for the control of movement and the maintenance of posture. It was long thought to rely on sensory signals including those from specialised muscle receptors, especially muscle spindles. However, cutaneous receptors are now known to provide information about perceived joint position and movement (1). Also, information from motor commands, previously known to bias force sensation, has recently been shown to generate sensations of limb position and movement (2) in some combination with peripheral signals. Such signals arising from muscle spindle receptors are capable of changing their discharge with muscle length but the magnitude of their responses are complicated by muscle thixotropy, and their central interpretation is complicated by fusimotor drives (3). The role of muscle afferent signals in force sensation has recently been re-evaluated (4). The emerging picture is that multiple sensory signals can be combined to generate different proprioceptive sensations. In addition, these multiple proprioceptive inputs must be combined with other sensory inputs (from the eyes and vestibular system) to generate the full awareness of our local and external surroundings. Such awareness requires additional information, not traditionally part of proprioception, derived from a body representation or image. This allows us to know the lengths and size of limbs, and even whether particular limbs belong to us. Future work needs to address how the body representation and proprioceptive input are blended to provide a useful sensory map. 1. Collins DG, Refshauge K & Gandevia SC (2005), *JNeurophysiol* 94: 1699-1706 2. Gandevia SC, Smith JL, Crawford M, Proske U & Taylor JL (2006), *JPhysiol* 571: 703-10 3. Allen TJ, Ansems GE & Proske U (2008), *ExpPhysiol* 93: 391-8 4. Luu BL, Day BL, Cole JD & Fitzpatrick RC (2011), *JPhysiol* 589: 3135-47.

SYM-06-04

**PERIPHERAL ENCODING OF PAINFUL AND ITCHING STIMULI IN MAN****Handwerker H.O.**

FAU - University of Erlangen/Nuernberg, Dept. Physiology&amp;Pathophysiology, Erlangen, Universitaetsstr. 17.

Single afferent nerve fiber recordings (microneurography) have recently lead to an increase of our knowledge on peripheral encoding of painful and itching stimuli. Our interest concentrated on two topics: (a) Can neuropathic pain and hyperalgesia be explained by the changed encoding in peripheral cutaneous nerve fibers, in particular in C-fibers? Recently molecular studies on patients have shown that changes in the properties of the conductile membrane, in particular of NaV channels, contribute to the changed encoding. Microneurography demonstrates the consequences of those changes for pain processing. (b) Itching, like pain is transmitted by slowly conducting nerve fibers. Which type of afferent encoding leads to the different sensations of pain and itch? It turned out that the answer to this question depends on the type of itching stimuli. Whereas histamine-dependent itch is mainly mediated by a special subgroup of mechano-insensitive C-fibers, histamine-independent itch seems to be mediated by a different nerve fiber group, polymodal nociceptors. Since the latter fiber group also mediates pain sensations, the encoding of "histamine-independent" itch remains enigmatic. Several hypotheses attempting to solve this puzzle will be discussed in this lecture. Though microneurography is a key method for studying peripheral encoding of sensory signals in humans, it has some disadvantages: not all nerves are likewise accessible with this method and C-fiber recordings are much more stable than recordings from thinly myelinated fibers which also contribute to pain and itch. Furthermore, molecular mechanisms, e.g. changes in gene expression cannot be manipulated and studied in humans for practical and ethical reasons. For getting a full picture of the peripheral encoding of pain and itch animal experiments remain essential.



## SYM-07-01

**TWO-CHAIN PROCESSING OF THE ORPHAN RECEPTOR SORCS2 SWITCHES FUNCTION FROM TROPHIC TO PRO-APOPTOTIC**

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<sup>1</sup>Dept. of Biomedicine, Aarhus University, Aarhus, Denmark. <sup>2</sup>Max-Delbrück-Center for Molecular Medicine, Berlin, Germany.

**Purpose:** To study the physiological role of SorCS2, an orphan receptor belonging to the Vps10p-domain gene family. **Methods:** Biochemistry, cell biology, and phenotypic characterization of a new knockout mouse model. **Results:** Balancing trophic and apoptotic cues is critical for proper development, activity, and regeneration of the nervous system. Here we identify SorCS2 as a unique neuronal receptor for proneurotrophins capable of both trophic and apoptotic signalling when coexpressed with p75<sup>NTR</sup>. CNS neurons express SorCS2 as a single-chain protein and SorCS2-deficiency in mice causes reduced growth cone collapse of dopaminergic neurons. This defect translates into hyperactivity and a paradoxical response to amphetamine reminiscent of ADHD, a phenotype shared with p75<sup>NTR</sup> knockouts. In contrast, sciatic nerve injury induces expression of two-chain SorCS2 in dying Schwann cells that are also positive for p75<sup>NTR</sup>. Notably, Schwann cell apoptosis is profoundly attenuated in Sorcs2<sup>-/-</sup> mice. **Conclusion:** We conclude that single-chain SorCS2 is required to secure neuronal integrity, while two-chain processing switches its activity from trophic to pro-apoptotic.

## SYM-07-02

**IDENTIFICATION OF AMINO ACIDS IN SORLA THAT INFLUENCE APP PROCESSING AND PROTECT AGAINST ALZHEIMER'S DISEASE**

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Department of Biomedicine, Aarhus University.

**Purpose:** We want to understand interactions of sorLA that influence the processing of Amyloid precursor protein. **Methods:** Protein interactions were measured by fluorescence lifetime imaging microscopy, proximity ligation assays, and co-immunoprecipitation. Protein sorting was followed by confocal and electron immunomicroscopy and live-cell imaging techniques. Protein processing was analyzed by Western blot and ELISA methods. **Results:** We have identified three amino acids in the extracellular domain of sorLA important for the direct interactions with APP. Substitutions of these residues within sorLA impair proper APP trafficking, maturation and processing. We have also identified the FANSHY sorting motif in the intracellular domain of sorLA as a binding site for the retromer complex. The interaction between sorLA and retromer is important for the retrograde sorting of sorLA from the tubule endosomal network to Golgi. Mutation of the FANSHY sequence also leads to changes in APP transport and Amyloid  $\beta$  peptide production. **Conclusions:** SorLA is a key regulator of APP trafficking, and we have shown that substitution of only a few amino acids in both the extracellular and intracellular domains of sorLA have major impact on Amyloid  $\beta$  peptide generation and thus Alzheimer's disease.

## SYM-07-03

**ROLES OF P75 IN THE DEVELOPMENT OF ALZHEIMERS DISEASE**

Zhou X.F.  
Flinders University.

The pathogenesis of Alzheimer's disease (AD) is not fully understood, and no strong disease-modifying therapies are currently available. Recent studies suggest that the pan-neurotrophin receptor, p75<sup>NTR</sup>, is a critical factor involved in the pathogenesis of AD. p75<sup>NTR</sup> is highly expressed in cholinergic neurons in the basal forebrain but its role in the AD development is not known. We found that p75<sup>NTR</sup> has differential roles in Abeta metabolism, increasing the production of amyloid-beta (A $\beta$ ), but preventing Abeta deposition in the brain of AD mice. Deletion of the p75<sup>NTR</sup> gene in APPSwe/PS1dE9 mice reduced soluble A $\beta$  levels in the brain and serum, but increased the accumulation of insoluble A $\beta$  and A $\beta$  plaque formation. A $\beta$  production by cortical neurons of APPSwe/PS1dE9 mice was reduced by deletion of p75<sup>NTR</sup> gene in vitro. Recombinant extracellular domain of p75<sup>NTR</sup> attenuated the oligomerization and fibrillation of synthetic A $\beta$ (42) peptide in vitro, and reduced local A $\beta$  plaques after hippocampus injection in vivo. In addition, deletion of p75<sup>NTR</sup> attenuated microgliosis but increased the microhemorrhage profiles in the brain. The deletion of p75<sup>NTR</sup> did not significantly change the cognitive function of the mice up to the age of 9 months. P75 interacts with APP and the interaction is enhanced by Abeta. Our data suggest that p75<sup>NTR</sup> plays a critical role in regulating A $\beta$  levels by both increasing A $\beta$  production and attenuating its aggregation.

## SYM-07-04

**THE INTRACELLULAR DOMAIN OF P75 NEUROTROPHIN RECEPTOR IS AN ALLOSTERIC MODULATOR OF THE TRK RECEPTORS: A NEW MODEL OF HOW THESE RECEPTORS BIND NEUROTROPHINS WITH HIGH-AFFINITY**

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The neurotrophin receptors, p75 neurotrophin receptor and TrkA, form a high-affinity complex that mediates the fundamental trophic actions of their ligand, nerve growth factor (NGF), both during development and in the adult nervous system. Although each receptor can signal independently in response to this ligand, together p75 and TrkA respond to the limiting concentrations of NGF found in vivo by signalling as a complex with a ligand-binding affinity 100 fold higher than that of either receptor alone. However, the mechanism by which the high-affinity receptor is generated remains controversial. Several years ago we made a small peptide (c29) of the p75 intracellular juxtamembrane "chopper" death domain that could prevent cell death. We have now found that the c29 peptide interacts with both TrkA and TrkB, and acts as an allosteric modulator of Trk, facilitating TrkA- and TrkB-mediated signalling, neurite outgrowth and neuronal survival. The endogenous p75 intracellular domain fragment, which contains the c29 sequence, also acts in this way. Importantly, the c29 peptide dramatically increases the binding of NGF to cells expressing TrkA. This suggests that the affinity of Trk for neurotrophins is modulated by an inside-out mechanism mediated by the chopper domain of p75.

## SYM-08-01

**IMPROVING CELL BASED THERAPY FOR PARKINSON'S DISEASE**

Bye C.R., Thompson L.H. and **Parish C.L.**  
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 Parkville, Victoria, Australia, 3010.

Parkinson's disease is characterized by the progressive degeneration of midbrain dopamine neurons, resulting in motor function disturbances. Whilst current therapies are limited, clinical trials have demonstrated that new dopamine neurones transplanted directly into the brain can structurally and functionally compensate for those lost in PD. Whilst providing proof-of-principle, these trials have also shown extensive variability amongst patients and exposed a number of caveats in the technology, including: limited tissue availability; poor cell survival; and insufficient reinnervation of target tissue. These hurdles highlight the need for further research, and provide the foundation for our research. Our focus is on optimising donor material, improving graft survival and promoting integration of grafted neurons. In order to tackle these problems we rely heavily on knowledge of developmental biology. How are dopamine neurones normally born in the foetus and what regulates the growth and guidance of their axons to appropriate targets? Understanding these processes and exploiting them in a stem cell transplantation context could significantly improve this technology. This presentation will focus on a recent birth dating study to identify optimal tissue for transplantation. This work includes classical ectopic transplantation into Parkinsonian rodents to restore DA transmission as well as efforts to restore normal circuitry through homotypic grafting and delivery of trophic cues.

## SYM-08-03

**HUMAN OLFACTORY NEUROSPHERE DERIVED CELLS AS A MODEL FOR STUDYING PARKINSON'S DISEASE**

**Mellick G.D.**  
 Eskitis Institute for Cell and Molecular Therapies, Griffith University.

Parkinson's disease (PD) is a complex disorder with unknown triggers. To piece together our current aetiological clues and to find common cellular targets that influence disease risk and progression, new cell model systems are required. Human cell-line models can form a logical link between human clinical studies, post-mortem pathological investigations and animal model systems. To be most effective these cell lines should be readily derived from living humans, available in sufficient quantity to enable manipulation and wide-spread investigation and represent the diversity of human genetic background and aetiology. Human olfactory neurosphere-derived (hONS) cell lines are one such novel model being developed by our research team at the Eskitis Institute for studying PD. We recently observed that hONS cells derived from patients with idiopathic PD (n=28) have a dysfunctional NRF2-mediated oxidative stress response pathway. We also showed that PD hONS exhibited a 16% decrease in glutathione levels and an 18% decrease in MTS metabolism compared to control-derived cell lines (n=26). These functional differences could be reversed by activating the NRF2 pathway with the molecule L-Sulforaphane. We subsequently went on to show that, compared to control cell lines, PD-derived hONS cells exhibited increased sensitivity to sub-lethal doses of the parkinsonism-related mitochondrial toxin, rotenone. Culturing hONS cells in the presence of 50nM rotenone over 120 hours revealed a statistically significant disease-related reduction in cell numbers (as assessed by the cyquant assay for DNA content) and increased markers of apoptosis in the PD cells compared to controls (Two-way ANOVA,  $p < 0.01$ ). Interestingly, a similar disease-related cell vulnerability was observed to 1.2 $\mu$ M Ptericidin A, a second mitochondrial complex I inhibitor. Purified mitochondria isolated from PD-derived hONS showed reduced complex I activity compared to those derived from healthy controls. Further experiments are interrogating the relationship between complex I deficiencies, oxidative stress and this interesting susceptibility phenotype in PD-derived hONS cells.

## SYM-08-02

**FUNCTION OF WNTS IN DOPAMINERGIC NEURON DEVELOPMENT AND REGENERATIVE MEDICINE FOR PARKINSON'S DISEASE**

**Arenas E.**  
 Dept Medical Biochemistry and Biophysics, Center of Excellence in Developmental Biology for Regenerative Medicine (DBRM), Karolinska Institute, Stockholm, Sweden.

Wnts are a family secreted lipid-modified and glycosylated proteins currently formed by 19 members. Wnts are known to regulate multiple functions in the developing brain, including polarity, patterning, specification, proliferation, differentiation and neurogenesis. However, the full extent of their activities on dopaminergic (DA) neurons and the molecular mechanisms by which they exert such functions are largely unknown. Our studies have focused on two of the most abundant Wnts present in the developing ventral midbrain: Wnt1, a Wnt that -catenin signalling pathway; and Wnt5a, that activates the Wnt/ Wnt/Planar Cell Polarity pathway. In the past we have shown that Wnt5a prevents excessive proliferation and promotes DA neuron differentiation in the midbrain in vivo. Moreover, we developed an application of Wnt5a to improve safety and efficiency of mouse neural and embryonic stem cells in cell replacement therapy approaches for Parkinson's disease (PD). More recently we have examined the function of Wnt1 in more detail, by analysing wnt1<sup>-/-</sup> mutant mice, and found that some of the actions of Wnt1 and Wnt5a seem to be complementary. We have thus investigated whether Wnt1 and Wnt5a collaborate or compete to promote DA neuron development. To investigate this possibility we analysed wnt1<sup>-/-</sup>;wnt5a<sup>-/-</sup> double mutant mice. These results allowed us to gain further understanding of the mechanisms that control midbrain DA neuron development. We are currently working to develop a novel protocol for the improved differentiation of human pluripotent stem cells into DA neurons. We think that by refining this process it will be possible to: (1) further improve the efficiency and safety of cell replacement therapies for PD; and (2) develop PD iPS cells as in vitro tools for disease modelling and drug screening.

## SYM-08-04

**CHANGES IN NEUROGENESIS IN THE AGEING AND PARKINSON'S DISEASE BRAIN: WHAT CAN WE LEARN ABOUT ENDOGENOUS REPAIR?**

**Werry E.L.**<sup>1,2,3</sup>  
<sup>1</sup>Neuroscience Research Australia, Randwick, NSW. <sup>2</sup>Brain Sciences University of New South Wales, Randwick, NSW. <sup>3</sup>Schizophrenia Research Institute, Randwick, NSW.

Stem cell-based restorative treatments are hoped to represent novel therapeutic approaches in a variety of neurodegenerative disorders. For such treatments to become a reality it may be useful to investigate whether the older human brain is a supportive neurogenic environment as most neurodegenerative diseases are disorders of later life. We examined the effect of ageing on neurogenesis levels and levels of putative neurogenesis-regulatory factors in the healthy adult human brain using ELISA and immunohistochemistry. Protein levels of four factors reported to regulate neurogenesis in other species, basic fibroblast growth factor, epidermal growth factor, glial-derived neurotrophic factor and brain-derived neurotrophic factor, were associated with aspects of neurogenesis in the human brain ( $p < 0.05$ ) and their levels remained unaltered across the adult lifespan. Investigations of neurogenesis in the common neurodegenerative disease Parkinson's disease (PD) revealed that reduced hippocampal volume in PD reflected reduced hippocampal neurogenesis ( $p < 0.05$ ), and levodopa transiently ameliorated the reduction in hippocampal proliferation. In contrast, in the subventricular zone only immature neuron number was significantly reduced in early PD ( $p < 0.05$ ), while progenitor cell numbers were preserved. These findings may inform the development of therapies based on stem cell technology.

## SYM-09-01

**LOCATION-DEPENDENT EFFECTS OF INHIBITION IN PYRAMIDAL NEURON DENDRITES**Schiller J.S.<sup>1</sup>, Jadi M.J.<sup>2</sup>, Mel B.M.<sup>2</sup> and Polsky A.P.<sup>3</sup><sup>1</sup>Technion Medical School Haifa Israel. <sup>2</sup>University of Southern California, Los Angeles. <sup>3</sup>National Institute of Neurological Disorders and Stroke. National Institutes of Health, Bethesda, MD 20892-3701 USA.

Cortical computations are critically dependent on interactions between pyramidal neurons (PNs) and a menagerie of interneuron types. A key feature distinguishing inhibitory interneurons is the spatial distribution of their synaptic contacts onto PNs — variously targeting perisomatic, dendritic, and/or axonal regions. However, the location-dependent effects of inhibition on active dendritic responses are not yet understood. We studied the effects of somatic vs. dendritic inhibition on local spike generation in layer 5 PN basal dendrites both in neocortical slices and compartmental models, with equivalent results: somatic inhibition divisively suppressed the amplitude of dendritic spikes recorded at the soma while minimally affecting the threshold level of dendritic excitation needed to trigger them. In contrast, dendritic inhibition elevated dendritic spike thresholds while minimally affecting their amplitudes. Our findings suggest that cortical circuits have the flexibility to achieve varying mixtures of gain vs. threshold inhibition in different neural pathways — and thus tailor their local computations— by managing different pathways' relative activation of soma- vs. dendrite-targeting interneurons.

## SYM-09-02

**INHIBITORY MICROCIRCUITS IN THE PRIMARY OLFACTORY CORTEX**

Bekkers J.M. and Suzuki N.

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The primary olfactory (or piriform) cortex is a primitive, three-layered paleocortex located in the ventral forebrain. As the first cortical recipient of olfactory information, the piriform cortex (PC) is thought to assemble 'odour images' from the many volatile chemicals that are detected by the nose. How such a simple cortical circuit performs this sophisticated synthetic task is unknown. The PC is also unusually susceptible to epilepsy and neurodegenerative diseases. For these reasons, the PC is increasingly being used as a model system for studying sensory processing and brain disorders. We have taken a 'bottom up' neurophysiological approach to our study of the PC, using acute brain slices from mice to identify the cell types and microcircuits that underlie its remarkable processing power. We have identified five major classes of inhibitory interneurons in the PC, four of them similar to those found in the neocortex, one of them unique to the PC. We have also characterised some of the inhibitory microcircuits in the PC, showing how particular types of interneurons generate feedforward and feedback synaptic inhibition in response to afferent input from the olfactory bulb. Finally, we are beginning to examine other roles of PC interneurons, such as preventing epileptiform activity. Future work will need to explore the operation of these inhibitory circuits in intact animals when they sniff an odour.

## SYM-09-03

**INHIBITION IN THE AMYGDALA: ROLE OF INTERCALATED NEURONS**Strobel C.<sup>1</sup> and Sah P.<sup>1</sup><sup>1</sup>Queensland Brain Institute. <sup>2</sup>University of Queensland.

Inhibition in the amygdala: Role of intercalated neurons. Pankaj Sah and Cornelia Strobel. Queensland Brain Institute, University of Queensland The amygdala is a temporal lobe structure that plays a key role in assigning emotional salience to sensory stimuli. It plays a central role in emotionally salient behaviours, and in particular plays a major role fear learning and extinction. The amygdaloid complex has a number of interconnected nuclei that together process incoming sensory information. Of these the basolateral and central amygdala are two main nuclei forming the input and output structure respectively. During fear learning, a converging body of data has found that learning results from synaptic plasticity at glutamatergic inputs to neurons in the basolateral amygdala. Following learning, repeated presentations of the conditioned stimulus leads to a reduction of the response — a process known as extinction. Extinction results from new learning rather than erasure of the previously learnt response. One influential theory for extinction suggests that it results from plasticity of synaptic inputs to the intercalated cell masses (ITCs). The ITCs are inhibitory neurons that act as feed-forward interneurons between the basolateral and central amygdala. In this talk I will describe ongoing studies on the properties of neurons in the intercalated cell masses. I will describe their physiological and synaptic properties.

## SYM-09-04

**HUMAN GENETIC EPILEPSY CAUSED BY A GABAA RECEPTOR MUTATION ALTERS CORTICAL INHIBITION AND INTERNEURON DENSITY**Petrou S.<sup>1,2</sup><sup>1</sup>Florey Neuroscience Institutes. <sup>2</sup>The Centre for Neuroscience, The University of Melbourne.

Purpose: Genetic generalised epilepsy (GGE) is a phenotypically diverse collection of common epilepsies that includes benign febrile seizures and severe epileptic encephalopathies such as Dravet syndrome. A GABRG2(R43Q) mutation was found in a large family with Childhood Absence Epilepsy and Febrile Seizures. Subsequent clinical studies showed that patients with the mutation had significantly altered cortical properties as compared to family members without the mutation. Electrophysiological studies in the GABRG2(R43Q) mouse model showed a selective change in inhibition in layer 2/3 cortical pyramidal neuron and studies in a conditional model showed that seizures are exacerbated in mice that had the mutation from conception as compared to those where the mutation was turned on after post natal day 21. In this study we further explore the neurodevelopmental consequences of the GABRG2(R43Q) mutation by assessing interneuron numbers and positioning within the cortex in seizure naïve mice as compared to littermate controls. Methods: For our comparative analysis only the C2 barrel was analysed in order to limit the impact of cortical micro-heterogeneity. Mice were sacrificed at P30 and the cortex serially sectioned, stained for parvalbumin, calbindin and calretinin. After reconstruction of the C2 barrel, individual interneurons were counted and their position determined. Barrels from 5 control and 5 mutant mice were counted. Results: Densities of parvalbumin- and calretinin-expressing inhibitory neurons were increased specifically in layers 4 to 6, showing for the first time altered cortical microanatomy in a GGE model of epilepsy. Conclusion: These changes may lead to abnormal wiring of the cortex contributing to absence seizure genesis in Gabrg2R43/Q43 mice and patients and may have future impact on how GGE is diagnosed.

## SYM-10-01

**PIKFYVE REGULATION OF NEURONAL TRAFFICKING AND SURVIVAL**

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**Purpose:** The lipid kinase PIKfyve has been shown to synthesize PtdIns(3,5)P<sub>2</sub> on endosomal membranes. Genetic alterations of the PIKfyve complex leading to even mild reduction in PtdIns(3,5)P<sub>2</sub> result in marked neurodegeneration. We have used the selective PIKfyve inhibitor, YM-201636, to investigate its functions in neurons and neuroendocrine cells, and how perturbations in these may contribute to neuronal cell death. **Results:** Blocking PIKfyve function by either expression of PIKfyve kinase-dead, knockdown using shRNA or acute PIKfyve inhibition using YM-201636 all resulted in a potentiation of neurosecretion in neuroendocrine cells. Similarly, 20 min YM-201636 treatment increases neurotransmitter release from synaptosomes and the neuromuscular junction. In primary hippocampal neurons, 24 hr YM-201636 treatment resulted in vacuolation of endolysosomal membranes followed by apoptosis-independent cell death. Endocytosis of marker proteins was unaffected, suggesting that direct defects in endocytosis do not underlie cell death. Many vacuoles contained amorphous intravacuolar membranes and inclusions reminiscent of autolysosomes. Accordingly, YM-201636 treatment increased the level of the autophagosomal marker protein LC3-II at the onset of vacuolation and this effect was potentiated by inhibition of lysosomal proteases. We further examined the levels of autophagy in PC12 cells stably expressing reporter LC3 constructs. Inhibition of PIKfyve led to the selective disappearance of autophagosomes suggesting that the increased LC3-II levels did not stem from de novo autophagosome formation. Furthermore, dual inhibition of PIKfyve and lysosomal proteases in GFP-LC3 expressing cells potentiated LC3-II accumulation, but not GFP-LC3 cleavage revealing a novel role for PIKfyve activity in the formation of fully degradative autolysosomes. **Conclusion:** PIKfyve therefore controls multiple trafficking processes in neurons, from exocytosis to the proteolysis of autophagocytosed proteins, a process that may be critical for neuronal survival.

## SYM-10-03

**TRANSCRIPTIONAL REGULATION OF CNS (RE-) MYELINATION**

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During both developmental myelination and remyelination following injury the development of oligodendrocytes and their subsequent myelination of axons is regulated by the coordinated action of a large number of transcription factors. Previous work has identified members of the Nkx, Sox and Olig families as having vital roles at various stages of the lineage. We have recently described a novel transcription factor, Myelin Gene Regulatory Factor (MRF), that is specifically expressed at the myelinating stage of the lineage. MRF is vital for the process of CNS myelination during development; conditional knockout mice lacking MRF within the oligodendrocyte lineage generate oligodendrocyte progenitors and pre-myelinating oligodendrocytes, however these oligodendrocytes are unable to express myelin genes or myelinate adjacent axons. These mice display a complete absence of CNS myelin and do not survive beyond the third postnatal week. Conversely, forced expression of MRF in oligodendrocyte progenitor stages induces a precocious expression of myelin genes. Using ChIP-Seq, we demonstrate that MRF binds directly to promoter and enhancer regions of genes encoding the protein components of myelin, as well as cytoskeletal, lipid metabolism and junctional proteins that underpin the myelination process. Although MRF is expressed to only low levels in the healthy adult white matter it is strongly induced during remyelination, suggesting that its role in promoting developmental myelination is likely to be conserved in remyelination. These findings establish MRF as a master-regulator of the CNS myelination process, with likely roles in myelin repair.

## SYM-10-02

**MAKING LIGHT WORK: VISUAL STIMULI AND NEURAL MECHANISMS OF REINFORCEMENT**

**Reynolds J.N.J.**

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The striatum receives converging neural signals from cortex, substantia nigra pars compacta (SNc) and thalamus that work together during positive reinforcement. Our focus has been on understanding how these signals interact to induce synaptic plasticity within the striatum in a manner that may credibly underlie the reinforcement of behaviour. Using intracellular recordings in vivo, we have shown that dopamine released phasically by rewarding electrical stimuli of SNc favours the potentiation of cortical inputs to striatal spiny neurons, which correlates with learning. For potentiation to be induced, dopamine cell activation must occur following motor cortical activity, analogous to the situation where an action is closely followed by a salient stimulus. Further, we found that dopamine cell activation must be accompanied by simultaneous depolarisation originating from a source other than the cortex. This source is likely to be the thalamus, based on recent experimental data and theoretical claims that salient stimuli simultaneously activate neurons within the SNc and the intralaminar thalamus. We verified this by recording the membrane potential of striatal neurons while flashing a light into a rats eye, after disinhibiting neurons in the superior colliculus to render visual inputs as salient. Visual stimuli strongly depolarised spiny neurons into an Up state via the intralaminar thalamus, and activated a burst-pause response in tonically firing cholinergic interneurons. The latter response is thought to arrest ongoing behaviour and facilitate synaptic plasticity induction in spiny neurons. Thus, the appearance of a salient visual stimulus potentiates recently active cortical synapses through a subcortical circuit that depolarises striatal neurons and drives phasic dopamine release. Through this mechanism, an action that reliably causes the appearance of a visual stimulus may be reinforced.

## SYM-10-04

**OLIGODENDROGENESIS AND MYELIN REMODELLING IN THE ADULT CENTRAL NERVOUS SYSTEM**

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During development and in adulthood oligodendrocyte progenitor cells (OPCs) express voltage gated sodium channels, receive synaptic input from neurons, proliferate and generate myelinating oligodendrocytes (OLs). **Purpose:** It is not known whether adult-born OLs continue to ensheath unmyelinated axons, or else participate in turnover or remodelling of existing OLs. We reasoned that if adult-born OLs primarily myelinate naive naked axons, then the rate of OL production should reflect the local density of unmyelinated axons. **Methods:** Using electrophysiology, EdU-labelling and transgenic lineage tracing (with PDGFRa-CreERT2 transgenic mice) we examined the membrane properties of OPCs, their proliferation and OL differentiation in different regions of the adult central nervous system including the optic nerve, in which practically all axons are myelinated by P60. **Results and Conclusions:** All OPCs were dividing and generating new myelinating OLs, even in the optic nerve of four month old mice. We found that 6.7 ± 1.4% (mean ± s.d., n=3) of all CC1+ OLs in the optic nerve are born between P120 and P185, providing strong evidence for OL turnover or remodelling during healthy adulthood.

## SYM-10-5

**GHRELIN RESISTANCE IN THE HYPOTHALAMUS OF DIET-INDUCED OBESE MICE**

**Andrews Z.B.**  
Monash University.

Leptin and insulin resistance are hallmarks of diet-induced obesity (DIO), however little is known about the actions of ghrelin in DIO mice. Because AMPK activity regulates ghrelin-induced food intake and AMPK activity is suppressed in the hypothalamus of DIO mice, we hypothesized that DIO would promote ghrelin resistance in the arcuate nucleus. Mice were fed a high fat diet for 12 weeks. DIO mice were given normal chow diet 3 days before feeding experiments to control for diet. Ghrelin (3 nmol) injected ICV clearly promoted food intake, either at the beginning of the light or dark phase, in normal chow diet mice but no effect was observed in DIO mice. To investigate the mechanisms involved, we examined cfos immunoreactivity in the arcuate nucleus of ghrelin-injected obese and control mice. Although ghrelin significantly stimulated cfos immunoreactivity in the arcuate of chow-fed mice, no effect was observed in DIO mice. Furthermore, ghrelin promoted NPY mRNA gene expression in chow-fed but not DIO mice. No difference in POMC mRNA gene expression was observed in any group. Interestingly, mRNA expression for the ghrelin receptor (GHSR) was increased in DIO mice compared to chow-fed controls. Despite the increase in GHSR mRNA in DIO mice, the lack of effect of ICV ghrelin suggests a defect in the GHSR underlies the observed ghrelin resistance. We suggest that the physiological role of ghrelin is not to induce obesity but rather prevent starvation by shifting an animal from negative to neutral energy balance. Ghrelin resistance is an evolutionary adaptive mechanism to prevent excessive weight gain.

## SYM-11-01

**SEQUENCING OF HIPPOCAMPAL AND CEREBELLAR TRANSCRIPTOMES: EXPLORING THE COMPLEXITY OF GENE REGULATION IN THE HUMAN BRAIN**

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The hippocampus and cerebellum represent anatomically and functionally distinct parts of the human brain. Our understanding of the differences between these two regions on the transcriptome level remains very limited, partly because of the technological drawbacks of microarray technology. The RNA-Seq technique offers the possibility of investigating the human transcriptome with unprecedented resolution, allowing researchers to not only to quantify transcripts levels but also to identify patterns of differential mRNA splicing and promoter usage on a genome-wide level. We used Illumina-based whole mRNA sequencing of samples from the human hippocampus and cerebellum. A bioinformatic analysis using TopHat, Cufflinks, and gene ontology enrichment revealed distinct expression patterns of a relatively low number of genes related to the molecular physiology of the neurons and glial cells. Moreover, we observed differences between the hippocampus and the cerebellum in the splicing patterns and promoter usage of the NHP2L1 and HLA-B genes. Both genes demonstrate expression of transcriptional isoforms with retained introns. Our findings indicate that distinct regions of the human brain present similar but distinct patterns of splicing and transcription start site usage. This emphasizes the importance of the tight regulation of gene expression in the human brain.

## SYM-11-02

**HUMAN ALCOHOLIC BRAIN: WHAT HAVE WE LEARNED AND WHERE ARE WE GOING?**

**Mayfield R.D.**  
University of Texas at Austin.

Long-term alcohol abuse produces lasting changes in the brain that can result in tolerance, physical dependence, craving, and other behavioral changes. Genomic technology has greatly improved our ability to study complex disorders such as alcohol dependence by allowing entire transcriptomes to be defined simultaneously. Early expression profiling studies in prefrontal cortex identified differentially expressed genes involved in myelination, ubiquitination, apoptosis, cell adhesion, neurogenesis, and neural disease. More recently, we have turned our attention to studying potential global mechanisms that control these changes in gene expression by studying small noncoding RNAs (miRNAs) and epigenetic mechanisms. We have identified a number of up-regulated miRNAs showing a large degree of overlap with our published cDNA microarray data. Functional classification of the predicted target genes of the regulated miRNAs includes apoptosis, cell cycle, cell adhesion, nervous system development and cell-cell signalling, suggesting that the reduced expression of genes in human alcoholic cases may be due to up-regulated miRNAs. We have also applied a novel systems biology approach to transcriptome profiling in postmortem human brains and generated a global view of brain alterations associated with alcohol abuse. We have identified cellular components and previously unrecognized epigenetic determinants of gene co-expression relationships and discovered novel markers of chromatin modifications in alcoholic brain, pointing to the central role of epigenetic mechanisms in alcohol dependence. To complement these studies we are using Next-Generation Sequencing technology. We are interested in determining the individual variation between alcoholic and control groups, including differences in genes detected, SNP calls, and novel/abnormal splice events. Our analysis has identified thousands of SNPs and splice variants that were previously unidentified. These changes at the transcriptional level likely reflect both pre-existing differences in gene expression and those altered as a consequence of alcohol consumption.

## SYM-11-03

**NEXT-GENERATION SEQUENCING PROVIDES NOVEL VIEWS OF SCHIZOPHRENIA PATHOPHYSIOLOGY**

**Shannon Weickert C.<sup>1,2,3</sup>**  
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Purpose: Transcriptomics allows an “unbiased” survey of global gene expression and microarrays have provided evidence that metabolic profiles, myelination markers and interneuron health are all altered in schizophrenia. Next-generation sequencing (NGS) provides a qualitatively different view of gene expression while still allowing identification of changes in levels of mRNAs. Methods: We have used the SOLiD system on prefrontal cortex samples from 20 males with schizophrenia and 20 matched controls. Sequencing achieved 135 million 50 base pair reads per individual with 40% mapping efficiency. Gene expression changes were confirmed through qPCR (n=74) and related to cellular pathology through immunohistochemistry for a neuronal marker (NeuN). Results: Over 115 of the 33,105 transcripts were significantly changed (FDR<0.05) which implicated both immune and cell migration pathways via Ingenuity. We found that chemokines (CCL1, CXCL8 and LIF) involved in cell migration were increased in schizophrenia. We tested if changes in inflammatory markers were related to the increased density of putatively migratory neurons in schizophrenia. Surprisingly, an upstream inducer of inflammation, COX2 mRNA, which was reduced in schizophrenia (despite induction of several chemokines), was negatively correlated with interstitial white matter neuron (IWMN) density (r=-0.3, p=0.013). Conclusion: About 1/3 of patients with schizophrenia have significantly up-regulated genes associated with “inflammation”. We suggest that chronic up-regulation of inflammatory responses could lead to compensatory down-regulation of COX2 mRNA in schizophrenia. The chronic up-regulation of chemoattractant chemokines would be expected to lead to inappropriate recruitment of new neurons to cortical regions in schizophrenia. Further work will be needed to test this intriguing new possibility that has emerged from our NGS approach.

## SYM-11-04

**TRANSCRIPTOMIC STUDIES OF ALZHEIMER'S DISEASE**

**Sutherland G.T.**<sup>1</sup>, Mills J.<sup>3</sup>, Twine N.A.<sup>3,4</sup>, Janitz M.<sup>3</sup> and Kril J.J.<sup>1,2</sup>  
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Purpose: Alzheimer's disease (AD) is predicted to become the leading health issue in Australia by 2050. Ageing and possession of the APOE ε4 allele are the two leading risk factors for AD but much remains unknown about how they moderate disease risk. The uniqueness of the human brain is largely derived at the level of transcription but, until recently, we have not had the tools to assay the breadth of RNA species contributing to this functional complexity. RNA-Seq can now detect all the coding and non-coding RNA species in the human brain. We recently published a RNA-Seq study of AD where the major finding was alternative promoter usage and splicing patterns in the APOE gene. This study provided insight into a unique mechanism for APOE-mediated risk but relied on a small number of uncharacterised brain tissue samples. We have subsequently carried out a follow-up quantitative PCR study designed to tease out the 'cause' and 'effect' relationships between APOE genotype, transcription dysfunction and AD pathology. Results and Discussion: There are complex relationships between APOE transcripts and AD pathology suggesting that 'cause' and 'effect' influences in AD pathogenesis will prove difficult to decipher from moderately and severely affected regions of the AD brain. However the progression of AD pathology is quite predictable and belatedly affected areas such as the primary visual cortex (PVC) do succumb to AD pathology in the most longstanding cases. Paradoxically these non-susceptible areas may provide a better environment for the detection of early pathogenic processes. The use and relevance of the PVC as a 'surrogate' in transcriptomic studies will depend on its degree of transcriptional similarity and relative response to ageing to susceptible areas such as the entorhinal cortex. Accordingly our ongoing RNA-Seq studies are aimed at examining these differentially susceptible regions in unaffected controls of various ages.

## SYM-12-01

**PROMOTING MYELINATION IN HUMAN NEWBORN BRAIN INJURY AND LEUKODYSTROPHIES**

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Purpose: This talk will address the rising incidence of cerebral palsy in the United States, its connection to white matter injury and the logic of approaches that might be used to promote more effective repair of endogenous oligodendrocyte precursor cells, or alternatively, cell replacement. Abstract: The oligodendrocyte is considered a key cellular target in newborn white matter injuries leading to cerebral palsy. While a feature of these conditions is the presence of oligodendrocyte precursors (OLP) blocked at a pre-myelinating stage, the mechanistic basis for inhibition of OLP differentiation is incompletely understood. Using a whole genome approach, we found that Wnt signaling acts to inhibit the differentiation of OLP to mature myelinating oligodendrocyte during development and remyelination in vivo. Dysregulation of Wnt-β-catenin signaling in OLP results in profound delay of remyelination in animal models (Fancy et al., 2009). We have gone on to definitively show that canonical Wnt signaling is active in OLP in situ both within white matter lesions of human neonates and active MS lesions in adults. Canonical Wnt signaling is limited by a β-catenin degradation complex including proteins Axin1 and Axin 2, providing a potential therapeutic approach to control the pathway. Indeed, data will be presented that a small molecule that stabilizes Axin2 and therefore inhibits the Wnt pathway leads to precocious OLP differentiation and myelin repair following demyelination in vivo. In contrast to the situation in MS, where OLPs are blocked in differentiation, in the fatal congenital leukodystrophy Pelizaeus-Merzbacher Disease (PMD), OLP are fundamentally defective in myelin formation, providing a rationale for cell replacement therapy in a human clinical trial to test the safety of cell-based therapeutics for myelin repair.

**SYMPOSIUM 12 – BUILDING BLOCKS OF THE BRAIN: GENERATION OF NEURONS AND GLIA IN THE DEVELOPING AND ADULT CNS**

*Sponsored by The School of Biomedical Sciences, The University of Queensland*

## SYM-12-02

**REGENERATION AND CELL REPLACEMENT IN HUMAN NEURODEGENERATIVE DISORDERS**

**Curtis M.A.**<sup>1,2</sup>, Kam M.<sup>1,2</sup>, Dragunow M.<sup>1,3</sup> and Faull R.L.M.<sup>1,2</sup>  
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In the rodent and human brain the subventricular zone (SVZ) consists of undifferentiated cells with a high level of plasticity to respond to neurodegenerative insults by proliferating and migrating toward the site of injury where they can differentiate to form mature neurons. In response to a number of neurodegenerative diseases there is an up-regulation of progenitor cell production, cytokine levels and migratory proteins in the SVZ, leading to an increase in the number of neurons. The SVZ contains three main cell types and these are progenitor cells, glial cells and migratory neuroblasts; glial cells are the most common cell type and in response to, for instance, Huntington's disease most of the SVZ cell proliferation is glial, but the number of precursors and neuroblasts is also increased. Animal models of stroke, Huntington's disease and Parkinson's disease have also been useful for studying proliferation, neurogenesis and other marked alterations in the SVZ. The reason that the SVZ is so interesting in the adult brain is that many key characteristics of the developmental SVZ are maintained. In this lecture I will highlight some of the recent results from my laboratory and others that reveal the high level of plasticity that the brain maintains even into adulthood. Finally I will show our recent results looking at neuroblast migration in the human rostral migratory stream, which is the pathway that SVZ cells take, in the absence of a neurodegenerative disorder, in order to replace dying olfactory bulb interneurons. The work of my laboratory has been to study the rostral migratory stream in normal Huntington's disease, Parkinson's disease and schizophrenic brains. These diseases have a profound impact on the germinal zones.

## SYM-12-03

**NUCLEAR FACTOR ONE X REGULATES NEURAL PROGENITOR CELL DIFFERENTIATION**

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Neural progenitor cells (NPCs) are self-renewing cells that have the ability to give rise to neurons and glia in the embryonic, neonatal and adult brain. Abnormal proliferation or differentiation of NPCs during development can lead to severe functional consequences, such as lissencephaly and microcephaly, both of which can cause significant mental retardation. As such, the regulatory process controlling whether neural progenitor cells either divide and self-renew or exit the cell cycle and differentiate is critical during development. Here we demonstrate that the transcription factor Nuclear Factor One X (Nfix), plays a central role in regulating NPC differentiation. During cortical development, Nfix is expressed by NPCs, and, moreover, Nfix<sup>-/-</sup> mice display delays in neuronal and glial differentiation within the cortex. At a mechanistic level, we demonstrate that Nfix promotes NPC differentiation in part via the repression of Sox9, a member of the SoxE family of transcription factors that has recently been implicated in promoting NPC self-renewal. Collectively, our data suggest that Nfix drives the differentiation of NPCs through the repression of Sox9 transcription.

## SYM-12-04

**ESTABLISHING AND MAINTAINING OLIGODENDROCYTE TOPOGRAPHY IN CNS WHITE MATTER IN HEALTH AND DISEASE**

**Merson T.D.**<sup>1,2</sup>, Ng S.W.<sup>1</sup>, Roth P.T.<sup>1</sup>, Finighan R.<sup>1</sup> and Kilpatrick T.J.<sup>1,2</sup>  
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Recently, it has been established that oligodendrocytes populate the brain in distinct waves derived from discrete progenitor populations. The initial source of cells in the forebrain derives from the medial ganglionic eminences and is subsequently eliminated during early postnatal life by a separate population of progenitors that derive from the cerebral cortex. This latter population is responsible for laying down a highly organised topographical arrangement of oligodendrocytes within the postnatal brain. In CNS white matter, oligodendrocytes are arranged in linear arrays that are frequently comprised of more than a dozen cells aligned head to tail in the direction of axonal tracts. To understand the mechanism by which these arrays are established, we investigated the clonal relationship between oligodendrocytes within these linear arrays. We used a transgenic mouse that carries a lacZ transgene on the X-chromosome that is subject to inactivation in approximately half of the cells during embryogenesis thereby enabling discrimination of clonally related cell populations on the basis of beta-galactosidase expression. Using this approach we have revealed that oligodendrocyte arrays comprise largely of clonally related cells and provide an explanation for areal differences in the severity of pathology in X-linked demyelinating disorders such as Pelizaeus-Merzbacher disease and connexin-32 mutations in heterozygous females. We next characterised how the clonal relationship between neighbouring oligodendrocytes is altered during regeneration of oligodendrocytes after a demyelinating insult. Using lineage tracing approaches we provide evidence that regeneration of oligodendrocytes in the corpus callosum is achieved via the contribution of two progenitor cell populations: oligodendrocyte progenitor cells and neural progenitor cells derived from the subependymal zone of the lateral ventricles. Our work provides new insight into the mechanisms by which oligodendrocyte migration and proliferation contribute to the development of oligodendrocyte arrays in early postnatal life and the relative contribution of different progenitor populations to the oligodendrocyte lineage during disease.

## SYM-13-02

**PRINCIPLES OF AXONAL GUIDANCE IN NOISY MOLECULAR GRADIENTS**

**Goodhill G.J.**  
 The University of Queensland.

Chemotaxis (detecting and following chemical gradients) plays a crucial role in many biological systems, including the processes of neural migration and axon guidance during brain development. Neurons and axonal growth cones sense external ligand gradients via the detection of spatial differences in receptor binding across their surface. However receptor binding is a fundamentally stochastic process, so that gradient detection can be considered as a form of reasoning in the face of uncertain sensory information. In previous work we considered the computations required to optimally detect gradients given this uncertainty, assuming a random distribution of receptors across the neuron or growth cone. Here we now consider what spatial configuration of the receptors themselves would be optimal for performing chemotaxis. We formulate this problem in Bayesian terms, and show that the optimal configuration depends on the sensing device's current assumptions about the gradient. This leads to testable predictions regarding the distribution of receptors that might be expected under different circumstances.

## SYM-13-01

**KEY ROLE OF NOISE, COUPLING, AND DELAY IN RESTING BRAIN FLUCTUATIONS**

**Jirsa V.**  
 Director of Research at the Centre National de la Recherche Scientifique (CNRS), Université de la Méditerranée in Marseille, France.

A broad body of experimental work has demonstrated that apparently spontaneous brain activity is not random. At the level of large-scale neural systems, as measured with functional MRI (fMRI), this ongoing activity reflects the organization of a series of highly coherent functional networks. These so-called resting-state networks (RSNs) closely relate to the underlying anatomical connectivity but cannot be understood in those terms alone. Here we review three large-scale neural system models of primate neocortex that emphasize the key contributions of local dynamics, signal transmission delays and noise to the emerging RSNs. We propose that the formation and dissolution of resting-state patterns reflects the exploration of possible functional network configurations around a stable anatomical skeleton.

## SYM-13-03

**STOCHASTIC RESONANCE AND OTHER BENEFITS OF RANDOM NOISE IN NEURAL SYSTEMS: BRIDGING THEORY AND EXPERIMENT**

**McDonnell M.D.**  
 Computational and Theoretical Neuroscience Laboratory, Institute for Telecommunications Research, University of South Australia.

**Purpose:** Although typically assumed to degrade performance, sometimes random fluctuations, or noise, can improve information processing in non-linear systems. One such form of 'stochastic facilitation', stochastic resonance, has been observed to enhance processing both in theoretical models of neural systems and in experimental neuroscience. However, the two approaches have yet to be fully reconciled. **Methods:** In this talk I will illustrate why this is so, using examples ranging from the auditory and somatosensory systems, to cortical local field potentials. **Conclusion:** Understanding the diverse roles of noise in neuronal information processing will require the design of experiments based on new theory and models, into which biologically appropriate experimental detail feeds back at various levels of abstraction. The new theory should begin with concrete and precise hypotheses regarding potential computational roles of specific neural systems.

## SYM-13-04

**NOISE DRIVEN OSCILLATIONS: A COMPUTATIONAL MODEL OF BIMANUAL TAPPING**Boonstra, T.<sup>1,2</sup>, Ashwin, P.<sup>3</sup> and **Breakspear M.**<sup>1,2,4,5</sup>

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As a coarse-grained approximation, large-scale cortical activity can be described as a system of coupled oscillators with appropriate connection topologies and phase interaction functions. In broad regions of parameter space, such systems robustly exhibit a form of winnerless competition known as heteroclinic cycles, characterized by slow transitions between partially synchronized cluster states. In a noise-free system, a typical trajectory dwells for increasingly longer periods of time near each state. In contrast, in the presence of noise, the system will cycle with a noise-dependent frequency. In this presentation we will explore this characteristic of heteroclinic cycles to realize coordinated timing in neural systems. In particular, we will employ this theory to address a difficult and unsolved problem in motor neuroscience, namely the cortical mechanisms of coordinated bimanual finger-tapping. Examples of rhythmic bimanual tapping are discussed showing  $n:m$  frequency coupling at the movement frequency. Crucially, the phase of the slow movement cycle is locked to the amplitude of oscillatory neural activity at faster time-scales (so-called phase-amplitude coupling), a property of empirical data that has previously lacked a sufficient explanation. The model has specific physiological implications and can hence be tested using appropriate experimental manipulations.