

Proposal Number: 1

Theme: Autonomic/neuroendocrine systems

Title: Mapping the neural circuitry of ingestive behaviours using a genetic approach

Philip J Ryan¹, Denovan Begg², Aneta Stefanidis³, Joel Geerling⁴

1. *Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia*

2. *School of Psychology, University of New South Wales, Sydney, NSW, Australia*

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4. *Iowa Neuroscience Institute, University of Iowa, Iowa City, Iowa, USA*

Neuroscience is currently undergoing a major discovery phase, whereby recent advances in genetically-encoded tools and techniques are enabling precise, cell-type targeted experiments in the brains of living, freely moving animals¹⁻⁴. We now have the capacity to construct a much more detailed and advanced understanding of neural circuits underlying distinct behaviours⁵. The neural circuits which modulate ingestive behaviours are model systems for behavioural investigation because they involve simple and specific substances i.e. food, water and salt, and can be investigated with relatively straightforward behavioural models, such as depletion/repletion paradigms⁶.

In this symposium, we propose to outline recent advances in our understanding of the neural circuitries which control ingestive behaviours using a genetic approach. Specifically, we will present the following topics: the role of the vagus nerve in the gut-brain interface in a rodent model of sleeve gastrectomy (Aneta Stefanidis); the role of the melanocortin system in fluid intake (Denovan Begg); the role of the oxytocin system in controlling fluid satiation (Philip Ryan); and the neural circuitry of salt intake (Joel Geerling). Each presentation will provide an overview of the neural circuits underlying these behaviours, including mapping and functional behaviours. These studies will have particular relevance for ANS researchers who investigate ingestive behaviours, but will also be highly relevant for neuroscientists studying more complex behaviours by providing a framework for studying neural circuits using genetic technology.

This symposium will showcase cutting-edge genetic techniques which are used to map and functionally characterise the neural circuits. These techniques include: optogenetics, which can rapidly activate or inhibit specific neurons by laser light; DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), which can activate or inhibit neurons over a longer time period (4-6 hours) by injecting a corresponding purpose-built drug; fluorescent tracers, which can map distinct neural pathways; and calcium imaging, which enables imaging of calcium dynamics, a correlate of neural activity, in hundreds of neurons simultaneously at single cell resolution in freely-behaving rodents. These techniques enable us to probe the brain in much finer detail than previously imagined, and construct detailed maps of brain circuitry, which will be beneficial for many neuroscientific laboratories.

References

1. Armbruster, B.N., Li, X., Pausch, M.H., Herlitze, S. & Roth, B.L. Evolving the lock to fit the key to create a family of G protein-coupled receptors potentially activated by an inert ligand. *Proc Natl Acad Sci U S A* **104**, 5163-5168 (2007).
2. Yizhar, O., Fenno, L.E., Davidson, T.J., Mogri, M. & Deisseroth, K. Optogenetics in neural systems. *Neuron* **71**, 9-34 (2011).
3. Deisseroth, K. Controlling the brain with light. *Sci Am* **303**, 48-55 (2010).
4. Sternson, S.M., Atasoy, D., Betley, J.N., Henry, F.E. & Xu, S. An Emerging Technology Framework for the Neurobiology of Appetite. *Cell Metab* **23**, 234-253 (2016).
5. Sternson, S.M. Hypothalamic survival circuits: blueprints for purposive behaviors. *Neuron* **77**, 810-824 (2013).

6. Sakai, R.R. The future of research on thirst and salt appetite. *Appetite* **42**, 15-19 (2004).

Speaker Details

Philip Ryan

Affiliation: Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia

ANS member type: Ordinary

Early Career Researcher: Yes

Title and summary of talk: MAPPING THE NEURAL CIRCUITRY OF FLUID SATIATION

Fluid satiation, or quenching of thirst, is a critical homeostatic signal to stop drinking; however, its underlying neurocircuitry is not well-characterised. Cutting-edge genetically-encoded tools and techniques are now enabling researchers to pinpoint discrete neuronal populations that control fluid satiation, revealing that hindbrain regions, such as the parabrachial nucleus and nucleus of the solitary tract, play key roles in decreasing fluid intake. In particular, I identify oxytocin receptor-expressing neurons in the parabrachial nucleus (Oxtr^{PBN}) as key regulators of fluid intake. Chemogenetic activation of Oxtr^{PBN} neurons in mice robustly suppressed non-caloric fluid intake, but not food intake after fasting, or salt intake after salt depletion. Genetically-encoded calcium indicators demonstrate increased activity of Oxtr^{PBN} neurons when drinking water, but not when ingesting a highly-caloric liquid diet or licking an empty bottle. Oxtr^{PBN} neurons project to the central amygdala, bed nucleus of the stria terminalis, median preoptic nucleus and organum vasculosum of lamina terminalis (OVLT). In addition, neurons in the nucleus of the solitary tract (NTS) substantially suppress fluid intake and activate Oxtr^{PBN} neurons, suggesting NTS neurons project to Oxtr^{PBN} neurons. Overall, my study suggests that Oxtr^{PBN} neurons form a key part of the neural circuitry which controls fluid satiation.

Citations:

Ryan PJ, Ross SI, Campos CA, Derkach VA, Palmiter RD. 2017. Oxytocin receptor-expressing neurons in the parabrachial nucleus suppress non-caloric fluid intake. *Nat Neurosci*. Dec; 20(12):1722-1733.

Denovan Begg

Affiliation: School of Psychology, UNSW Sydney

ANS member type: Ordinary

Early Career Researcher/HDR student?: ECR

Title and summary of talk: FLUID AND ELECTROLYTE DISTURBANCES MEDIATED BY MELANOCORTIN-4 RECEPTOR-DEFICIENCY

Melanocortin-4 receptor (Mc4r)-signalling has been extensively studied with regard to energy balance, however, the role of Mc4r ablation on fluid balance is unresolved. We found that basal water intake in rats lacking Mc4r (Mc4r^{-/-}) was lower than in wildtype (Mc4r^{+/+}) rats. Water intake was also lower in Mc4r^{-/-} rats than Mc4r^{+/+} in response to fluid deprivation, hypovolemic challenge and peripheral angiotensin-converting enzyme inhibition. However, when administered hypertonic saline, Mc4r^{+/+} and Mc4r^{-/-} rats had similarly increased fluid intake. Mc4r^{-/-} rats had reduced CRH in the paraventricular nucleus of hypothalamus (PVN), heart rate, and renin expression in the kidney; suggesting a reduced sympathetic output from the PVN. Using Mc4r^{-/-} mice, and Mc4r^{-/-} mice with reinstatement of Mc4r in Sim1 neurons in the PVN, we found that following food and fluid deprivation, Mc4r^{-/-} mice drank significantly less water than Mc4r^{+/+} mice. Sim1-cre Mc4r mice drank the same as their cre controls, demonstrating that Mc4r in Sim1-expressing cells of the PVN are essential for normal sympathetic stimulation of RAS function. Overall, the data reveal a previously unreported role for the PVN Mc4r in fluid balance.

Citations:

Mul JD, Seeley RJ, Woods SC, **Begg DP**. Angiotensin-converting enzyme inhibition reduces food intake and weight gain and improves glucose tolerance in melanocortin-4 receptor deficient female rats. *Physiol Behav*. 2013;121:43-8.

Begg DP. Disturbances of thirst and fluid balance associated with aging. *Physiol Behav*. 2017;178:28-34.

Begg DP, Steinbrecher KA, Mul JD, Chambers AP, Kohli R, Haller A, Cohen MB, Woods SC, Seeley RJ. Effect of guanylate cyclase-C activity on energy and glucose homeostasis. *Diabetes*. 2014 Nov;63(11):3798-804.

Begg DP, Sinclair AJ, Weisinger RS. Reductions in water and sodium intake by aged male and female rats. *Nutr Res*. 2012; 32(11):865-72.

Begg DP, Sinclair AJ, Weisinger RS. Thirst deficits in aged rats are reversed by dietary omega-3 fatty acid supplementation. *Neurobiol Aging*. 2012; 33(10):2422-30.

Dr. Aneta Stefanidis

Affiliation: Metabolic Neurosciences Laboratory Department of Physiology, Monash Biomedicine Discovery Institute, Monash University

ANS member type: Ordinary

Early Career Researcher/HDR student?: ECR, (7 years FTE)

Title and summary of talk: MECHANISMS UNDERLYING THE IMPACT OF BARIATRIC SURGERY ON FOOD INTAKE AND THERMOGENESIS.

Currently the most effective and durable treatment for morbid obesity is bariatric surgery. Vertical Sleeve Gastrectomy (VSG) is the most widely performed bariatric surgery and it confers both significant weight loss and improved glucose regulation. The vagus nerve is an important conduit for information transfer between the gut and brain that underpins some of the efficacy of VSG. Data, derived from our rat model of VSG, indicates that an increase in energy expenditure via brown adipose tissue (BAT) contributes substantially to the weight loss in VSG. The current studies aim to investigate whether vagal afferent neurons are necessary for the efficacy of VSG and interrogate the role of these vagal afferents in the mediation of VSG-induced satiety, thermogenic response and the promotion of weight loss. Furthermore, in order to distinguish whether the efficacy of VSG is mediated by the compartments of the gut that the vagal afferents innervate, these studies utilise a Cre-recombinase expressing retrogradely transported virus in combination with a Cre-dependent caspase virus to selectively ablate afferents innervating specific gastrointestinal regions. Targeting these subpopulations of sensory vagal neurons allows discrimination between their requirement in VSG mediated shifts in food intake and recruitment of BAT to elicit weight loss.

Citations:

A Stefanidis, N Forrest, WA Brown, JB Dixon, PB O'Brien, J Kampe, BJ Oldfield.

An investigation of the neural mechanisms underlying the efficacy of the adjustable gastric band. *Surgery for Obesity and Related Diseases* 12 (4), 828-838. Citations: 4

A Stefanidis, NM Wiedmann, ES Adler, BJ Oldfield. Hypothalamic control of adipose tissue *Best Practice & Research Clinical Endocrinology & Metabolism* 28 (5), 685-701. Citations: 16

A Stefanidis, BJ Oldfield. Neuroendocrine mechanisms underlying bariatric surgery-insights from human studies and animal models *J Neuroendocrinol*. 2017 Oct;29(10). doi: 10.1111/jne.12534. Citation:1

Joel C. Geerling, MD, PhD

Affiliation: Department of Neurology, Iowa Neuroscience Institute, University of Iowa Hospital and Clinics

ANS member type: Ordinary
Early Career Researcher/HDR student?: ECR

Title and summary of talk: BRANCHED, ASCENDING PATHWAYS INFORM THE FOREBRAIN ABOUT SODIUM DEFICIENCY AND DRIVE SODIUM APPETITE

A prolonged sodium (volume) deficiency alters hedonic, appetitive, and other behaviors. These changes are mediated by the brain, and mimic in large part the hypermineralocorticoid state. Rats and mice have a population of neurons in the caudal nucleus of the solitary tract that integrate visceral and hormonal signals related to bodily sodium deficiency, including both aldosterone and angiotensin II. Two subsets of these aldosterone-sensitive “HSD2 neurons” convey this information from the caudal medulla, via parallel axonal projections that ascend to target multiple regions of the forebrain. HSD2 neurons project to either a subregion of the bed nucleus of the stria terminalis implicated in driving sodium appetite or, via relay neurons expressing FoxP2 in the pre-locus coeruleus and lateral parabrachial nucleus, to stress-related regions of the diencephalon. Following evidence that their projections to the BSTvL promote sodium appetite, we propose that HSD2 neurons projecting to the parabrachial complex mediate the dysphoric symptoms linked to hypermineralocorticoid and sodium-deficient states.

Citations:

Resch JM, Fenselau H, Madara JC, Wu C, Campbell JN, Lyubetskaya A, Dawes BA, Tsai LT, Li MM, Livneh Y, Ke Q, Kang PM, Fejes-Tóth G, Náráy-Fejes-Tóth A, **Geerling JC**, Lowell BB. Aldosterone-Sensing Neurons in the NTS Exhibit State-Dependent Pacemaker Activity and Drive Sodium Appetite via Synergy with Angiotensin II Signaling., *Neuron*. 2017 September 27;96(1):190-206.e7. PMID:28957668. doi: 10.1016/j.neuron.2017.09.014.

Verstegen AMJ, Vanderhorst V, Gray PA, Zeidel ML, **Geerling JC**. Barrington's nucleus: Neuroanatomic landscape of the mouse "pontine micturition center"., *The Journal of comparative neurology*. 2017 July 1;525(10):2287-2309. PMID:28340519. doi: 10.1002/cne.24215.

Geerling JC, Yokota S, Rukhadze I, Roe D, Chamberlin NL. Kölliker-Fuse GABAergic and glutamatergic neurons project to distinct targets., *The Journal of comparative neurology*. 2017 March 14. PMID:28032634. doi: 10.1002/cne.24164.

Abbott SB, Machado NL, **Geerling JC**, Saper CB. Reciprocal Control of Drinking Behavior by Median Preoptic Neurons in Mice., *The Journal of neuroscience*. 2016 August 3;36(31):8228-37. PMID:27488641. doi: 10.1523/JNEUROSCI.1244-16.2016.

Geerling JC, Kim M, Mahoney CE, Abbott SB, Agostinelli LJ, Garfield AS, Krashes MJ, Lowell BB, Scammell TE. Genetic identity of thermosensory relay neurons in the lateral parabrachial nucleus., *American journal of physiology. Regulatory, integrative and comparative physiology*. 2016 January 1;310(1):R41-54. PMID:26491097. doi: 10.1152/ajpregu.00094.2015.

Proposal Number: 10

Theme: Clinical disorders and injury of the nervous system

Title: Neuroinflammation in Neurodegenerative Diseases

Estella Newcombe ¹ , Alison M Goate ² , Mike Dragunow ³ , Shane Liddelow ⁴ , Judith Camats-Perna ¹

1. *University of Queensland, St Lucia, QLD, Australia*
2. *Icahn School of Medicine at Mount Sinai, New York*
3. *The University of Auckland, Auckland*
4. *Neuroscience Institute, NYU Langone, New York*

Chronic neuroinflammation has become a major subject of research in academia and industry due to its significance on the onset and progression of age-dependent neurodegenerative diseases, in particular Alzheimer's disease (AD). Neuroinflammation comprises cellular and biochemical responses of the nervous system to injury, infection or degeneration. These responses are directed at mitigating the triggering factors (*i.e.*, β -amyloid, tau) by involving CNS immunity to defend against potential harm. In this symposium, we will discuss the most recent evidence covering a large spectrum of the cellular and biochemical repertoire related to the brain immune responses during neurodegeneration. **Dr Alison Goate**, from the Icahn School of Medicine at Mount Sinai (USA), will focus on microglia and present her recent genetic data to demonstrate the enrichment of microglial expressed genes in AD subjects, particularly those that are regulated by the transcription factor PU.1. **Dr. Michael Dragunow**, from The University of Auckland (NZL), will present his results on pericytes and their role in the blood-brain barrier (BBB) function, and show data supporting the detrimental impact of pericyte-mediated neuroinflammation in neurodegenerative disorders. **Dr Shane Liddelow**, from the NYU Langone Health (USA), will talk about astrocytes and discuss new evidence that a subpopulation of astrocytes drives death of neurons in neurodegenerative disorders, pointing the way forward for developing new treatments for these diseases. Finally, **Dr Camats-Perna**, from the QLD Brain Institute (AUS), will demonstrate novel evidence that the imbalance in the levels of pro- and anti-inflammatory mediators can be target to mitigate the neuropathological process in AD. In summary, our symposium will provide a unique perspective on the roles of distinct cell populations and chemical mediators in the onset and progression of chronic neuroinflammation and neurodegenerative diseases. We believe this will be of interest to the majority of the ANS attendees, and will also offer an opportunity for interaction with outstanding leaders in the neuroinflammation field.

Dr. Alison M Goate (alison.goate@mssm.edu) - Icahn School of Medicine at Mount Sinai

Genetic evidence supporting a causal role of microglia in Alzheimer's disease risk

Summary: Although Alois Alzheimer observed that microglia can be found around amyloid plaques, but it was generally considered that microgliosis was a consequence of disease. In recent years genome-wide association studies of rare and common variation have implicated many genes in risk for late onset AD. Pathway analyses have demonstrated an enrichment for genes involved in innate immunity and LD Score regression analyses demonstrate that AD heritability is enriched in the epigenetic signature of myeloid cells, including microglia. These data suggest that microglia are playing a causal role in disease risk. I will present genetic data across the frequency spectrum to demonstrate the enrichment of microglial expressed genes, particularly those that are regulated by the transcription factor PU.1.

Citations of up to 5 papers published by the speaker over the past 5 years

- Huang et al., A common haplotype lowers PU.1 expression in myeloid cells and delays onset of Alzheimer's disease. *Nat Neurosci*. 2017 Aug;20(8):1052-1061. PMID: 28628103
- Pimenova et al., A Tale of Two Genes: Microglial Apoe and Trem2. *Immunity*. 2017 Sep 19;47(3):398-400. PMID: 28930654
- Sims et al., Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nat Genet*. 2017 Sep;49(9):1373-1384. PMID: 28714976
- Jin et al., Coding variants in TREM2 increase risk for Alzheimer's disease. *Hum Mol Genet*. 2014 Nov 1;23(21):5838-46. PMID: 24899047

Dr. Michael Dragunow (m.dragunow@auckland.ac.nz) - The University of Auckland

Brain capillaries as drivers and targets of neuroinflammation.

Summary: Neuroinflammation is considered a key aspect of neurodegeneration with most studies focusing on the key role played by microglia in this process. Less work has been conducted on the role of other brain cell types in neuroinflammation. In particular, capillary pericytes and endothelial cells may also play important roles in driving neuroinflammation, linking systemic inflammation to brain inflammation, and also as targets of systemic and microglial-mediated neuroinflammatory processes. In this talk, I will review this data and in particular propose pericyte inflammation as a key target for drug development to treat neurodegenerative disorders.

Citations of up to 5 papers published by the speaker over the past 5 years

- Rustenhoven et al., Brain Pericytes As Mediators of Neuroinflammation. *Trends Pharmacol Sci.* 2017 Mar;38(3):291-304. PMID: 28017362
- Jansson et al., Interferon- γ blocks signalling through PDGFR β in human brain pericytes. *J Neuroinflammation.* 2016 Sep 21;13(1):249. PMID: 27654972
- Rustenhoven et al., TGF-beta1 regulates human brain pericyte inflammatory processes involved in neurovasculature function. *J Neuroinflammation.* 2016 Feb 11;13:37. PMID: 26867675

Dr. Shane Liddelow (Shane.Liddelow@med.nyu.edu) - Neuroscience Institute @ NYU Langone

What do reactive astrocytes do?

Summary: Reactive astrocytes are rapidly generated following brain injuries and neurodegenerative/neuroinflammatory diseases, however their role in trauma and disease states is poorly understood. Previously, we distinguished two reactive astrocyte subclasses dependent on the type of inducing injury. We named these classes “A1” and “A2”, and based on gene profiles we hypothesized that A1 were harmful whereas A2 were helpful. We have shown that the harmful A1 reactive astrocytes are induced by neuroinflammatory microglia. Specifically, we found that activated microglia induce A1s by secreting $\text{IL-1}\alpha$, $\text{TNF}\alpha$, and C1q – factors that are necessary and sufficient to induce A1s both *in vitro* and *in vivo*. A1s have little ability to promote neuronal survival, outgrowth, synaptogenesis or phagocytosis and instead are powerfully neurotoxic. We further showed that A1s are present in multiple human neurodegenerative diseases, and that death of axotomized CNS neurons is prevented when A1 formation is blocked with neutralizing antibodies to $\text{IL-1}\alpha$, $\text{TNF}\alpha$, and C1q . We now show the role of A1 neurotoxic reactive astrocytes in the context of neurodegeneration, in both acute (ischemia) and chronic (glaucoma) mouse models. Taken together our findings strongly suggest that A1s drive death of neurons in neurodegenerative disorders and point the way forward for developing new treatments for these diseases.

Citations of up to 5 papers published by the speaker over the past 5 years

- Liddelow SA, ..., Barres BA (2017) Activated microglia induce neurotoxic reactive astrocytes via $\text{IL-1}\alpha$, $\text{TNF}\alpha$, and C1q . *Nature* 541:481-487. PMID: 28099414.
- Shi Y, ..., Liddelow SA, ..., Holtzman D. ApolipoproteinE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature* 549:523-527. PMID: 28959956.
- Bennett ML, ..., Liddelow SA, ..., Barres BA (2016) New tools for studying microglia in the mouse and human CNS. 178 citations. *Proc Natl Acad Sci USA* 113(12):E1738-1746. PMID: 26884166. First in field paper that identifies a new toolset for the purification, culture, and imaging of microglia.
- Zhang Y, ..., Liddelow SA, ..., Wu JQ (2014) An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J Neurosci* 34(36):11929-41197. PMID: 25186741. 911 citations. Demonstrating commitment to providing tools for the research community, this manuscript provides a searchable database of cell-type specific transcriptomes from the mouse brain.
- Clarke LE, Liddelow SA, ..., Barres BA. Characterization of the gaining mouse astrocyte transcriptome. *Proc Natl Acad Sci USA* 115(8):E1896-E1905. PMID: 29437957. First study to show aged reactivity in astrocytes in brain regions most susceptible to neurodegeneration.

Early career fellow: Dr. Judith Camats-Perna (j.camatsperna@uq.edu.au) – QLD Brain Institute

Inflammatory Resolution in Alzheimer's Disease

Summary: The initiation of an inflammatory response is critical to the survival of an organism. However, when inflammation fails to reach resolution, a chronic inflammatory state may occur, and it becomes a major cofactor in Alzheimer's disease (AD). Comprehending the biological basis for altered innate immunity and inflammation in AD is a challenge that has substantial clinical importance, as restoration or preservation of immunological responses is likely to have a great importance to the lengthen of healthier lifespan. The discoveries that resolution of inflammation is a highly coordinated and active process controlled by endogenous pro-resolving and anti-inflammatory mediators, and that inflammatory cells undergo classical and alternative activation, highlight new potential molecular targets to regulate inflammation and treat chronic inflammatory diseases. Here, we will discuss novel findings from studies in human samples that demonstrate a severe impairment in signaling pathways associated with the regulation of inflammatory resolution. In addition, pre-clinical data will be presented to support the idea that restoring the activity of regulatory anti-inflammatory interleukins or pro-resolving lipid pathways can elicit protective immunity and mitigate AD-like pathology. In the future, it may be possible to generate therapies to regenerate and/or replace the endogenous inflammatory resolution pathways to prevent and/or treat AD.

Citations of up to 5 papers published by the speaker over the past 5 years

- Parra-Damas A, Chen M, Enriquez-Barreto L, Ortega L, Acosta S, Perna JC, Fullana MN, Aguilera J, Rodriguez-Alvarez J and Saura CA (2017). CRTCL function during memory encoding is disrupted in neurodegeneration. *Biol Psychiatry* 81, 111–123. PMID: 27587263
- Camats Perna J, Engelmann M (2017) Recognizing others: rodent's social memories. *Curr Top Behav Neurosci* 30:25–45. PMID: 26643999
- Perna JC, Wotjak CT, Stork O, Engelmann M (2015) Timing of presentation and nature of stimuli determine retroactive interference with social recognition memory in mice. *Physiol Behav* 143:10–14. PMID: 25703187
- Bhardwaji D, Nager M, Camats J, David M, Benguira A, Adopazo Canti C, Herreros J. 2013. Chemokines induce axon outgrowth downstream of hepatocyte growth factor and TCF/beta-catenin signaling. *Front Cell Neurosci* 7:52. PMID: 23641195
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Proposal Number: 11

Theme: Cognition/learning and behaviour

Title: Computational Psychiatry

Marta I Garrido ¹ , Phillip Corlett ² , Ivana Dzafic ¹ , Daniel Bennett ³ , Michael Breakspear ⁴

1. *The University of Queensland, Brisbane, QLD, Australia*
2. *Yale University, New Haven, Connecticut, USA*
3. *Princeton University, Princeton, NJ, USA*
4. *Queensland Institute of Medical Research, Brisbane, QLD, Australia*

Computational psychiatry is an emergent field that brings together fundamental neuroscience principles and clinical applications, in a mechanistic and mathematically informed manner. It comprises two distinct approaches, a theoretically motivated and a pragmatically moved. Theoretically motivated approaches strive to test mechanistic accounts of altered brain function that leads to aberrant behavior. Examples of these include using computational models drawn from reinforcement learning (**Bennett**) as well as Bayesian approaches to modelling behaviour (**Corlett**) and brain connectivity (**Dzafic** and **Breakspear**). Pragmatically driven approaches on the other hand, take advantage of machine learning techniques and brain imaging (**Dzafic**) to inform personalised diagnostics, as well as predict treatment-response outcome and prognosis. In this symposium, we will present work employing both theoretically driven and pragmatically moved approaches to computational psychiatry applied to the context of Bipolar disorder (**Bennett**) and Schizophrenia (**Corlett, Dzafic, and Breakspear**). This proposal benefits from having two international speakers, as well as good gender balance (across chair and speakers). Importantly, it showcases the work done by researchers at different career stages (from early career to Professor).

Speaker 1: Dr Philip Corlett, Yale University

philip.corlett@yale.edu

Talk title: Predictive Coding and Psychotic Symptoms

Brief summary of content and significance:

Psychotic symptoms represent a profound departure from consensual reality. They must involve the brain's mechanisms for perception and belief. Under predictive coding theory, the brain contains an internal model of the world, organized hierarchically, with top-down predictions and bottom-up prediction errors. Depending on their relative precision, either prior beliefs dominate and errors are ignored; or prediction errors prevail, leading to new learning. In this framework, delusions form when prediction errors have inappropriate precision, and hallucinations arise from overly precise prior beliefs. I will present empirical data, from functional neuroimaging and computational modeling of behavior, to support these assertions. Psychotic symptoms may represent an evolving non-linear palliative response to noise generated lower in the hierarchy by perturbed glutamate. These data portend symptom and illness-phase specific interventions for psychosis, including interventions targeted at the specific neural circuits underpinning predictive coding.

Selected recent publications:

1. **Corlett PR**, Fletcher PC. Computational Psychiatry. *Lancet Psychiatry*. 2014. Epub. Anticevic A, Gancsos M, Murray J, Repoys G, Driesen N, Ennis D, Nicciu M, Morgan P, Surti T, Bloch M, Ramani R, Smith M, Wang XJ, Krystal JH, Corlett PR. NMDA receptor function in large-scale anti-correlated neural systems with implications for cognition and schizophrenia. *PNAS* 109(41): 2012. PMCID: PMC34786
2. Powers III AR, Mathys, CD, **Corlett PR**. Pavlovian conditioning-induced hallucinations result from the over-weighting of perceptual priors. *Science*. 2017. 357(6351):596-600
3. Powers III AR, Bien C, **Corlett PR**. Aligning computational psychiatry with the hearing voices movement. *JAMA Psychiatry* 2018 (In press).
4. **Corlett PR**: I Predict, Therefore I Am: Perturbed Predictive Coding Under Ketamine and in Schizophrenia. *Biol Psychiatry*. 2017 Mar 15. PMID: 28190425
5. Feeney EJ, Groman SM, Taylor JR, **Corlett PR**: Explaining Delusions: Reducing Uncertainty Through Basic and Computational Neuroscience. *Schizophr Bull*. 2017 Mar 1. PMID: 28177090

Speaker 2: Dr Ilvana Dzafic, Queensland Brain Institute, The University of Queensland

i.dzafic@uq.edu.au

Early Career Researcher

Talk title: Neural dynamics underlying psychotic experiences in healthy people

Brief summary of content and significance:

Recently the traditional view of psychosis as a discrete disorder has been challenged. A new view has emerged postulating *psychosis as a continuum*, which extends into the healthy (non-clinical) population. Healthy individuals can experience psychotic-like experiences, such as hallucinations and delusion, placing them at an increased risk to develop a schizophrenia-spectrum disorder. In this talk, I will present work that has examined the neural mechanisms that influence and can predict psychotic experiences in the healthy population before the onset of illness. To explore the neural circuitry underpinning psychotic experiences we implemented computational modelling and machine learning techniques. Our findings present a significant leap forward in the understanding of the neurobiological underpinnings of psychotic-like experiences in the healthy population. Importantly, these findings have the potential to inform neuromodulation therapies that target top-down networks in people with psychosis.

Selected recent publications:

1. **Dzafic, Ilvana**, Martin, Andrew K., Hocking, Julia, Mowry, Bryan and Burianová, Hana (2016) Dynamic emotion perception and prior expectancy. *Neuropsychologia*, 86 131-140. doi:10.1016/j.neuropsychologia.2016.04.025
2. Martin Andrew K., **Dzafic, Ilvana**, Robinson, Gail A., Reutens, David and Mowry, Bryan (2016) Mentalizing in schizophrenia: A multivariate functional MRI study. *Neuropsychologia*, 93 158-166. doi:10.1016/j.neuropsychologia.2016.10.013.
3. **Dzafic, Ilvana**, Randeniya, R., Garrido M.I. Reduced top-down connectivity as an underlying mechanisms for psychotic experiences in healthy people. <https://www.biorxiv.org/content/early/2018/04/07/296988>

Speaker3: Dr Daniel Bennett, Princeton University

Early Career Researcher

danielbrianbennett@gmail.com

Talk title: Reinforcement learning and mood instability in bipolar disorder

Brief summary of content and significance:

Mood instability is a psychiatric syndrome characterised by heightened emotional reactivity, intense oscillations of mood, and injurious mood states such as mania and depression. In this talk I will describe how this syndrome can be captured within the computational framework of reinforcement learning. Specifically, I will present recent theoretical work showing how mood instability may arise from a bidirectional feedback loop between mood states and the valuation of environmental reinforcers, potentially implicating recurrent cortex-basal ganglia circuits in the maintenance of pathological mood states. I will also describe empirical tests of this model in healthy individuals and those with bipolar disorder.

Selected recent publications:

1. **Bennett, D.**, Yücel, M., & Murawski, C. (2017). Errors of statistical inference in the Information Sampling Task. *Biological Psychiatry*. DOI: [10.1016/j.biopsych.2017.05.023](https://doi.org/10.1016/j.biopsych.2017.05.023)
2. **Bennett, D.**, Oldham, S., Dawson, A., Parkes, L., Murawski, C., & Yücel, M. (2016). Systematic overestimation of reflection impulsivity in the Information Sampling Task. *Biological Psychiatry*. DOI: [10.1016/j.biopsych.2016.05.027](https://doi.org/10.1016/j.biopsych.2016.05.027)
3. **Bennett, D.**, Bode, S., Brydevall, M., Warren, H. & Murawski, C. (2016) Intrinsic valuation of information in decision making under uncertainty. *PLOS Computational Biology*. DOI: [10.1371/journal.pcbi.1005020](https://doi.org/10.1371/journal.pcbi.1005020)
4. Carter, O., **Bennett, D.**, Nash, T., Arnold, S., Brown, L., Cai, R. Y., Allen, Z., Dluzniak, A., McAnally, K., Burr, D., & Sundram, S. Multiple sensory deficits are not limited to schizophrenia but support a dimensional view of psychosis. *Translational Psychiatry*, 7, e1118.
5. **Bennett, D.**, Dluzniak, A., Cropper, S., Partos, T., Sundram, S., & Carter, O. (2016). Selective impairment of global motion integration, but not global form integration, in schizophrenia and bipolar affective disorder. *Schizophrenia Research: Cognition*, 3, 11-14.

Speaker 4: Professor Michael Breakspear

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Talk Title: Volatility theory of schizophrenia**Brief summary of content and significance:**

Brain structure reflects the influence of evolutionary processes that pit the costs of anatomical wiring against the computational advantages conferred by its complexity. The processes shaping this exchange remain poorly understood. We address this problem by introducing subtle perturbations to network topology of the human connectome, while preserving the geometrical embedding and wiring length of the brain. We first show that the presence of widely distributed hubs confers a wiring cost that the human brain minimizes. Although slight perturbations of brain networks can reduce the wiring length of inter-hub connections, these perturbations quickly disconnect inter-hemispheric links to prefrontal hubs and yield daughter networks with lower complexity and that substantially differ from one another. If the variation in structure is permitted to accumulate, strong peripheral connections progressively connect to central nodes and hubs shift toward the middle of the brain. Intriguingly, the fragility of hubs to disconnections shows a significant association with the acceleration of grey matter loss in schizophrenia ($r=0.36$; $p=0.0014$). Together with effects on wiring cost, we suggest that fragile prefrontal hub connections and topological volatility act as evolutionary influences on complex brain networks whose set point may be perturbed in neurological and psychiatric disorders.

Selected recent publications:

1. **Breakspear, M** (2017) Dynamic models of large-scale brain activity. *Nature Neuroscience* (doi:10.1038/nn.4497)
2. Fornito, A., Zalesky, A., **Breakspear, M** (2015). The connectomics of brain disorders. *Nature Reviews Neuroscience* 16: 1-14.
3. **Breakspear M**, Roberts G, Green MJ, Nguyen VT, Frankland A, Levy F, Lenroot R, Mitchell PB (2015) Network dysfunction of emotional and cognitive processes in those at genetic risk of bipolar disorder. *Brain* 138: 3427-3439.
4. Iyer KK, Roberts JA, Hellström-Westas L, Wikström S, Hansen-Pupp I, Ley D, Vanhatalo S, **Breakspear M** (2015). Cortical burst dynamics predict clinical outcome early in extremely preterm infants. *Brain* 138: 2206-2218. (*Clinical Neurology*: 7/217, *Neurosciences*: 15/278). 28 citations.
5. Zalesky A, Fornito A, Cocci L, Gollo LL, **Breakspear M** (2014). Time-resolved resting-state brain networks. *Proceedings of the National Academy of Sciences, USA* 11: 10341-10346.

Proposal Number: 25

Theme: Motor systems

Title: Beyond dopamine: Targeting alternative pathological hallmarks for the treatment of Parkinson's disease

Asheeta Prasad , Kay Double , Trent Woodruff , Richard Gordon , Lyndsey Collins-Praino

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, affecting 7-10 million people worldwide and 1 in every 350 Australians. Pathologically, PD is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, leading to the characteristic motor impairments of the disease. Consequently, the current gold standard treatment for PD is dopamine replacement therapy via levodopa, a therapy that becomes less effective over time and is associated with debilitating side effects, including dyskinesias (i.e. involuntary muscle movements) and "on-off" effects. Thus, new treatment options that may modify the disease process of PD, while treating both motor and non-motor symptoms of the disease, are critical. Such treatment options are unlikely to be found, however, until we look beyond dopamine, the topic of the current seminar.

In addition to dopaminergic neuron loss, Parkinson's disease also includes a number of other pathological changes, including alpha synuclein transmission, excessive microglial activation and pro-inflammatory cytokine production, and protein misfolding events. In our symposium, we will explore each of these contributors to PD pathology in greater depth and discuss why each may represent a potential novel therapeutic strategy for the disease.

First, A/Professor Kay Double from the University of Sydney will explore the role of SOD1 proteinopathy in PD, with a focus on how preventing initial misfolding events via modulation of copper binding may lead to improvement in motor function in the disease. Next, A/Professor Trent Woodruff from the University of Queensland will discuss the pathological spread of alpha synuclein in PD and how the innate immune system may drive this process. In her talk, Dr Lyndsey Collins-Praino from the University of Adelaide will examine the pathological consequences of excessive microglial activation in PD and will propose Fyn kinase inhibition as a novel therapeutic strategy to block this activation. Finally, Dr Richard Gordon from the University of Queensland will cover neuroprotection studies in PD models of mitochondrial dysfunction and synuclein pathology.

Dopaminergic neuron loss is only one piece of the complex pathological puzzle in PD, and to truly make progress on an effective treatment for disease modification, it is critical that we understand other contributors to the condition. Given the growing prevalence of PD and the variety of molecular mechanisms being discussed, we believe that this symposium will be of significant interest and wide appeal to Society members. Furthermore, we have worked to ensure equal gender representation, as well as drawing upon researchers both at early and more established phases of their research careers and including speakers 3 geographic distribution. We have also considered women with children and cultural diversity for this symposium. We believe that this diversity will be of broad appeal to Society members, and set a positive example particularly for student members.

Speaker 1: Dr. Lyndsey E. Collins-Praino

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Title: Fyn kinase inhibition as a novel therapeutic strategy to prevent pathological microglial activation in Parkinson's disease

Synopsis: In recent decades, a growing body of evidence has supported the hypothesis that inflammation-derived oxidative stress and neurotoxicity may be a “silent driver” in the degeneration of dopamine-producing neurons in Parkinson's disease (PD). Seminal work by McGeer and colleagues (1988) first demonstrated increased levels of activated microglia in the brains of PD patients, and multiple subsequent studies have reported increased levels of pro-inflammatory mediators in PD. Despite growing awareness of the role of microglial activation in PD, however, the exact mechanisms that may lead to this activation are currently unknown. One upstream regulator that may play a critical role in this process is Fyn kinase, an SRC-family kinase. Fyn has been shown to regulate neuroinflammation in several neurodegenerative diseases. Recently, Panicker and colleagues (2015) demonstrated that Fyn was required for pro-inflammatory responses, including cytokine release, in cell culture and animal models of PD, indicating that it may be a major upstream regulator of inflammation in the disease. Our work builds upon these original findings and introduces Fyn kinase inhibition as a novel therapeutic strategy for the disease. Excitingly, this approach has utility for the cognitive impairment seen in PD, currently a major area of unmet clinical need.

5 publications from the past 5 years:

1. Arulsamy, A., Teng, J, Colton, H., Corrigan, F., **Collins-Praino, L.E.** (In press). Evaluation of early chronic functional outcomes and their relationship to pre-frontal cortex and hippocampal pathology following moderate-severe traumatic brain injury. *Behav Brain Res.*
2. **Collins-Praino, L.E.**, Arulsamy, A., Katharesan, V., Corrigan, F. (2018). The effect of an acute systemic inflammatory insult on the chronic effects of a single mild traumatic brain injury. *Behav Brain Resh* 336, 22-31.
3. **Collins-Praino, L.E.**, Corrigan, F. (2017). Does neuroinflammation drive the relationship between tau hyperphosphorylation and dementia development following traumatic brain injury? *Brain Behav Immunity* 60, 369-382.
4. **Collins-Praino LE**, Paul NE, Ledgard F, Podurgiel SJ, Kovner R, Baqi Y, Müller CE, Senatus PB, Salamone JD. (2013). Deep brain stimulation of the subthalamic nucleus reverses oral tremor in pharmacological models of parkinsonism: Interaction with the effects of adenosine A2A antagonism. *Eur J Neurosci* 38(1), 2183-2191.

5. Salamone JD, **Collins-Praino LE**, Pardo M, Podurgiel SJ, Baqi Y, Müller CE, Schwarzschild MA, Correa M. (2013). Conditional neural knockout of the adenosine A(2A) receptor and pharmacological A(2A) antagonism reduce pilocarpine-induced tremulous jaw movements: Studies with a mouse model of parkinsonian tremor. *Eur Neuropsychopharmacol* 23(8), 972-977.

Speaker 2: Professor Kay Double

Discipline of Biomedical Science and Brain and Mind Centre School of Medical Sciences
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Title: A proposed novel mechanism for neurodegeneration in Parkinson's disease

Brief summary of content and significance

Our discovery that neurotoxic superoxide dismutase-1 (SOD1) proteinopathy in *SOD1*-associated familial amyotrophic lateral sclerosis (fALS) is recapitulated in idiopathic Parkinson's disease suggests that these two phenotypically-distinct disorders share an etiological pathway, and tractable therapeutic target(s). The absence of *SOD1* mutations in Parkinson's disease indicates *SOD1* mutations are not the sole cause of SOD1 protein misfolding occasioning oligomerization and toxicity, and reinforces the importance of non-genetic factors, such as protein metallation and post-translational modification in determining SOD1 stability and function. Therapies aimed at modulating protein aggregation in neurodegenerative disease have met with limited success to date, however increasing our understanding of initial protein misfolding events may lead to the development of therapies which target biomolecular events upstream of protein deposition. Treatments that modulate SOD1 copper binding, a key factor in preventing initial misfolding events, have yielded remarkable improvements in motor function and cell loss in multiple animal models of both *SOD1*-fALS and Parkinson's disease, resulting in phase 1 clinical trials. These data indicate targeted supplementation of neuronal copper levels constitutes a beneficial therapeutic strategy in both Parkinson's disease and *SOD1*-associated fALS, and that its efficacy lies in the restoration of physiological structure and function of copper-dependent proteins such as SOD1.

Citations of up to 5 papers published by the speaker over the past 5 years

Trist, B.G., Davies, K.M., Cottam, V., Genoud, S., Ortega, R., Roudeau, S., Carmona, A., De Silva, k., Wasigner, V., Lewis, S.J.G., Sachdev, P., Smith, B., Troakes, C., Vance, C., Shaw, C., Al-Sarraj, S., Ball, H., Halliday, G., Hare, D.J. and **Double, K.L.** (2017) Amyotrophic lateral sclerosis-like superoxide dismutase 1 proteinopathy is associated with neuronal loss in Parkinson's disease brain. *Acta. Neuropathol.* 134(1), 113-127. doi:10.1007/s00401-017-1726-6

Trist, B.G., Fifita, J.A., Freckleton, S.E., Hare, D.J., Lewis, S.J.G., Halliday, G.M., Blair, I.P., **Double, K.L.** (2018) Accumulation of dysfunctional SOD1 protein in Parkinson's disease is not associated with mutations in the *SOD1* gene. *Acta Neuropathol.* 135, 155-146. doi: 10.1007/s00401-017-1779-6.

Hare, D.J and **Double, K.L.** (2016) Iron and dopamine: a toxic couple. *Brain*, Apr;139(Pt 4):1026-35. Review. PMID:26962053

Davies, K.M., Julian F. B. Mercer, J.F.B., Chen, N., **Double, K.L.** (2016) Copper dyshomeostasis in Parkinson's disease: Implications for pathogenesis and indications for novel therapeutics. *Clin. Sci.* **130**, 565-574. doi: 10.1042/CS20150153.

Davies, K.M., Bohic, S., Carmona, A., Ortega, R., Cottam, V., Hare, D.J., Finberg, J.P.M., Reyes, S., Halliday, G.M., Mercer, J.F.B., **Double, K.L.** (2014) Copper pathology in vulnerable brain regions in Parkinson's disease. *Neurobiol Aging*, **35**, 858-866.

Speaker 3: Trent M. Woodruff, PhD

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Title: Innate immune drivers of pathological synuclein spread in Parkinson's disease.

Brief summary of content and significance

Parkinson's disease (PD) is characterized by a profound loss of nigral dopaminergic neurons accompanied by chronic neuroinflammation and extensive α -synuclein (Syn) inclusions. Fibrillar Syn is implicated in cell-to-cell transmission and neuronal degeneration in PD. However, the mechanisms linking Syn pathology and dopaminergic neuronal loss to chronic microglial neuroinflammation have not been defined. We have shown that activation of two key innate immune systems are key drivers of Syn-mediated dopaminergic degeneration in PD. Both the inflammasome, and the complement cascades are elevated in human post-mortem PD brains, and both immune systems are strongly activated in multiple mouse PD models, early in the onset of the disease. Fibrillar Syn activated microglial NLRP3 inflammasomes driving IL-1 β secretion, a process that was partially dependent on complement C5a receptor activation. Therapeutic blockade of NLRP3 or complement C5a receptors, using potent orally active drugs, markedly reduced dopaminergic degeneration in several PD models, with NLRP3 inhibition also reducing pathological Syn spread *in vivo*. These findings suggest that microglial C5a receptors and NLRP3 inflammasomes are a sustained source of neuroinflammation that drive progressive neuropathology and Syn spread in PD, and highlights these innate immune factors as a druggable, disease-modifying therapeutic targets for this disease.

Citations of up to 5 papers published by the speaker over the past 5 years

Coulthard LG, Hawksworth OA, Woodruff TM. (2018). Complement: The Emerging Architect of the Developing Brain. *Trends Neurosci.* pii: S0166-2236(18)30070-5.

Coulthard LG, Hawksworth OA, Li R, Balachandran A, Lee JD, Sepehrband F, Kurniawan N, Jeanes A, Simmons DG, Wolvetang E, Woodruff TM. (2017). Complement C5aR1 Signaling Promotes Polarization and Proliferation of Embryonic Neural Progenitor Cells through PKC ζ . *J Neurosci.* 37(22):5395-5407.

Lee JD, Kumar V, Fung JN, Ruitenberg MJ, Noakes PG, Woodruff TM. (2017). Pharmacological inhibition of complement C5a-C5a₁ receptor signalling ameliorates disease pathology in the hSOD1^{G93A} mouse model of amyotrophic lateral sclerosis. *Br J Pharmacol.* 174(8):689-699.

Mantovani S, Gordon R, Li R, Christie DC, Kumar V, Woodruff TM. (2016). Motor deficits associated with Huntington's disease occur in the absence of striatal degeneration in BACHD transgenic mice. *Hum Mol Genet.* 25(9):1780-91.

Woodruff TM, Lee JD, Noakes PG. (2014). Role for terminal complement activation in amyotrophic lateral sclerosis disease progression. *Proc Natl Acad Sci USA*. 111(1):E3-4.

Speaker 4: Richard Gordon, PhD DABT

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Title: Therapeutic switching of an orally-active drug to target neuroinflammation and neuropathology in Parkinson's disease

Brief summary of content and significance

This talk will present results from a Michael J Fox Foundation funded research project on validating the therapeutic efficacy of an orally-active and CNS permeable repurposed therapeutic in pre-clinical models of Parkinson's disease (PD). Novel findings on neuroinflammatory pathways and protective mechanisms modulated by this class of drugs will be discussed in the context of neuroprotection studies in PD models of mitochondrial dysfunction and synuclein pathology. This talk will also discuss progress towards clinical translation of this class of drugs through innovative new research partnerships and clinical trial initiatives for drug repurposing that have recently been established.

Citations of up to 5 papers published by the speaker over the past 5

1. Deora V, Albornoz EA, Zhu K, Woodruff TM and **Gordon R**. The ketone body β -hydroxybutyrate does not inhibit synuclein mediated inflammasome activation in microglia. **Journal of Neuroimmune Pharmacology**, 2017;1-7. doi:10.1007/s11481-017-9754-5.
2. Chen W, Foo SS, Zaid A, Teng TS, Herrero LJ, Wolf S, Tharmarajah K, Vu LD, van Vreden C, Taylor A, Freitas JR, Li RW, Woodruff TM, **Gordon R** et al. Specific inhibition of NLRP3 in chikungunya disease reveals a role for inflammasomes in alphavirus-induced inflammation. **Nature Microbiology** 2017, 2(10):1435-1445.
3. **Gordon R**, Neal ML, Luo J, Langley MR., et al. Prokineticin-2 upregulation during neuronal injury mediates a compensatory protective response against dopaminergic neuronal degeneration. **Nature Communications**, 2016; 7 12932.1-12932.18.
4. **Gordon R**, Singh N, Lawana V, Ghosh A et al. Protein kinase C δ upregulation in microglia drives neuroinflammatory responses and dopaminergic neurodegeneration in experimental models of Parkinson's disease. **Neurobiology of Disease**, 2016; 93 96-114 (Cover Article).
5. Mantovani S, **Gordon R**, Li R, Christie DC, Kumar V, Woodruff TM. Motor Deficits Associated with Huntington's Disease Occur in the Absence of Striatal Degeneration in BACHD Transgenic Mice. **Human Molecular Genetics**, 2016; 25 9: 1780-1791.
6. Brennan FH, **Gordon R.**, Lao HW, Biggins PJ, Taylor SM, Franklin RJ, Woodruff TM, Ruitenberg MJ. The Complement Receptor C5aR Controls Acute Inflammation and Astroglia following Spinal Cord Injury. **The Journal of Neuroscience** 2015; 35 (16): 6517-31 (Cover article).
7. Panicker N, Saminathan H, Jin H, Neal ML, Harischandra, DS, **Gordon R**, Luo J. Anantharam, Vellareddy, Kanthasamy AG. and Kanthasamy A (2015) Fyn kinase regulates microglial neuroinflammatory responses in cell culture and animal models of Parkinson's disease. **The Journal of Neuroscience**, 2015, 35 27: 10058-10077.

Proposal Number: 28

Theme: New techniques in neuroscience

Title: Exploring neuronal function through advanced imaging techniques

Bruce G. Mockett ¹ , Fred A. Meunier ² , Laura F. Gumy ¹ , Ruth M. Empson ¹ , Andrew H. Micallef ³

1. *University of Otago, Dunedin, OTAGO, New Zealand*
2. *Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia*
3. *The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia*

Understanding neuronal function at both the cellular level and the circuitry level is a core goal of neuroscience research. This symposium explores the ways in which modern microscopy techniques are contributing to achieving this goal and provides a picture of the challenges still to be addressed. Our ability to peer into the three-dimensional structure of cells and to observe biological processes in real-time at the molecular level was initially driven by the development of confocal microscopy in the 1990s, and more latterly by the rapid expansion of multi-photon and super-resolution microscopy. This symposium will present the application of a variety of high-resolution imaging techniques that are at the forefront of present day cellular neuroscience research and highlight their contribution to our knowledge of neuronal function. Some of the techniques that will be presented include super-resolution microscopy to track the movement of single particles within neurons, thus allowing the tracing of cellular organelles over time rather than simply obtaining a snapshot through the use of more conventional techniques, multi-photon imaging to understand the mechanisms underlying axonal transport, and calcium imaging to understand cellular connectivity at the circuitry level. None of this visualization would be possible without the ongoing development of light-emitting reporter molecules that can be attached to proteins of interest or genetically expressed at pre-determined locations. Thus, the symposium will also cover the current state of the development of genetically-expressed molecules and provide examples of their use in neuroscience research. One of the great challenges of biological research is to confirm that processes observed in *in vitro* experiments are the same as those occurring *in vivo* in normally behaving animals. In recent years, developments in microscopy have brought us closer to this goal through the introduction of cranial window techniques, *in vivo* imaging and laser technology that allows us to image deeper into brain tissue than was previously possible. These developments will feature in the talks to be presented. Overall, this symposium will be of broad interest to researchers who require high-resolution imaging of cellular structure or processes in either *in vivo* or *in vitro* preparations to address questions that conventional imaging techniques have not previously been able to resolve.

Name: Frederic A. Meunier

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Affiliation: Queensland Brain Institute, Clem Jones Centre for Ageing Dementia Research, University of Queensland

ANS membership: Ordinary

Early Career or student: No

Title: Synapses under the nanoscope

Summary:

A number of new developments in single molecule imaging has allowed us to image and track individual synaptic vesicles within the confinement of the presynapse. Moreover, we have also designed new ways of imaging molecules involved in vesicular exocytosis in live neurons and within live synapses of small organisms. In this talk I will be presenting our latest results in the nanoscale imaging of the functioning synapse.

Citations:

1. Joensuu M, Martínez-Mármol R, Padmanabhan P, Glass NR, Durisic N, Pelekanos M, Mollazade M, Balistreri G, Amor R, Cooper-White JJ, Goodhill GJ, **Meunier FA**. (2017). Visualizing endocytic recycling in live neurons by subdiffractional tracking of internalized molecules (sdTIM). *Nature Protocols*. 12(12):2590-2622.
2. Bademosi AT, Steeves J, Karunanithi S, Zalucki OH, Gormal, RS, Liu S, Lauwers E, Verstreken P, Anggono V, **Meunier FA** and van Swinderen B. (2018). Trapping of syntaxin1A in presynaptic nanoclusters by a clinically relevant general anesthetic. *Cell Reports*. 22, 1-14. doi: 10.1016/j.celrep.2017.12.054.
3. Bademosi AT, Lauwers E, Amor R, Verstreken P, van Swinderen B and **Meunier FA**. (2018). *In vivo* single-molecule tracking at the *Drosophila* presynaptic motor nerve terminal. *J. Vis. Exp.* 131. doi: 10.3791/56952.
4. Bademosi AT, Lauwers E, Padmanabhan P, Odierna L, Chai YJ, Papadopoulos A, Goodhill GJ, Verstreken P, van Swinderen B, **Meunier FA**. (2017). *In vivo* single molecule imaging of syntaxin1A reveals polyphosphoinositide- and activity-dependent reversible trapping in presynaptic nanoclusters. *Nature Communications*. 8:13660.
5. Joensuu M, Padmanabhan P, Durisic N, Bademosi AT, Cooper-Williams L, Morrow IC, Harper CB, Jung W, Parton RG, Goodhill GJ, Papadopoulos A, **Meunier FA**. (2016) Sub-diffractional tracking of internalized molecules reveals heterogeneous motion states of synaptic vesicles. *Journal of Cell Biology*. 215(2):277-292.

Name: Laura Gummy
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New Zealand
Membership type: Ordinary
Early Career Researcher: Yes
Title: **Visualising intracellular transport in neurons**

Summary:

Intracellular trafficking of cellular material is essential to maintain cell structure and function. This involves the movement of cellular cargoes by motor proteins that move along cytoskeletal microtubules. Such trafficking is especially critical for neurons because the extreme length of axons (up to 1 metre) demands that cargoes originating in the cell body travel very long distances to reach their target destinations. Despite the importance of long-range transport to proper cell functioning, knowledge on the basic mechanisms regulating the distribution of cargoes in axons over long distances are poorly understood. To date, the bottleneck limiting advances in this area have been due to technical challenges in imaging of intracellular trafficking over long distances as evidenced by a paucity of literature in the field.

I recently developed a novel imaging method to visualise long distance transport in mammalian axons. I found that secretory vesicle motility along the axon depends on the switch between the activities of different motor proteins by a microtubule associated protein. Since my study, similar findings have been replicated in other model systems, demonstrating that imaging methods can be used to answer important biological questions spanning the whole range from molecular resolution to imaging of whole organisms.

Publications

Gummy LF* and Hoogenraad CC* (2018). Local mechanisms regulating selective cargo entry and long-range trafficking in axons. **Current Opinion in Neurobiology** 51:23-28. *Co-corresponding

Gummy LF, Katrukha EA, Grigoriev I, Jaarsma D, Kapitein LC, Akhmanova A, Hoogenraad CC (2017). MAP2 defines a pre-axonal filtering zone to regulate KIF1-versus KIF5-dependent cargo transport in sensory neurons. **Neuron** 94:347-362.

Ruane PT*, **Gummy LF***, Bola B, Anderson B, Wozniak MJ, Hoogenraad CC, Allan VJ (2016). Tumour Suppressor Adenomatous Polyposis Coli (APC) localisation is regulated by both Kinesin-1 and Kinesin-2. **Scientific reports** 6:27456. *Co-first authors

Gumy LF*, Katrukha EA, Kapitein LC, Hoogenraad CC* (2014). New insights into mRNA trafficking in axons. **Developmental Neurobiology** 74:233-44. *Co-corresponding

Gumy LF, Chew DJ, Tortosa E, Katrukha EA, Kapitein LC, Tolkovsky AM, Hoogenraad CC, Fawcett JW (2013). The Kinesin-2 family member KIF3C regulates microtubule dynamics and is required for axon growth and regeneration. **Journal of Neuroscience** 33:11329-45.

Name: Ruth Empson

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Title: **Genetically encoded voltage indicators for imaging synaptic circuit activity**

Summary

Monitoring of membrane voltage at the cellular, circuit, and system levels is critical for understanding brain function. Voltage-sensitive dye and calcium-sensitive dye imaging allow parallel detection of electrical activity across populations of interconnected neurons in a variety of preparations. Game-changing advances in the conceptualization and development of optogenetic tools, including genetically encoded indicators of voltage (GEVIs) and calcium (GECIs), make this an exciting time. Compared with low-molecular-weight calcium and voltage indicators (dyes), the optogenetic imaging approaches are 1) cell type specific, 2) less invasive, 3) can relate activity with structure, and 4) can facilitate long-term recordings. The potential and promise are huge for the direct monitoring of the emergence of learned behaviours and underlying circuit mechanisms. Here I will highlight some of the promise and challenges of GEVIs for understanding movement-related synaptic circuit activity.

Motor and Cerebellar Architectural Abnormalities during the Early Progression of Ataxia in a Mouse Model of SCA1 and How Early Prevention Leads to a Better Outcome Later in Life. Ibrahim MF, Power EM, Potapov K, **Empson RM**. Front Cell Neurosci. **2017** 11:292 IF = 5.1

Prolonged type 1 metabotropic glutamate receptor dependent synaptic signaling contributes to spino-cerebellar ataxia type 1 Power, EM, Morales, A, **Empson, RM** J Neuroscience May 4 36 (18) (**2016**) IF = 6.4

Voltage imaging to understand connections and functions of neuronal circuits. Antic SD, **Empson RM**, Knopfel T. (equal contributions) J Neurophysiol. Apr 13;jn.00226.2016. doi: 10.1152/jn.00226.2016. (**2016**) IF = 2.6

Validation of optical voltage reporting by the genetically encoded voltage indicator VSFP-Butterfly from cortical layer 2/3 pyramidal neurons in mouse brain slices. **Empson RM**, Goulton C, Scholtz D, Gallero-Salas Y, Zeng H, Knöpfel T. Physiol Rep. Jul 29;3(7). Selected for Editor's Choice. (**2015**)

Transgenic mice for intersectional targeting of neural sensors and effectors with high specificity and performance. Linda Madisen, Aleena R. Garner, Daisuke Shimaoka, Amy S. Chuong, Nathan C. Klapoetke, Lu Li, Alexander van der Bourg, Yusuke Niino, Ladan Egolf, Claudio Monetti, Hong Gu, Maya Mills, Adrian Cheng, Bosiljka Tasic, Thuc Nghi Nguyen, Susan M. Sunkin, Andrea Benucci, Andras Nagy, Atsushi Miyawaki, Fritjof Helmchen, **Ruth**

M. Empson, Thomas Knöpfel, Edward S. Boyden, R. Clay Reid, Matteo Carandini, Hongkui Zeng *Neuron* 85(5):942-58. doi: 10.1016/j.neuron.2015.02.022. **(2015)**. IF = 14.6

Name: Andrew H. Micallef

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Ordinary Member

Student: Yes

Title: **Contribution of active dendritic encoding in layer 2/3 pyramidal neurons to somatosensory processing *in vivo***

Summary:

In the canonical cortical circuit information is anatomically segregated between the feed-forward pathway, driven by input from the sensory thalamic nuclei, and a feed-back stream, integrating information across brain regions. Layer 2/3 pyramidal neurons are thought to combine information from both streams. However it is unknown how this occurs in the context of an active behavioural task. Therefore, we developed a somatosensory association task where mice were trained to lick report the delivery of a vibratory stimulus to the forepaw while head-restrained under a 2-photon microscope. We imaged from the superficial tuft dendrites of cortical layer 2/3 pyramidal neurons sparsely labelled with the genetic calcium indicator Gcamp6f while animals simultaneously performed this reward-association task. This allowed us to align calcium transients to behavioural outcome and identify a subset of dendrites with behaviourally relevant activity. Application of APV revealed an NMDA dependence specific to transients occurring in the behavioural epoch. In contrast we saw no effect on the prevalence of spontaneous activity. Taken together, NMDA-dependent calcium transients in the tuft dendrites of layer 2/3 pyramidal neurons do not simply encode sensory input, their activity is directly correlated with the behavioural performance.

Relevant publications:

Micallef, A. H., Takahashi, N., Larkum, M. E., & Palmer, L. M. (2017). A Reward-Based Behavioral Platform to Measure Neural Activity during Head-Fixed Behavior. *Frontiers in Cellular Neuroscience*, 11, 95.

Murphy, S.M., Palmer, L.M., Nyffeler, T., Müri, R., Larkum, M.E. 2016. Transcranial Magnetic Stimulation (TMS) inhibits cortical dendrites. *eLife*. 5:e13598, 1-12.

Palmer, L.M., Shai, A.S., Reeve, J.E., Anderson, H.L., Paulsen, O., Larkum, M.E. 2014. NMDA spikes enhance action potential generation during sensory input. *Nature Neuroscience*. 17(3). 383-390

Palmer, L.M. 2014. Dendritic integration in pyramidal neurons during network activity and disease. Brain Re. Bull. 103. 2-10.

Proposal Number: 35

Theme: Other

Title: The emerging neuronal RNA regulatory mechanisms in health and disease

Jocelyn Widagdo¹, Guo-Li Ming², Murray J Cairns³, Guy Barry⁴, Victor Anggono¹

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3. *The School of Biomedical Sciences and Pharmacy, The University of Newcastle, Newcastle, NSW, Australia*
4. *QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia*

The regulation of transcriptome is key to cellular processes underlying neuronal function, brain development, synaptic plasticity, learning and memory. The abundance, localisation and function of neuronal messenger RNAs (mRNAs) are tightly controlled by several cis- or trans-acting mechanisms to ensure precise splicing, trafficking, turnover and translation of mRNAs in a context- and an activity-dependent manner. Mechanistic studies into how these post-transcriptional mechanisms operate have provided valuable insights into how dynamic RNA regulation underpins normal brain functions, and when perturbed, can lead to profound impact on neuronal biology and the nervous system. Indeed, dysregulations of mRNA processing are often associated with several human neurological disorders, including schizophrenia and motor neuron disease.

Recent advances in sequencing technologies have revealed that more 90% of the mammalian genome is actively transcribed, however only ~2% encodes for functional proteins, leading to pervasive transcription of non-coding RNAs. Non-coding RNAs, such as long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), are highly abundant in the brain and represent important classes of trans-acting mRNA regulators that actively shape the neuronal transcriptome. miRNAs are well-known for their role in post-transcriptional mRNA silencing, while lncRNAs are more versatile and can influence miRNA and mRNA stability, chromatin remodeling and enzymatic activity of key signalling proteins.

The emerging role of chemical modifications on RNA has led to the realisation of the importance of the “epitranscriptomic” regulation as a pervasive cis-regulatory element in controlling brain function. The methylation of adenosine (N6-methyladenosine or m6A) is the most abundant internal modification on eukaryotic mRNAs and is widespread in the mammalian brain. Research on m6A in neuroscience is still at its infancy but recent key findings highlight the biological significance of m6A and its dynamic regulation by intrinsic (development) and extrinsic stimuli (experience or injury).

This symposium brings together national and international experts, who have made significant contributions to our understanding of how miRNAs (Dr. Murray Cairns, University of Newcastle), lncRNAs (Dr. Guy Barry, Queensland Institute of Medical Research) and RNA methylation (Dr. Guo-li Ming, University of Pennsylvania, USA and Dr. Jocelyn Widagdo, University of Queensland) regulate brain function in health and disease. We believe that this topic is timely and will be of interest to the broad neuroscience community. The proposed symposium is carefully designed to include speakers that represent gender (2 males and 2 females) and geographic diversity, as well as encompassing early- (Dr. Jocelyn Widagdo), mid- (Dr. Guy Barry) and late-career scientists (Dr. Guo-li Ming and Dr. Murray Cairns), while maintaining the quality of scientific content at a high standard. We believe that this will be an exciting symposium with dynamic discussion at the upcoming ANS2018 meeting.

Epitranscriptomic m6A Regulation of Axon Regeneration in the Adult Mammalian Nervous System

Guo-li Ming

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N6-methyladenosine (m6A) affects multiple aspects of mRNA metabolism and regulates developmental transitions by promoting mRNA decay. Little is known about the role of m6A in the adult mammalian nervous system. Using sciatic nerve lesion in mouse as an in vivo injury model, we found that axonal injury elevates levels of m6A-tagged transcripts encoding many regeneration-associated genes and protein translation machinery components in the adult mouse dorsal root ganglion (DRG). Single-base resolution m6A-CLIP mapping further reveals a dynamic m6A landscape in the adult DRG upon injury. Loss of either m6A methyltransferase complex component Mettl14, or m6A-binding protein Ythdf1, globally attenuates injury-induced protein translation in adult DRGs and reduces functional axon regeneration in the peripheral nervous system in vivo. Furthermore, we found that Pten deletion-induced axon regeneration of retinal ganglion neurons in the adult central nervous system is attenuated upon Mettl14 knockdown. Our study reveals a critical epitranscriptomic mechanism in promoting injury-induced protein synthesis and axon regeneration in the adult mammalian nervous system.

* ANS membership: N/A (overseas)

Publications (Citations – Google Scholar)

Weng YL, Wang X, An R, Cassin J, Vissers C, Liu Y, Liu Y, Xu T, Wang X, Wong S, Joseph J, Dore LC, Dong Q, Zheng W, Jin P, Wu H, Shen B, Zhuang X, He C, Liu K, Song H, **Ming GL**. Epitranscriptomic m6A Regulation of Axon Regeneration in the Adult Mammalian Nervous System *Neuron*. 2018 Jan 17. (4 cites)

Yoon KJ, Rojas Ringeling F, Vissers C, Jacob F, Pokrass M, Jimenez-Cyrus D, Su Y, Kim NS, Zhu Y, Zheng L, Kim S, Wang X, Dore L, Jin P, Regot S, Zhuang X, Canzar S, He C, **Ming GL**, Song H. Temporal Control of Mammalian Cortical Neurogenesis by m6A Methylation. *Cell*. 2017 Sep 28. (21 cites)

Yoon KJ, Song G, Qian X, Pan J, Xu D, Rho HS, Kim NS, Habela C, Zheng L, Jacob F, Zhang F, Lee EM, Huang WK, Ringeling FR, Vissers C, Li C, Yuan L, Kang K, Kim S, Yeo J, Cheng Y, Liu S, Wen Z, Qin CF, Wu Q, Christian KM, Tang H, Jin P, Xu Z, Qian J, Zhu H, Song H, **Ming GL**. Zika-Virus-Encoded NS2A Disrupts Mammalian Cortical Neurogenesis by Degrading Adherens Junction Proteins. *Cell Stem Cell*. 2017 Aug 16. (10 cites)

Weng YL, An R, Cassin J, Joesph J, Mi R, Wang C, Zhong C, Jin SG, Pfeifer GP, Bellacosa A, Dong X, Hoke A, He Z, Song H, **Ming GL**. An Intrinsic Epigenetic Barrier for Functional Axon Regeneration. *Neuron*. 2017 Apr 19; 94(2):337-346. (4 cites)

Qian X, Nguyen HN, Song MM, Hadiono C, Ogden SC, Hammack C, Yao B, Hamersky GR, Jacob F, Zhong C, Yoon KJ, Jeang W, Lin L, Li Y, Thakor J, Berg DA, Zhang C, Kang E, Chickering M, Nauen D, Ho CY, Wen Z, Christian KM, Shi PY, Maher BJ, Wu H, Jin P, Tang H, Song H, **Ming GL**. Brain-Region-Specific Organoids Using Mini-bioreactors for Modeling ZIKV Exposure. *Cell*. 2016 May 19; 165(5):1238-54. (327 cites)

m6A-epitranscriptomic regulation of neuronal plasticity

Jocelyn Widagdo* and Victor Anggono

Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, 4072, Australia.

Methylation of adenosine by *N*⁶-methyladenosine (m⁶A) is the most prevalent internal modification on eukaryotic RNA. This post-transcriptional modification modulates the splicing, stability or translation of mRNAs. In mammalian brain, the level of m⁶A is developmentally upregulated and peaks in adulthood, however the role of m6A in regulating neuronal plasticity remains elusive. Our study demonstrated that m6A is dynamically regulated in the medial prefrontal cortex of mice exposed to the fear conditioning paradigm. , An antibody-based m6A capture technique followed by RNA sequencing (MeRIP-seq) analysis revealed that approximately 250 distinct loci were modulated across hundreds of transcripts, the majority of which is associated with dendritic functions and synaptic plasticity. Targeted knockdown of FTO, an m6A-demethylase, in the mouse prefrontal cortex led to enhanced consolidation of cued fear memory, supporting the physiological role of m6A in learning associated plasticity. Interestingly, the levels of m6A can also be dynamically regulated by chronic synaptic inactivity. The loss of Mettl3 function, an m6A methyltransferase, blunt the ability of neurons to scale the amount of excitatory postsynaptic glutamate receptors. These results demonstrate the importance of m6A signalling in homeostatic synaptic plasticity, potentially by fine-tuning mRNA turnover and translation rate of synaptic molecules.

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ANS membership : Ordinary (Early Career Researcher)

Publications (Citations – Google Scholar)

1. Zhu T, XLH Yong, Xia D, **Widagdo J[#]**, Anggono V[#] (2018) Ubiquitination mediates proteasomal degradation and nuclear translocation of the fat mass and obesity-associated (FTO) protein. *J. Mol. Biol.* 430: 363-371. [#]co-senior authors.
2. Tan MC*, **Widagdo J^{*,#}**, Chau YQ, Zhu T, Wong JJ, Cheung A, Anggono V[#] (2017) The activity-induced long non-coding RNA Meg3 modulates AMPA receptor surface expression in primary cortical neurons. *Front. Cell. Neurosci.* 11: 455. (6 citations) ^{*}co-first [#]co-corresponding authors.
3. **Widagdo J^{*}**, Fang H*, Jang SE, Anggono V (2016) PACSIN1 regulates the dynamic of AMPA receptor trafficking. *Sci. Rep.* 6: 31070. (10 citations) ^{*}co-first author.
4. **Widagdo J[#]**, Zhao Q, Kempen MJ, Tan MC, Ratnu VS, Wei W, Leighton L, Spadaro PA, Edson J, Anggono V, Bredy TW[#] (2016) Experience-dependent accumulation of *N*⁶-methyladenosine in the prefrontal cortex is associated with memory processes in mice. *J Neuroscience.* 36: 6771-77. (28 citations) [#]co-corresponding authors.
5. **Widagdo J**, Chai YJ, Ridder MC, Chau YQ, Johnson RC, Sah P, Huganir RL, Anggono V (2015) Activity-dependent ubiquitination of GluA1 and GluA2 regulates AMPA receptor intracellular trafficking and degradation. *Cell Rep.* 10: 783-95. (42 citations, highlighted by the Faculty of 1000).

Exploring the molecular determinants and behavioural consequences of posttranscriptional dysregulation in schizophrenia

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The molecular determinants of behaviour and cognition are encoded throughout the genome, including many segments expressed as non-coding RNA. These molecules provide a regulatory matrix, that enable complex patterns of intracellular translation to support neural development, neuroplasticity and cognitive function. While these systems provide tremendous specificity and flexibility, there is also significant potential for genomic and epigenomic variation in non-coding RNA expression that can adversely affect neurodevelopment and function. We previously observed substantial dysregulation of miRNA expression in schizophrenia and have identified several sources of variation related to both the underlying genetic factors as well as environmental exposures and experience. In recent work we have been characterizing the molecular determinants of posttranscriptional dysregulation and modeling their neurobehavioural impact in cellular and animal systems. This research suggests that these risk factors are capable of modifying neurodevelopmentally sensitive gene pathways and networks that manifest as neurocognitive deficits relevant to schizophrenia and other psychiatric disorders.

* *ANS membership: Ordinary*

Publications (Citations – Google Scholar)

- MC1. Goldie BJ, Fitzsimmons C, Weidenhofer J, Atkins JR, Wang DO, **Cairns MJ**. (2017) miRNA enriched in human neuroblast nuclei bind the MAZ transcription factor and their precursors contain the MAZ consensus motif. *Front. Mol. Neurosci.* 10:259 (0 cites)
- MC2. Mahmoudi E, **Cairns MJ** (2017) MiR-137: an important player in neural development and neoplastic transformation. *Mol. Psychiatry.* 22:44-55. (21 cites)
- MC3. Wu JQ, Green MJ, Gardiner EJ, Tooney PA, Scott RJ, Carr VJ, **Cairns MJ**. (2016) Altered neural signaling and immune pathways in peripheral blood mononuclear cells of schizophrenia patients with cognitive impairment: A transcriptome analysis. *Brain Behavior and Immunity.* 53:194-206. (9 cites)
- MC4. Hollins SL, Zavitsanou K, Walker FR, **Cairns MJ** (2014) Alteration of imprinted Dlk1-Dio3 miRNA cluster expression in the entorhinal cortex induced by maternal immune activation and adolescent cannabinoid exposure. *Translational Psychiatry* 4:e452 (20 cites)
- MC5. Goldie BJ, Dun MD, Lin M, Smith ND, Verrills NM, Dayas CV, **Cairns MJ**. (2014) Activity-associated miRNA are packaged in Map1b-enriched exosomes released from depolarised neurons. *Nucleic Acids Res.* 42:9195-9208. (62 cites)

Long non-coding RNAs and the dynamic regulation of human brain function

Maina Bitar¹, Elizabeth O'Brien¹, Panos Roussos², Kristen J Brennand² and **Guy Barry**¹,

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Human evolution over only the past 2 million years has witnessed an incredible non-uniform expansion of the human brain (almost tripling in size) and the acquisition of many higher order cognitive functions such as creativity, imagination and reasoning. Comparative genomics have uncovered valuable insight, especially the expansion of primate and human specific non-coding regulatory and repeat-containing regions, but how these translate into higher order cognitive abilities is unknown. We have found that the expression of distinct subsets of long non-coding RNAs (lncRNAs) is dynamically regulated during neurogenesis and aging, and in response to neuronal depolarisation. Some activity-dependent lncRNAs are associated with altered neuronal function such as observed in epilepsy and schizophrenia. Furthermore, we find that there are significant differences in transcriptomic responses between iPSC-derived neurons from schizophrenia sufferers and controls, which are only evident upon activity, suggesting that psychiatric conditions may arise from fragilities in newly evolved regulatory mechanisms. These results present evidence that lncRNAs are essential for proper regulation of neuronal function, and how activity-dependent regulation by non-coding RNAs has contributed to the evolution and function of the human brain.

* *ANS membership: Ordinary*

Publications (Citations – Google Scholar)

Barry G, Briggs JA, Hwang DW, Nayler SP, Fortuna PR, Jonkhout N, Dachet F, Maag JL, Mestdagh P, Singh EM, Avesson L, Kaczorowski DC, Ozturk E, Jones NC, Vetter I, Arriola-Martinez L, Hu J, Franco GR, Warn VM, Gong A, Dinger ME, Rigo F, Lipovich L, Morris MJ, O'Brien TJ, Lee DS, Loeb JA, Blackshaw S, Mattick JS, Wolvetang EJ. The long non-coding RNA NEAT1 is responsive to neuronal activity and is associated with hyperexcitability states. *Sci Rep*. 2017 Jan 5;7:40127. (8 Cites)

Roussos P, Guennewig B, Kaczorowski DC, **Barry G**, Brennand KJ. Activity-Dependent Changes in Gene Expression in Schizophrenia Human-Induced Pluripotent Stem Cell Neurons. *JAMA Psychiatry*. 2016 Nov 1;73(11):1180-1188. (6 Cites)

Briggs JA, Wolvetang EJ, Mattick JS, Rinn JL, **Barry G**. Mechanisms of Long Non-coding RNAs in Mammalian Nervous System Development, Plasticity, Disease, and Evolution. *Neuron*. 2015 Dec 2;88(5):861-877. (68 Cites)

Barry G, Guennewig B, Fung S, Kaczorowski D, Weickert CS. Long Non-Coding RNA Expression during Aging in the Human Subependymal Zone. *Front Neurol*. 2015 Mar 9;6:45. (7 Cites)

Barry G, Briggs JA, Vanichkina DP, Poth EM, Beveridge NJ, Ratnu VS, Nayler SP, Nones K, Hu J, Bredy TW, Nakagawa S, Rigo F, Taft RJ, Cairns MJ, Blackshaw S, Wolvetang EJ, Mattick JS. The long non-coding RNA Gomafu is acutely regulated in response to neuronal activation and involved in schizophrenia-associated alternative splicing. *Mol Psychiatry*. 2014 Apr;19(4):486-94. (172 Cites)

Proposal Number: 26

Theme: New techniques in neuroscience

Title: Genetically-encoded calcium imaging techniques for interrogating neural circuits in vivo

Philip Jean-Richard-dit-Bressel¹, Malinda Tantirigama², Lucy M Palmer³, Su Young Han⁴

1. *School of Psychology, University of New South Wales, Kensington, NSW, Australia*
2. *Eccles Institute of Neuroscience, John Curtin School of Medical Research, Australia National University, Acton, ACT, Australia*
3. *Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, VIC, Australia*
4. *Centre for Neuroendocrinology and Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin, Otago, New Zealand*

Measuring neural activity is fundamental to neuroscience. Historically, attempts to accurately and specifically measure neural activity have been hampered by trade-offs in spatial and temporal resolution, cell specificity, scalability, accessibility, and the option of measuring during ethologically-relevant states (e.g. in awake, freely-behaving animals).

Recent developments in genetically-encoded calcium indicators (GECIs), e.g. the development of a stable, highly sensitive GECI, GCaMP6, along with advances in imaging techniques, have made chronic, cell-type and circuit-specific measurement of neuronal activity in awake, freely-behaving animals much more accessible.

This symposium, with diversity in speaker gender and geographical location, demonstrates the use of these techniques *in vivo*, as well as highlight local Australasian expertise to attendees interested in applying these techniques to their own research. Discussions with a broad group of ANS members has indicated that there is a great deal of interest in a symposium around these techniques, with many wishing to implement these techniques in their own laboratories.

These techniques include two-photon microscopy and wide-field fluorescence microscopy, for measurement of large yet specifically-defined populations of neurons in head-fixed yet behaving animals down to the resolution of axons and dendrites. Dr Malinda Tantirigama, a postdoc with Prof John Bekkers at Australia National University, will present two-photon and wide-field fluorescence microscopy methodology and data. Dr Lucy Palmer from the Florey Institute will present on two-photon imaging of dendrites and axons.

Another technique, fibre photometry, allows bulk measurement of calcium transients within cell populations and/or their terminals in freely-moving animals. This technique uses equipment utilised in typical optogenetics experiments (e.g. optic fibres, light stimulation control), making it well-suited in combination with, and relatively accessible to, laboratories already using optogenetics. The proposer of this symposium, Dr Philip Jean-Richard-dit-Bressel, a postdoc with Prof Gavan McNally at University of New South Wales, and Dr Su Young Han, a postdoc with Prof Allan Herbison at University of Otago, will speak on theoretical and practical aspects of setting up and producing data using this technique.

The most recently developed technique in this field, mini-endoscopes, allows the measurement of neural activity in freely-moving animals at the resolution of individual cells via an implanted GRIN lens. This high spatial resolution allows users to identify distinct neuronal ensembles without restricting an animal's movement. Head mounted mini-microscopes from Inscopix or

open-source options from UCLA are two options in this space. Dr Philip Jean-Richard-dit-Bressel and Dr Su Young Han will present their experiences setting up and using Inscopix (Jean-Richard-dit-Bressel) and UCLA (Han) miniscopes.

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ANS member type

Ordinary member

Early Career Researcher/HDR student?

ECR

Title and summary of talk (no more than 200 words)**Illuminating odour processing with two-photon calcium imaging *in vivo*.**

To understand how the brain works it is essential to study neural network activity during active information processing in live animals. Addressing this challenge requires the tracking of neuronal activity in identified cell types *in vivo*. Two-photon calcium imaging allows fluorescence readout of activity as a proxy for spike firing in many neurons at the same time. We have adopted this technology using the ultrasensitive, genetically-encoded fluorescent calcium indicator GCaMP6 to study circuit activity in the primary olfactory cortex of anaesthetised mice while the animal is smelling odours. In this talk, I will present our strategies for labelling and imaging from specific neuronal populations using virus carrying GCaMP6 combined with either two-photon or wide-field fluorescence microscopy. I will provide our workflow for obtaining data from up to 200 neurons simultaneously, as well as the post-processing pipeline we use to extract biologically relevant information from these datasets (i.e. movement correction, region-of-interest segmentation, and inference of neuronal activity). In summary, I will present the practical aspects of *in vivo* two-photon calcium imaging in order to inform Australasian scientists about how this amazing technique can illuminate their research.

List citations of up to 5 relevant papers published in the past 5 years.

LB Gerrard*, **MLS Tantirigama***, JM Bekkers. 2018. Pre- and postsynaptic activation of GABAB receptors modulates principal cell excitation in the piriform cortex. *Frontiers in Cellular Neuroscience* 12:28. *Joint first authors.

MLS Tantirigama, HHY Huang, JM Bekkers. 2017. Spontaneous activity in the piriform cortex extends the dynamic range of cortical odor coding. *Proceedings of the National Academy of Sciences USA* 114(9): 2407-2412.

MLS Tantirigama, MJ Oswald, AJ Clare, HE Wicky, RC Day, SM Hughes, RM Empson. 2016. Fezf2 expression in layer 5 projection neurons of mature mouse motor cortex. *Journal of Comparative Neurology* 524(4): 829-845.

MLS Tantirigama, MJ Oswald, C Duynstee, SM Hughes, RM Empson. 2014. Expression of the developmental transcription factor Fezf2 identifies a distinct subpopulation of layer 5 callosal projection neurons in mature mouse motor cortex. *Journal of Neuroscience* 34(12): 4303-4308.

MJ Oswald, **MLS Tantirigama**, I Sonntag, SM Hughes, RM Empson. 2013. Diversity of layer 5 projection neurons in the mouse motor cortex. *Frontiers in Cellular Neuroscience* 7:174.

Name and affiliation

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ANS member type

Ordinary member

Early Career Researcher/HDR student?

No

Title and summary of talk (no more than 200 words)**Probing cortical dendritic and axonal activity during reward association using two-photon microscopy**

Two-photon microscopy enables morphological and functional assessment of subcellular processes in vivo. Here, we use resonant scanning two-photon microscopy to measure Ca²⁺ activity in dendrites and axons within the somatosensory cortex during a reward-based association behaviour. Practical aspects of two-photon imaging will be discussed, detailing the Ca²⁺ indicator delivery and subsequent chronic window surgical preparation. The advantages and disadvantages of using two-photon microscopy for assessing neural activity during awake behaviour will also be highlighted. Finally, examples will be shown illustrating the role of cortical dendrites and thalamic axons during a sensory-based reward association task.

List citations of up to 5 relevant papers published in the past 5 years.

Micallef, A.H., Takahashi, N., Larkum, M.E., **Palmer, L.M.** 2017. Measuring neural activity during reward-based behavior: an Arduino and Python based perceptual Go/No-Go platform. *Frontiers in Cellular Neuroscience*. 11: 156.

Murphy, S.M., **Palmer, L.M.**, Nyffeler, T., Muri, R., Larkum, M.E. 2016. Transcranial Magnetic Stimulation (TMS) inhibits cortical dendrites. *eLife*. 5:e13598, 1-12.

Mayrhofer, J.M., Haiss, F., Hänni, D., Weber, S., Barrett, M.J., Ferrari, K., Maechler, P., Saab, A., Stobart, J., Wyss, M.T., Zuend, M., Johannssen, H., Osswald, H., **Palmer, L.M.**, Revol, V., Schuh, C., Urban, C., Hall, A., Innerhofer, E., Larkum, M.E., Zeilhofer, H.U., Ziegler, U., and Weber, B. 2015.

Design and performance of an ultra-flexible two-photon microscope for in vivo research. Biomedical Optics Express. 6(11): 4228-37.

Palmer, L.M., Shai, A.S., Reeve, J.E., Anderson, H.L., Paulsen, O., Larkum, M.E. 2014. NMDA spikes enhance action potential generation during sensory input. Nature Neuroscience. 17(3). 383-390

Palmer, L.M. 2014. Dendritic integration in pyramidal neurons during network activity and disease. Brain Re. Bull. 103. 2-10.

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ANS member type

Ordinary member

Early Career Researcher/HDR student?

ECR

Title and summary of talk (no more than 200 words)

Using fibre photometry to investigate neural circuits for reward and aversion

Fibre photometry permits chronic measurement of Ca^{2+} transients in a cell- and circuit-specific manner, without restrictions on anatomical targets or an animal's movement. It is a highly accessible technique, sharing several features with *in vivo* optogenetic manipulation. This talk describes the theoretical and practical facets of using fibre photometry. Two examples of how this technique is being used to understand the neural underpinnings of complex behaviour will be presented: contributions of basolateral amygdala cell populations to aversive learning, and ventral tegmental area dopamine neuron activity in reward.

List citations of up to 5 relevant papers published in the past 5 years.

Jean-Richard-dit-Bressel P, Killcross S, McNally GP (*in press*). Behavioural and neurobiological mechanisms of punishment: Implications for psychiatric disorders. *Neuropsychopharmacology*.

Sengupta A, Yau JOY, **Jean-Richard-dit-Bressel P**, Liu Y, Millan ZE, Power JM, McNally GP (2018). Basolateral amygdala glutamatergic neurons maintain aversive emotional salience. *Journal of Neuroscience*.

Jean-Richard-dit-Bressel P, McNally GP (2016). Lateral, not medial, prefrontal cortex contributes to punishment and aversive instrumental learning. *Learning & Memory*, 23, 607-617.

Jean-Richard-dit-Bressel P, McNally GP (2015). The role of the basolateral amygdala in punishment. *Learning & Memory* 22: 128-137.

Jean-Richard-dit-Bressel P, McNally GP (2014). The role of the lateral habenula in punishment. *PLoS One* 9(11): e111699. doi:10.1371/journal.pone.0111699

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ANS member type

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ECR

Title and summary of talk (no more than 200 words)**Real-time observation of gonadotrophin-releasing hormone pulse generator activity using fiber photometry and miniature micro-endoscopes**

In vivo calcium imaging has emerged as an increasingly popular tool in neuroscience for recording the activity of genetically-defined neuronal populations in behaving animals. As well as recording from brain structures close to the dorsal surface of the brain, although more problematic, this technology can be also applied to imaging deep brain structures. Using fiber photometry with a genetically-encoded fluorescent calcium indicator GCaMP6, we have recently shown that the kisspeptin neurons in the arcuate nucleus (ARN) exhibit intermittent, synchronized calcium events that define the secretion pattern of luteinizing hormone (Clarkson, Han *et al.*, 2017). This talk will present strategies for targeting deep-brain neuronal populations using an adeno-associated virus encoding GCaMP6s and the surgical procedures for implanting optic fibers. Long-term and 24-h recordings from ARN kisspeptin neurons in intact and gonadectomized male mice will be presented, demonstrating the stability of the recordings over time.

Current studies are employing the open-source UCLA miniscope to examine neural activity at a single-cell resolution and practical aspects of this system will be discussed.

List citations of up to 5 relevant papers published in the past 5 years.

Clarkson J*, Han SY*, Piet R, McLennan T, Kane GM, Ng J, Porteous RW, Kim JS, Colledge WH, Iremonger KJ and Herbison AE. (2017). Definition of the hypothalamic GnRH pulse generator in mice. *PNAS*. 114(47):E10216-E10223. doi: 10.1073/pnas.1713897114. *Joint first authors

Han SY, McLennan T, Czielesky K and Herbison AE. (2015). Selective optogenetic activation of arcuate kisspeptin neurons generates pulsatile luteinizing hormone secretion. *PNAS*. 112(42):13109-13114.

Choe KY, **Han SY**, Gaub P, Shell B, Voisin DL, Knapp BA, Barker PA, Brown CH, Cunningham JT, Bourque CW. (2015). High salt intake increases blood pressure via BDNF-mediated downregulation of KCC2 and impaired baroreflex inhibition of vasopressin neurons. *Neuron*. 85(3):549-560.

Han SY, Bouwer GT, Seymour AJ, Korpai AK, Schwenke DO and Brown CH. (2015). Induction of hypertension blunts baroreflex inhibition of vasopressin neurons in the rat. *Eur J Neurosci*. 42(9):2690-2698

Han SY, Gray E, Hughes G, Brown CH, Schwenke DO. (2014). Increased sympathetic drive during the onset of hypertension in conscious Cyp1a1-Ren2 rats. *Pflügers Arch – Eur J Physiol*. 466:459-466

Proposal Number: 14

Theme: Cognition/learning and behaviour

Title: The neural basis of decision making in a changing environment

Marcello Rosa ¹ , Keiji Tanaka ² , Jason Mattingley ³ , Katerina Semendeferi ⁴ , Farshad A Mansouri ¹

1. *Monash University, Clayton, VICTORIA, Australia*
2. *RIKEN Center for Brain Science, Saitama, Japan*
3. *Queensland Brain Institute, University of Queensland, Brisbane*
4. *Department of Anthropology, University of California in San Diego, San Diego*

In a complex and changing environment, the validity of tasks or goals might change in terms of their associated reward and cost, and we often face the necessity to make a strategic decision to adaptively shift between these goals. Cognitive flexibility emerges from executive functions that coordinate participation of various cognitive processes to select and achieve goals in a changing environment. Recent studies suggest that a distributed network of sub-cortical and cortical regions, particularly prefrontal cortex, play essential roles in these cognitive abilities. This symposium aims at presenting and discussing the latest findings and models describing the neural substrate and underlying mechanisms of cognitive flexibility in a changing environment. The scientists presenting in this symposium have recently proposed comprehensive models to describe the neural architecture of executive control of goal-directed behaviour (Mansouri et al., *Nature Reviews Neuroscience* 2009, 2017; *Trends in Neuroscience* 2017).

In this symposium, findings from various experimental approaches in humans and non-human primates will be presented and discussed:

Katerina Semendeferi (University of California San Diego) will present findings from neuroanatomical studies comparing human and nonhuman primate brain. Keiji Tanaka (RIKEN institute) will describe the findings from imaging studies in the context of cognitive tasks. Jason Mattingley (Queensland Brain Institute) will present findings from psychophysical and brain stimulation studies in humans. Farshad Mansouri (Monash University) will present findings from electrophysiology and behavioural studies in non-human primates.

Specifying the contribution of the prefrontal cortex and other brain regions to cognitive flexibility is important not only for understanding the mechanistic basis of higher order cognitive functions in primates (including possibly some unique forms of intelligent human behaviour), but also because this knowledge may help us to understand some of the underlying causes of the behavioural deficits associated with a range of neuropsychiatric disorders linked to impaired cognitive ability in adapting in a changing environment.

This symposium will provide the opportunity to discuss the latest findings and models of higher brain functions and stimulate collaborations between Australian and international investigators. This will also provide an educational platform for students and early career researchers to get familiar with the latest findings and theoretical models regarding some of the most complex aspect of cognition.

Speaker 1: Dr. Keiji Tanaka (RIKEN Center for Brain Science, Japan), keiji@riken.jp, not an ANS member.

Title: Neural substrates of intuition in shogi and soccer experts

Abstract: Intuition, i.e., quick, largely unconscious problem-solving capability, situates at the core of experts' superior capability. We measured brain activities of professional players in shogi, Japanese chess, while they quickly generated the idea of the best next-move and of professional soccer players while they quickly selected the pass target in soccer games. We found a close association of activities in the head of the caudate nucleus, a part of the basal ganglia, with the quick selections in both domains. The loop circuits that the basal ganglia make with the cortex have a characteristic structure, a combination of focused direct pathway and spreading direct and indirect pathways, which is advantageous for a quick selection of an action among many candidates. We suggest that the caudate head plays an essential role in experts' intuition in a wide range of domains by supporting quick selections.

Recent papers:

- 1- Wan X, Cheng K, **Tanaka K**. Neural encoding of opposing strategy values in anterior and posterior cingulate cortex. *Nature Neuroscience* 18, 752-759 (2015).
- 2- Mansouri FA, Buckley MJ, Mahboubi M, **Tanaka K**. Behavioral consequences of selective damage to frontal pole and posterior cingulate cortices. *Proceedings of National Academy of Sciences USA* 112, E3940-9 (2015).
- 3- Kuriki I, Sun P, Ueno K, **Tanaka K**, Cheng K. Hue selectivity in human visual cortex revealed by functional magnetic resonance imaging. *Cerebral Cortex* 25, 4869-4884 (2015).
- 4- Mansouri FA, Buckley MJ, **Tanaka K**. The essential role of primate orbitofrontal cortex in conflict-induced executive control adjustment. *Journal of Neuroscience*, 34, 11016-11031 (2014).
- 5- Kuwabara M, Mansouri FA, Buckley MJ and **Tanaka K**. Cognitive control functions of anterior cingulate cortex in macaque monkeys performing a Wisconsin Card Sorting Test analog. *Journal of Neuroscience* 34, 7532-7547 (2014).

Speaker 2: Dr. Jason Mattingley (Queensland Brain Institute, University of Queensland, Brisbane), j.mattingley@uq.edu.au, full ANS member.

Title: Bayesian inference as a model of complex perceptual decision making in humans

Abstract: Virtually every aspect of waking life requires a decision. What are the brain processes that underlie decision making in humans? Bayes' theorem postulates that the probability of a hypothesis (e.g., Has it rained today?) given an observation (e.g., the streets are wet) is a weighted sum of the probability of the hypothesis on its own (e.g., it seldom rains in Brisbane) and the probability of the observation given the hypothesis (e.g., when it rains the streets are always wet). Bayes' rule has been used successfully to model different aspects of human cognition, from shape constancy to spatial navigation. I will introduce a number of behavioural tasks we have used to test whether complex perceptual decision making follows Bayes' rule. In a typical task, observers must integrate two discrete sources of information to reach a single decision, such as deciding on the average direction of two patches of moving dots. While observers perform these tasks, we measure neural activity using EEG and fMRI. Our findings suggest that people combine different sources of information in a weighted fashion, and that the weights are proportional to the quality of each source. In other words, complex perceptual decisions in humans follow Bayesian inference rules.

Recent papers:

1. Garrido MI, Rowe EG, Halász V, **Mattingley JB** (in press). Bayesian mapping reveals that attention boosts neural responses to predicted and unpredicted stimuli. *Cerebral Cortex*. (Accepted: 15/03/17).
2. Harris AM, Dux PE, **Mattingley JB**. Detecting unattended stimuli depends on the phase of prestimulus neural oscillations. *Journal of Neuroscience*, 38, 3092-3101 (2018).
3. Cocchi L, Sale MV, Gollo LL, Bell PT, Nguyen VT, Zalesky A, Breakspear M, **Mattingley JB**. A hierarchy of timescales explains distinct effects of local inhibition of primary visual cortex and frontal eye fields. *eLife*, 5:e15252 (2016). (DOI: <http://dx.doi.org/10.7554/eLife.15252>).
4. Painter DR, Dux PE, Travis SL, **Mattingley JB**. Neural responses to target features outside a search array are enhanced during conjunction but not unique-feature search. *Journal of Neuroscience*, 34, 3390-3401 (2014).
5. Harrison WJ, Retell JD, Remington RW, **Mattingley JB**. Visual crowding at a distance during predictive remapping. *Current Biology*, 23, 793-798 (2013).

Speaker 3: Dr. Katerina Semendeferi (Department of Anthropology, University of California in San Diego), ksemende@ucsd.edu, not an ANS member.

Title: Frontal cortex in evolution and disease

Abstract: Comparative human and nonhuman primate brain studies demonstrate significant changes in neural frontal and limbic systems including cortical and subcortical structures. The human frontal lobe is large in absolute terms, but its relative to the rest of the brain size is remarkably similar across humans and apes. In human evolution an overall increase in brain size was accompanied by subtle but potentially critical changes in systems that underlie higher order cognitive and emotional functions. A series of studies demonstrates specific changes at the cellular and architectonic levels in multiple neural systems, including brain regions like the orbitofrontal cortex, frontal pole, amygdala, anterior cingulate that are linked intimately to systems involved in, among other capabilities, planning, imagination, motivation, and inhibition. Increased research on typical frontal lobe and amygdala development, structure and function reveals that these structures are also vulnerable in neurological and psychiatric disorders, including autism and Williams Syndrome. A phylogenetically recent reorganization of frontal cortical, amygdala and striatal circuitry took place that may be critical to the emergence of human-specific social and emotional functions.

Recent papers:

- 1- Lew, C.H., Groeniger, K.M., Bellugi, U., Stefanacci, L., Schumann, C.M., **K. Semendeferi** (2018) A postmortem stereological study of the amygdala in Williams syndrome. *Brain Structure and Function*, 223(4):1897-1907.
- 2- Hanson, K.L., Lew C.H., Hrvoj-Mihic B., Groeniger K.M., Halgren E., Bellugi U. and **K. Semendeferi** (2018) Increased glia density in the caudate nucleus in Williams syndrome: implications for frontostriatal dysfunction in autism. *Developmental Neurobiology*, online.
- 3- Hrvoj-Mihic, B, Hanson K.L., Lew C.H., Stefanacci, L., Jacobs, B, Bellugi U and K. **Semendeferi** (2017) Basal dendritic morphology of cortical pyramidal neurons in Williams syndrome: prefrontal cortex and beyond. *Frontiers in Neuroscience* Vol 11, Article 419.
- 4- Lew, C.H., **Semendeferi, K.** (2017). Evolutionary Specializations of the Human Limbic System. In: Kaas, J (ed.), *Evolution of Nervous Systems* 2e. vol. 4, pp. 277–291. Oxford: Elsevier.

Horton Lew, C., C. Brown, U. Bellugi, and **K. Semendeferi** (2017) Neuron density is decreased in the prefrontal cortex in Williams syndrome. *Autism Research* 10(1):99-112. Thanathom Chailangkarn, Cleber A. Trujillo, Beatriz C. Freitas, Branka Hrvoj-Mihic, Roberto H. Herai, Diana X. Yu, Timothy T. Brown, Maria C. Marchetto, Cedric Bardy, Lauren McHenry, Lisa Stefanacci*, Anna Järvinen, Yvonne M. Searcy, Michelle DeWitt, Wenny Wong, Philip Lai, M. Colin Ard, Kari L. Hanson*, Sarah Romero, Bob Jacobs, Anders M. Dale, Li Dai, Julie R. Korenberg, Fred H. Gage, Ursula Bellugi, Eric Halgren, Katerina **Semendeferi** & Alysson R. Muotri (2016) A human neurodevelopmental model for Williams syndrome. *Nature* 536(7616):338-343

Speaker 4: Dr. Farshad A. Mansouri (Department of Physiology, Monash University), Farshad.Mansouri@monash.edu, ANS membership TBA.

Title: The role of prefrontal cortex in cognitive flexibility and control

Abstract: In a complex and changing environment, the validity of rules or goals might change in terms of their associated reward and cost, and we often face the necessity to make a strategic decision to adaptively shift between these behavioural rules or goals. Such a decision entails assessment of the value (cost and benefit) of current and alternative rules or reward resources for the individual, and also for the group, in socially advanced species. A distributed neural network involving prefrontal and medial frontal cortices regulates the use of cognitive resources to optimize exploitation of current reward resources, while minimizing the associated cost. This is referred to as executive control of goal directed behaviour. Recent studies suggest that dorsolateral prefrontal, orbitofrontal and anterior cingulate cortices are involved in optimizing the exploitation of the current reward sources however, the most rostral part of the prefrontal cortex (frontopolar cortex) plays a crucial role in adjusting the tendency for exploitation, versus exploration of other alternative resources, by assessing the value of alternative tasks/goals and re-distribution of our cognitive resources.

Recent papers:

- 1- **Mansouri FA**, Koechlin E, Rosa MGP, Buckley MJ. (2017) Managing competing goals - a key role for the frontopolar cortex. *Nature Reviews Neuroscience* 18, 645-657.
- 2- **Mansouri FA**, Buckley MJ, Mahboubi M, Tanaka K. Behavioral consequences of selective damage to frontal pole and posterior cingulate cortices. *Proceedings of National Academy of Sciences USA* 112, E3940-9 (2015).
- 3- **Mansouri FA**, Egner T, Buckley MJ. (2017) Monitoring demands for executive control: shared functions between human and nonhuman primates. *Trends in Neurosciences* 40, 5-27.
- 4- **Mansouri FA**, Buckley MJ, Tanaka K. The essential role of primate orbitofrontal cortex in conflict-induced executive control adjustment. *Journal of Neuroscience*, 34, 11016-11031 (2014).
- 5- **Mansouri FA**, Acevedo N, Illipparampil R, Fehring DJ, Fitzgerald PB, Jaberzadeh S. (2017) Interactive effects of music and prefrontal cortex stimulation in modulating response inhibition. *Scientific Reports* 7, 18096.

Proposal Number: 20

Theme: Development and regeneration

Title: Wiring the brain for function

Linda Richards ¹ , Victor Tarabykin ² , Laura Fenlon ¹ , Amanda Wood ³ , Jozef Gecz ⁴

1. *Queensland Brain Institute, University of Queensland, Brisbane, ACT, Australia*
2. *Director Institute of Cell Biology and Neurobiology, Charité – Universitätsmedizin, Berlin, Germany*
3. *Clinical Sciences, Murdoch Children's Research Institute, Melbourne, VIC, Australia*
4. *Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia*

During brain development, the formation of neural connections is regulated by genetic and molecular mechanisms that control the axonal growth trajectory and the cellular environmental guideposts that provide guidance cues to growing axons. Precise connectivity in the brain underpins the brain's ability to function. This symposium includes molecular and anatomical studies in mice and human brain imaging, genetics and cognitive function in people with brain wiring disorders. The techniques used and questions addressed by the speakers are state-of-the-art with respect to the field. This symposium will be of interest to the wider membership of ANS as it combines mechanistic studies in animal models with direct relevance to human developmental brain disorders. There has not been a symposium of a similar topic at ANS in the recent past. The international speaker, Prof. Tarabykin, has not visited Australia before and therefore many of the ANS members will not have heard him speak. He is an excellent molecular and developmental biologist and one of the leaders in the field.

The symposium is chaired by two young MD/PhD scientists and includes gender and regional balance as well as speakers at a variety of career levels. Dr Fenlon is an early career researcher and an outstanding communicator, Dr Wood is a mid-career researcher who recently returned to Australia from the UK (this would provide an opportunity for ANS members to hear about her exciting work for the first time) and Prof. Tarabykin and Gecz are senior superstar scientists.

Speaker 1 (International speaker): Prof. Victor Tarabykin MD, PhD, Professor of Cellular Neurobiology, Director Institute of Cell Biology and Neurobiology, Charité – Universitätsmedizin Berlin, GERMANY.

Email: Victor.Tarabykin@charite.de

Title: Molecular control of cortical wiring

Description: The pyramidal neurons of the mammalian neocortex form two major types of long-range connections—corticocortical and cortico-subcortical. The transcription factors Satb2 and Ctip2 are critical regulators of neuronal cell fate that control interhemispheric versus corticofugal connections respectively. We investigated the axon guidance molecules acting downstream of Satb2 and Ctip2 that establish these connections. We could show that the expression of two Netrin1 receptors- DCC and Unc5C is under direct negative regulation by Satb2 and Ctip2, respectively. Further, we show that the Netrin1–Unc5C/DCC interaction is involved in controlling the interhemispherical projection in a subset of early born, deep layer callosal neurons. However, DCC/Unc5C pathway is not involved in the establishment of callosal projections formed by later born, upper layer neurons. Using conditional mutagenesis we identified Sema7a as a key molecule that controls development of cortico-cortical connections of upper layer neurons. Sema7a does not act as a ligand but as a receptor in this process. It requires interaction with Sema4d for proper navigation of axons of the upper layer neurons.

Relevant Publications:

1. Srivatsa S., Parthasarathy S, Molnar Z., **Tarabykin V.** Sip1 downstream effector ninein controls neocortical axonal growth, ipsilateral branching and microtubule stability. **Neuron**, (2015), 2015 Mar 4;85(5):998-1012. doi: 10.1016/j.neuron.2015.01.018. PMID: 25741725
2. Srivatsa S, Parthasarathy S, Britanova O, Bormuth I, Donahoo AL, Ackerman SL, Richards LJ, **Tarabykin V** Unc5C and DCC act downstream of Ctip2 and Satb2 and contribute to corpus callosum formation. **Nature Commun.** 2014 Apr 17;5:3708. doi: 10.1038/ncomms4708.
3. Seuntjens E, Nityanandam A, Miquelajauregui A, Debruyne J, Stryjewska A, Goebbels S, Nave K, Huylebroeck D., **Tarabykin V.** Sip1 regulates sequential fate decisions by feedback signaling from postmitotic neurons to progenitors. (2009) **Nature Neuroscience** 12(11):1373-80
4. Britanova O, de Juan Romero C, Cheung A, Kwan KY, Schwark M, Gyorgy A, Vogel T, Akopov S, Mitkovski M, Agoston D, Sestan N, Molnár Z, **Tarabykin V.** Satb2 is a postmitotic determinant of upper layer neurons specification in the neocortex (2008) **Neuron** 57(3):378-92.
5. Miquelajauregui A., Van de Putte T., Polyakov A., Nityanandam A., Boppana S., Karabinos A., Higasi Y., Seuntjens E., Huylebroeck D., and **Tarabykin V.** Smad-interacting protein-1 (Sip1/Zfhx1b) acts upstream of Wnt signaling in the mouse hippocampus and controls its formation (2007) **PNAS** 104 (31) 12919-12924

Speaker 2: Dr Laura Fenlon, PhD, The University of Queensland, Queensland Brain Institute

Email: l.fenlon@uq.edu.au

Title: The development and plasticity of interhemispheric connections

Description: The left and right cerebral cortices are initially separated during early development, and ultimately interconnect in order to perform bilaterally coordinated functions. The corpus callosum, the largest fibre tract in the human brain, is primarily responsible for connecting the two cortical hemispheres. In this talk I will discuss recent advances in our understanding of how the corpus callosum develops, including its dependency on electrical activity and the subtle disruptions that may occur in neurodevelopmental disorders such as autism. I will also outline recent work investigating the plasticity of intercortical connections, where axons that cannot form a normal corpus callosum may reroute through alternative paths to ectopically connect the two hemispheres. These findings histologically demonstrate long-range axonal plasticity, and have wide implications for diagnostic and therapeutic applications in many disorders of neurological miswiring. Taken together, this work significantly advances our understanding of cortical connectivity and misconnectivity, as well as the potential for plasticity under pathological conditions.

Relevant Publications:

- 1) Mitew, S., Gobius, I., **Fenlon, L.R.**, McDougall, S.J., Hawkes, D., Xing, Y.L., Bujalka, H., Gundlach, A.L., Richards, L.J., Kilpatrick, T.J., Merson, T.D., & Emery, B. (2018). Pharmacogenetic stimulation of neuronal activity increases myelination in an axon-specific manner. *Nature Communications*. 9(1):306.
- 2) **Fenlon, L.R.**, Suárez, R., & Richards, L.J. (2017). The anatomy, organisation and development of contralateral callosal projections of the mouse somatosensory cortex. *Brain and Neuroscience Advances*. 1: 1-9..
- 3) **Fenlon, L.R.** & Richards, L. J. (2015). Contralateral targeting of the corpus callosum in normal and pathological brain function. *Trends in Neuroscience*. 38(5): 264-272.
- 4) **Fenlon, L.R.**, Liu, S., Gobius, I., Kurniawan, N.D., Murphy, S., Moldrich, R.X., Richards, L.J. (2015). Formation of functional areas in the cerebral cortex is disrupted in a mouse model of autism spectrum disorder. *Neural Development*. 10(10).
- 5) Suárez, R., **Fenlon, L.R.**, Marek, R., Avitan, L., Sah, P., Goodhill, G. J., Richards, L. J. (2014). Balanced Interhemispheric Cortical Activity is Required for Correct Targeting of the Corpus Callosum. *Neuron*. 82(6): 1289-1298. **(Co-first authorship)**

Speaker 3: Associate Professor Amanda Wood, PhD, Principal Research Fellow, Clinical Sciences, Murdoch Children's Research Institute, Melbourne Australia.

Email: amanda.wood@mcri.edu.au

Title: **Cognitive and neural features of developmental callosal disorders**

Description: The corpus callosum plays an important role in mediating information transfer between the cerebral hemisphere that is necessary for many cognitive functions. Disconnection syndromes provided key data on topographic representation of function and highlighted the importance of regional callosal morphology for specific functions. Disorders of cortical development affecting the callosum are also associated with cognitive and behavioural impairments. Data on a group of children with agenesis of the corpus callosum will be presented. Neuropsychological findings indicate that a higher than expected proportion of children with callosal agenesis who present to clinical services experience neuropsychological impairments. The specific pattern of impairments points to opportunities for early support and intervention. The neural basis for these difficulties was explored through quantitative analysis of whole brain diffusion weighted and resting state BOLD MRI scans. A widespread difference in cortical connectivity was observed. These data highlight the critical role of the corpus callosum in normal development of neural pathways that underpin cognitive and behavioural development.

Relevant Publications:

1. Siffredi, V, Anderson, V., McIlroy, A., **Wood, AG**., Leventer, R., Spencer-Smith, M. (2018) A neurobehavioral profile for agenesis of the corpus callosum? Functioning in school-age children *JINS*, 24(5), 445-455
2. Webb, E, Elliot, L., Carlin, D., Wilson, M., Hall, K., Netherton, J., Reed, J., Barrett, TG., Sawlani, V., Clayden, JD., Arlt, W., Krone, N., Peet, AC & **Wood AG** Quantitative MRI brain in congenital adrenal hyperplasia: *in vivo* assessment of the cognitive and structural impact of steroid hormones, *Journal of Clinical Endocrinology and Metabolism* (accepted 16th November 2017) doi: 10.1210/jc.2017-01481
3. Anderson VA., Spencer-Smith, M., **Wood, AG** (2011) Do children's brains recover better? Plasticity, reorganisation and neurobehavioral change after early brain insult, *Brain*, 134, 2197-2221.
4. **Wood AG**, Saling, MM, Jackson, GD, Reutens, DC. (2008) Asymmetry of language activation relates to regional callosal morphology following early cerebral injury. *Epilepsy Behav*, 12, pp. 427-433.
5. Walterfang, M, **Wood, AG** Yung, AR, Reutens, D, Wood, SJ, Chen, J, Stuart, G, Phillips, L, Velakoulis, D, McGorry, PD, Pantelis, C. (2008). Morphology of the Corpus Callosum At Different Stages Of Schizophrenia: A Cross-Sectional Study in First-Episode and Chronic Schizophrenia, *British Journal of Psychiatry*, 192: 429-434

Speaker 4: Prof. Jozef GECZ, PhD, FAA, FAHMS, FFSc(RCPA), NH&MRC Senior Principal Research Fellow, Channel 7 CRF Chair for the Prevention of Childhood Disability, Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide.

Email: jozef.gecz@adelaide.edu.au

Title: Expect unexpected, unbiased genomics of neurodevelopmental disorders.

Description: Systematic, unbiased and as of late next generation, genome-wide surveys of DNA variation transformed our understanding of the genetic origins of a wide spectrum of neurodevelopmental disorders (NDDs). Intellectual disability research and in particular on the human X-chromosome led the field, currently enumerating more than 1100 genes. Epilepsies, now with more than 260 genes; autisms, possibly involving in excess of 1200 genes and cerebral palsies, with at least 40 genes identified so far, extended significantly our understanding of the genetic architecture of early neurodevelopment. Among these NDD genes are a few with notable mutation pleiotropy and considerable variability in clinical expressivity. I will focus part of this talk on the protocadherin 19 gene, PCDH19, which we implicated in an infant onset epilepsy, intellectual disability, autism and other behavioural problems syndrome. Surprisingly, we found this cell adhesion, axon bundling molecule to co-regulate gene expression with at least estrogen receptor alpha (ESR1). PCDH19 NDD disorder is also characterised by the fact that only cellular mosaics are affected while gene 'knockouts' are not. Such disease-driving cellular mosaicism can be due to either random X-inactivation in PCDH19 mutation carrier females or postzygotic somatic mosaicism due to de novo PCDH19 mutation in males. We have now a solid understanding of the underlying brain and cell autonomous drivers of the PCDH19 NDD.

Relevant Publications:

1. Dibbens LM, Tarpey PS, Hynes K, Bayly MA, Scheffer IE, Smith R, Bomar J, Sutton E, Vandeleur L, Shoubbridge C, Edkins S, Turner SJ, Stevens C, O'Meara S, Tofts C, Barthorpe S, Buck G, Cole J, Halliday K, Jones D, Lee R, Madison M, Mironenko T, Varian J, West S, Widaa S, Wray P, Teague J, Dicks E, Butler A, Menzies A, Jenkinson A, Shepherd R, Gusella JF, Afawi Z, Mazarib A, Neufeld MY, Kivity S, Lev D, Lerman-Sagie T, Korczyn AD, Derry CP, Sutherland GR, Friend K, Shaw M, Corbett M, Kim HG, Geschwind DH, Thomas P, Haan E, Ryan S, McKee S, Berkovic SF, Futreal PA, Stratton MR, Mulley JC, Gécz J. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. *Nat Genet.* 40(6):776-81, 2008.
2. Pham DH, Tan CC, Homan CC, Kolc KL, Corbett MA, McAninch D, Fox AH, Thomas PQ, Kumar R, Gecz J. Protocadherin 19 (PCDH19) interacts with paraspeckle protein NONO to co-regulate gene expression with estrogen receptor alpha (ER α). *Hum Mol Genet.* 26(11):2042-2052, 2017.
3. Pederick DT, Richards KL, Piltz SG, Kumar R, Mincheva-Tasheva S, Mandelstam SA, Dale RC, Scheffer IE, Gecz J, Petrou S, Hughes JN, Thomas PQ. Abnormal Cell Sorting Underlies the Unique X-Linked Inheritance of PCDH19 Epilepsy. *Neuron.* 97(1):59-66.e5, 2018.
4. Kolc KL, Sadleir LC, Scheffer IE, Ivancevic A, Roberts R, Pham D, and Gecz J. A systematic review and meta-analysis of 271 PCDH19-variant individuals identifies psychiatric comorbidities, and association of seizure onset and disease severity. *Mol Psych*, in press 2018.
5. Homan CC, Pederson S, To TH, Tan C, Piltz S, Corbett M, Wolvetang E, Thomas PQ, Jolly LA, and Gecz J. PCDH19 regulation of neural progenitor cell differentiation suggests

asynchrony of neurogenesis as a mechanism underpinning PCDH19
Girls Clustering Epilepsy. Neurobiol Dis, under revision.

Proposal Number: 22

Theme: Glia

Title: Microglia: Architects of the brain

Michele Binder ¹ , Manual Graeber ² , Jenna Ziebell ³ , Erica Fletcher ⁴ , Trevor Owens ⁵

1. *Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia*
2. *The University of Sydney Brain and Mind Centre, The University of Sydney, Camperdown, NSW, Australia*
3. *Wicking Dementia Research and Education Centre, University of Tasmania, Hobart, Tasmania, Australia*
4. *Anatomy and Neuroscience, University of Melbourne, Parkville, VIC, Australia*
5. *Department of Neurobiology Research, University of Southern Denmark, Odense, Denmark*

Microglia, a type of immune cell found exclusively within the central nervous system (CNS), initially develop from haematopoietic stem cell precursors in the yolk sac, and colonise all regions of the CNS early in development. Although early studies of microglial functions were predominantly concerned with their role in immune responses under pathological conditions, it is now clear that microglia perform many essential tasks in the non-diseased CNS, including maintenance of homeostasis, as well as having a critical role in synaptic pruning during normal brain development and response to learning. This symposium will discuss recent advances in defining and understanding the role of microglia in brain development and maintenance, focusing on synapse formation and connectivity, axonal integrity and in myelination.

The development of a mature nervous system requires the proliferation and differentiation of a number of cell types, as well as ensuring appropriate communication between these cells. In this symposium, speakers will discuss the role of microglia in synaptic pruning, ensuring the formation of mature neuronal circuits. We will also explore the emerging role of microglia in synaptic connectivity via real-time two-photon imaging in conjunction with more traditional immunohistochemical, protein and RNA analysis. The role of microglia in shaping neural maturation will be highlighted in a presentation exploring the effect of genetic deletion of the fractalkine receptor, revealing a novel function of microglia in regulating post-natal neuronal development within the retina. Finally, our international speaker will discuss his recent work exploring the role of a specific subset of CD11c-positive microglia found within white matter tracts during early postnatal development, which appear to be essential for early oligodendrocyte precursor cell development, and thus ultimately for myelination.

This symposium brings together national and international leaders in the dynamic field of microglial regulation of neural development, providing important insight into an area of research that is relevant to all neuroscientists on a number of levels. Firstly, the role of microglia in regulating normal brain development has clear relevance for understanding the cellular mechanisms by which functional neuronal circuits are established and maintained. Secondly, our expanding knowledge of the role of microglia in normal development provide insight into the mechanisms underlying a wide variety of neurological diseases.

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- **Contact details**

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<http://sydney.edu.au/medicine/people/academics/profiles/manuel.graeber.php>

- ANS member type - Ordinary
- Early Career Researcher/HDR student? - no
- **Title and summary of talk (no more than 200 words)**

Microglia functions beyond inflammation

The term "neuroinflammation" has become highly ambiguous. It was originally meant to describe inflammatory changes in the nervous system context emphasising location, hence "neuro"-inflammation although this was always considered tautological by neuropathologists because classical as well as sterile inflammation can occur in the nervous system like in any other organ system. Accordingly, the term "neuroinflammation" has been used to describe inflammation in multiple sclerosis or infectious conditions. In recent years, however, triggered by neuroimaging results that reveal PET signals of glial activation in all common CNS pathologies, usage of the term has been much widened and it is now effectively synonymous with the traditional neurohistological term, gliosis. Furthermore, using sensitive immunocytochemical methodology or autoradiographic ligand binding, which detect glial activation at the molecular level, a range of additional conditions such as sleep loss, obesity or chronic pain have also been called "neuroinflammatory". At the same time, the important role glial cells play in synaptic plasticity has been overshadowed by the "neuroinflammation" hypothesis.

- **List citations of up to 5 relevant papers published in the past 5 years.**

1: Svahn AJ, Becker TS, Graeber MB. Emergent properties of microglia. *Brain Pathol.* 2014 Nov;24(6):665-70. doi: 10.1111/bpa.12195. PubMed PMID: 25345896.

2: Graeber MB. Neuroinflammation: no rose by any other name. *Brain Pathol.* 2014 Nov;24(6):620-2. doi: 10.1111/bpa.12192. PubMed PMID: 25345892.

3: Filiou MD, Arefin AS, Moscato P, Graeber MB. 'Neuroinflammation' differs categorically from inflammation: transcriptomes of Alzheimer's disease, Parkinson's disease, schizophrenia and inflammatory diseases compared. *Neurogenetics.* 2014 Aug;15(3):201-12. doi: 10.1007/s10048-014-0409-x. Epub 2014 Jun 15. PubMed PMID: 24928144.

4: Filiou MD, Banati RB, Graeber MB. The 18-kDa Translocator Protein as a CNS Drug Target: Finding Our Way Through the Neuroinflammation Fog. *CNS Neurol Disord Drug Targets.* 2017;16(9):990-999. doi: 10.2174/1871527316666171004125107. PubMed PMID: 28982340.

- **Name and Affiliation**

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- **ANS member type**

Ordinary

- **Early Career Researcher/HDR student?**

No

- **Title and summary of talk (no more than 200 words)**

How do microglia-synapse dynamics change with ageing and Alzheimer's disease?

Historically, microglia are referred to as the immune cells of the central nervous system, rapidly changing morphology and function when homeostasis is breached. However, evidence is mounting that microglia have many more roles than currently described, including at the synapse. Synapses are the connection of a pre-synaptic neuronal membrane to a post-synaptic neuronal terminal, with support from surrounding glia. As part of "normal" development, synaptic remodelling occurs. This remodelling leads to larger circuit reorganisation, changes in synaptic connectivity, and ultimately, brain plasticity. Throughout the normal life-time experience produces multiple, dissociable changes in the brain, including increases in dendritic length, changes in spine density, synapse formation, glial activity, and altered metabolic activity. These synaptic dynamics have been intensely studied, however, synaptic connectivity in relation to microglia has received little attention. This talk will explore the emerging role of microglia in synaptic connectivity via real-time two-photon imaging in conjunction with more traditional immunohistochemical, protein and RNA analysis. By exploring the dynamic microglia:synapse relationship in the adult we will be able to interpret altered microglia:synapse connectivity in experimental model of Alzheimer's disease.

- **List citations of up to 5 relevant papers published in the past 5 years.**

Taylor SE, Morganti-Kossmann MC, Lifshitz J, Ziebell JM (2014). Rod Microglia: A morphological definition. PLoS One, 9(5), Article e97096.

Ziebell JM, Adelson PD, Lifshitz J (2015). Microglia: dismantling and rebuilding circuits after acute neurological injury. Metabolic Brain Disease, 30(2), 393-400.

Rowe, RK, Ziebell, JM, Harrison, JL, Law, LM, Adelson, PD, Lifshitz, J. (2016). Aging with traumatic brain injury: Effects of age at injury on behavioural outcome following diffuse brain injury in rats. Developmental neuroscience, 38 (3), 195-205.

Ziebell JM, Rowe RK, Muccigrosso MM, Reddaway JT, Adelson PD, Godbout JP, Lifshitz J (2017). Aging with a traumatic brain injury: could behavioral morbidities and

endocrine symptoms be influenced by microglial priming? *Brain, Behavior, and Immunity*, 59, 1-7.

Ziebell, JM, Ray-Jones, H, Lifshitz, J (2017). Nogo presence is inversely associated with shifts in cortical microglial morphology following experimental diffuse brain injury. *Neuroscience*, 359, 209-223.

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ANS member type: Full member

Early Career Researcher/HDR student? No

Summary***Microglial regulation of retinal integrity***

Microglia are the resident immune cells of the CNS and their response to infection, injury and disease has been well documented. More recently, microglia have been shown to play a role in normal CNS development, with the fractalkine-Cx3cr1 signaling pathway of particular importance. Our work has characterized the importance of interactions between the light sensitive photoreceptors within the retina and microglia. Notably, our work shows that genetic removal of Cx3cr1 (*Cx3cr1^{GFP/GFP}*), is associated with loss of cone photoreceptor function and integrity from an early age. Detailed evaluation of the genesis of this deficit revealed a novel role for microglia in regulating post-natal neuronal development within the retina. Specifically, loss of the fractalkine-Cx3cr1 signalling pathway was associated with changes in the cell's cilium, an important structure in the transport of proteins from one part of the cell to another. Our work highlights a role for microglia in shaping neural maturation.

References:

1. Jobling AI, Waugh M, Vessey KA, Phipps JA, Trogrlic L, Greferath U, Mills SA, Tan ZL, Ward MM, Fletcher EL The role of microglial Cx3cr1 pathway in the postnatal maturation of retinal photoreceptors. J Neuroscience (revised manuscript currently under revision).
2. Phipps JA, Vessey KA, Brandli A, Nag N, Tran MX, Jobling AI, Fletcher EL (2018) The role of angiotensin II/AT1 receptor signalling in regulating retinal microglial activation. Invest Ophthalmol Vis Sci 59:487-498.
3. Vessey KA, Gu BJ, Jobling AI, Phipps JA, Greferath U, Tran MX, Dixon MA, Baird PN, Guymer RH, Wiley JS Fletcher EL (2017) Loss of function of P2X7 receptor scavenger activity in aging mice: a novel model for investigating the early pathogenesis of age related macular degeneration. Am J Pathol 187:1670-1685
4. Tochitsky I, Helft Z, Meseguer V, Fletcher RB, Vessey KA, Telias M, Denlinger B, Malis J, Fletcher EL, Kramer RH (2016) How Azobenzene photoswitches restore visual responses to the blind retina. Neuron 92:100-113.
5. Greferath U, Guymer RH, Vessey KA, Brassington K, Fletcher EL (2016) Correlation of histological features with in vivo imaging of reticular pseudodrusen. Ophthalmology 123:1320-1331

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- **ANS member type**

Non-member

- **Early Career Researcher/HDR student?**

No

- **Title and summary of talk (no more than 200 words)**

Microglia in the developing and adult brain

Microglia are tissue macrophages of the central nervous system (CNS). Their primary functions are as part of innate CNS immunity, to clear debris and damaged cells, and to signal for immune response in the CNS. Microglia play a major role in homeostatic regulation in the CNS, including by production of Type I interferons (IFN), as well as other cytokines and chemokines. Cytokine secretion profiles and microglial phenotypes are themselves influenced by developmental and degenerative cues, including bidirectional interaction with astrocytes, and their recent phagocytic experience. They therefore interpret local needs and conditions for appropriate immune response.

We apply experimental ligands to drive endogenous anti-inflammatory responses in mouse CNS. Induction of Type I IFN by myeloid cells, including microglia, is particularly protective against EAE. A CD11c⁺ microglial subset are very effective inducers of Insulin-like Growth Factor-1 (IGF1). This subset is over-represented in neonatal CNS, where transcriptomic analysis suggests a role in neuronal development and myelination. Targeted deletion of IGF1 revealed a critical role in primary myelination. Transfer of neonatal CD11c⁺ microglia ameliorated EAE in adult mice. Factors that mediate this protection are being identified, and we are examining whether macrophages from other tissues are also protective.

- **List citations of up to 5 relevant papers published in the past 5 years.**

Wlodarczyk A, Holtman IR, Krueger M, Yogev N, Bruttger J, Khorooshi, R, Benmamar-Badel, A, de Boer-Bergsma JJ, Martin, NA, Karram K, Kramer, I, Boddeke EWGM, Waisman A,

- Eggen BJL and Owens T. 2017. A novel microglial subset plays a key role in myelinogenesis in developing brain. *EMBO J.* 36: 3292-3308.
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- Khorrooshi, R., Mørch, M, Berg, CT, Holm, TH, Dieu, RT, Dræby, D, Issazadeh-Navikas, S, Weiss, S, Lienenklaus, S and Owens, T. 2015. Induction of endogenous Type I interferon within the central nervous system plays a protective role in experimental autoimmune encephalomyelitis. *Acta Neuropathologica*, 130:107-118.
- Wlodarczyk, A., Løbner, M., Cédile, O., & Owens, T. 2014. Comparison of microglia and infiltrating CD11c+ cells as antigen presenting cells for T cell proliferation and cytokine response. *J. Neuroinflammation* 11:57-65.
- Khorrooshi, R., A. Wlodarczyk, N. Asgari, & T. Owens. 2013. Neuromyelitis optica-like pathology is dependent on type I interferon response. *Exp Neurol* 247: 744-747.

Proposal Number: 34

Theme: Other

Title: Dendritic spines: From Morphology to Function

Merja Joensuu ^{1 2}, Fred A Meunier ¹, Valentin Nägerl ³, Tong Wang ¹, Ramon Martinez-Marmol ¹, Pirta Hotulainen ²

1. *Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, St Lucia, QLD, Australia*
2. *Minerva Foundation Institute for Medical Research, Helsinki, Uusimaa, Finland*
3. *Institut Interdisciplinaire de NeuroSciences (IINS), Université de Bordeaux, Bordeaux, France*

Dendritic spines are the major targets of synapses in the brain. The dendritic density and morphology is involved in neural plasticity (e.g. long term potentiation, LTP), which is implicated in cognitive functions such as learning and memory. Dendritic spines are highly dynamic structures, and their morphology and stabilization are influenced by synaptic activity. This extrinsic regulation of spine morphogenesis underlies experience-dependent brain development and information storage within the brain circuitry. This symposium will present the latest development on the role of dendritic spines in information processing and plasticity of brain circuits are symptomatic in several neuropathological disorders such as autism spectrum disorder (ASD), schizophrenia and age-related neurodegenerative diseases such as Alzheimer's Disease.

Speakers

Valentin Nägerl is a full professor of neuroscience and bio-imaging at the University of Bordeaux and heads a research group at the University of Bordeaux, France. He has worked with the Nobel laureate Stefan Hell, and currently his team develops and applies super-resolution microscopy techniques to discover and unravel the morpho-functional mechanisms of neural plasticity in the mammalian brain. He will present his recent work on establishing chronic *in vivo* super-resolution imaging of dendritic spines in the hippocampus using 2P-STED microscope to reach this deeply embedded brain structure. He will also discuss the combination of 3D-STED microscopy with fluorescent labeling of the extracellular fluid (ECF) to develop super-resolution shadow imaging (SUSHI) of brain ECF in living organotypic brain slices.

The symposium will have two Early Career Scientists from the University of Queensland (QBI) presenting their work: Dr Iris Wang and Dr Ramón Martínez-Mármol. Dr Wang will discuss how LTP induces transient extra-synaptic exocytosis of N-methyl-D-aspartate (NMDA) receptors in mature hippocampal neurons using super-resolution imaging. Dr Martínez-Mármol will talk about the nanoscopic compartmentalization of Tau and Fyn proteins in neurons using single particle tracking photo-activated localization microscopy (sptPALM), and how their sub-diffractional distribution can modulate their function in health and during Alzheimer's Disease.

Adjunct Professor Pirta Hotulainen is a principal investigator in the Minerva Foundation Institute for Medical Research, Finland. She is one of the leading actin and dendritic spine specialists, and her work has described the role of actin cytoskeleton regulators in spine morphogenesis, elongation and development. She will talk about regulation of the actin cytoskeleton and changes in dendritic spine morphology contributing to functional changes in synapses and behavioral changes. She will also discuss how defective actin regulation in dendritic spines of contributes the brain function of ASD patients.

The goal of this symposium is to unveil the latest developments in this exciting field allowing the audience gain better understand of mechanisms that control dendritic spine morphology and insight into control of dendritic spine organisation and functions in health and disease, with a special emphasis on the latest super-resolution techniques that enables the visualization subdiffractional structures in real time and in their native environment. Understanding the structure-function relationship of synapses has broad implications not only for understanding the etiology of many diseases but also generally for defining the cellular basis of nervous system function and disorders.

Super-resolution microscopy for neuroscience

U. Valentin Nägerl

*Interdisciplinary Institute for Neuroscience,
University of Bordeaux / CNRS, France***ANS member type:** Will become ordinary member in the case of successful symposium proposal**Early career scientist:** No**Summary:**

The advent of super-resolution microscopy has created unprecedented opportunities to study the mammalian central nervous system, which is dominated by anatomical structures whose nanoscale dimensions critically influence their biophysical properties. I will present our recent methodological advances 1) to analyze dendritic spines in the hippocampus *in vivo* and 2) to visualize the extracellular space of the brain.

We established chronic *in vivo* super-resolution imaging of dendritic spines in the hippocampus, based on an upright 2P-STED microscope equipped with a long working distance objective and ‘hippocampal window’ to reach this deeply embedded structure. We measured spine density on pyramidal neurons in the CA1 area and determined spine turnover by repetitive imaging. Spine density was two times higher than reported by conventional 2P microscopy, and around 40% of all spines turned over within 4 days, indicating a high level of structural remodeling.

We combined 3D-STED microscopy and fluorescent labeling of the extracellular fluid to develop super-resolution shadow imaging (SUSHI) of brain ECS in living brain slices. SUSHI enables quantitative analysis of ECS structure and produces sharp negative images of all cellular structures, providing an unbiased view of unlabeled brain cells with respect to their complete anatomical context in a live tissue setting.

5 relevant papers from last 5 years

1. Pfeiffer T, Poll S, Bancelin S, Inavalli VVGK, Keppler K, Fuhrmann M, **Nägerl UV**. Chronic STED imaging reveals high turnover of dendritic spines in the hippocampus *in vivo* (*in revision at eLife*)
2. Tønnesen J, Inavalli VVGK, **Nägerl UV**. (2018) Super-resolution imaging of the extracellular space in living brain tissue. *Cell*. 172:1108-1121
3. Chéreau R, Saraceno GE, Angibaud J, Cattaert D, **Nägerl UV**. (2017) Super-resolution imaging reveals activity-dependent plasticity of axon morphology linked to changes in action potential conduction velocity. *Proc Natl Acad Sci U S A*. 114:1401-1406
4. Pfeiffer T, Avignone E, **Nägerl UV**. (2016) Induction of hippocampal long-term potentiation increases the morphological dynamics of microglial processes and prolongs their contacts with dendritic spines. *Sci Rep*. 6:32422
5. Tønnesen J, Katona G, Rózsa B, **Nägerl UV**. Spine neck plasticity regulates compartmentalization of synapses. *Nat Neurosci*. 17:678-85

Long-term potentiation of synaptic transmission induces the transient extra-synaptic exocytosis of GluN2A containing N-methyl-D-aspartate (NMDA) receptors in mature hippocampal neurons

Tong Wang*, Xiaojun Yu, Hillary Yong, Se-Eun Jang, He Huang, Nela Durisic, Bret Collins, and Victor Anggono

** Clem Jones Centre for Ageing Dementia Research,
Queensland Brain Institute, The University of Queensland, Australia*

ANS member type: Ordinary member

Early career scientist: Yes

Summary:

The synaptic plasticity initiated by NMDA glutamate receptors is the primary mechanism underlying learning and memory formation. GluN2A containing NMDA receptors are the dominant form in mature neurons and are required for the induction of long term potentiation (LTP). However, the surface level of NMDA-GluN2A receptors in the post-synaptic neurons is generally believed to be stable and unaffected by the induction of LTP. Here, by detecting the surface GluN2A-NMDA receptor levels using both biochemical assays and immuno-fluorescent super-resolution microscopy, we uncovered a group of extra-synaptic GluN2A-NMDA receptors following glycine induced LTP. Then by associating these highly-mobile GluN2A-NMDAR single-molecules with the exocytosis events, we further revealed that these extra-synaptic receptors are derived from the transient exocytosis induced by glycine induced LTP, and are gated by the opening of NMDA channels. These results provide the first direct evidence showing the surface GluN2A-receptors are highly fluctuated, and synaptic potentiation induces the exocytosis of a specialized vesicle pool, which releases the GluN2A-NMDA receptors onto the extra-synaptic regions and causes an transient increase of these surface receptors in postsynaptic neurons.

5 relevant papers from last 5 years

1. **Wang T**, Martin S, Nguyen TH, Harper CB, Gormal RS, Martinez-Marmol R, Karunanithi S, Coulson EJ, Glass NR, Cooper-White JJ, van Swinderen B, Meunier FA (2016) Flux of signalling endosomes undergoing axonal retrograde transport is encoded by presynaptic activity and TrkB. *Nature Communications*. 7: 12976
2. Harper CB, Papadopoulos A, Martin S, Matthews DR, Morgan GP, Nguyen TH, **Wang T**, Nair D, Choquet D, Meunier FA (2016) Botulinum neurotoxin type-A enters a non-recycling pool of synaptic vesicles. *Scientific Reports*. 6: 19654
3. Narayana VK, Tomatis VM, **Wang T**, Kvaskoff D, Meunier FA (2015) Profiling of free fatty acids using stable isotope tagging uncovers a role for saturated fatty acids in neuroexocytosis. *Cell Chemical Biology*. 22: 1552-61
4. **Wang T**, Martin S, Papadopoulos A, Harper CB, Mavlyutov TA, Niranjana D, Glass NR, Cooper-White JJ, Sibarita JB, Choquet D, Davletov B, Meunier FA (2015) Control of autophagosome axonal retrograde flux by presynaptic activity unveiled using botulinum neurotoxin type A. *Journal of Neuroscience*. 35: 6179-94
5. Xu XH, Deng CY, Liu Y, He M, Peng J, **Wang T**, Yuan L, Zheng ZS, Blackshear PJ, Luo ZG (2014) MARCKS regulates membrane targeting of Rab10 vesicles to promote axon development. *Cell Research*. 24: 576-94

Fyn and Tau under the nanoscope

Ramón Martínez-Mármol, Pranesh Padmanabhan, Jürgen Götz, Frederic A. Meunier

*Clem Jones Centre for Ageing Dementia Research,
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ANS member type: Yes

Early career scientist: Yes

Summary:

Deposits of amyloid- β (A β) and hyperphosphorylated Tau protein constitute the histological hallmark lesions of Alzheimer's disease (AD). The dendritic spines have been proposed to be one of the cellular structures involved in the initiation and progression of AD. The Src kinase Fyn has a critical role mediating the A β dendritic toxicity. Fyn activity is affected by oligomeric A β and can modulate Tau local translation into the cell body of neurons. In addition, Tau is required for the efficient targeting of Fyn to the dendritic compartment, suggesting a mutual effect of these two proteins of crucial importance for the development of AD. However, despite intense scrutiny, their normal functions are still not well understood and the underlying mechanisms that govern their actions remain obscure.

We have used sptPALM (single particle tracking photo-activated localization microscopy) to uncover (i) the nanoscopic level of compartmentalization of Tau and Fyn proteins in neurons and (ii) how their sub-diffractional distribution can modulate their function in health and during AD.

We have discovered that Tau and Fyn nanoscale organisation differs amongst neuronal compartments and is affected by various physiological and pathological conditions. Understanding the molecular mechanisms involved in controlling the nanoscale dynamic organisation of these two crucial proteins during AD could open new strategies to fight against this devastating neurological disorder.

5 relevant papers from last 5 years

1. Polanco JC, Li C, Bodea LG, **Martínez-Mármol R**, Meunier FA, Götz J. Amyloid- β and tau complexity - towards improved biomarkers and targeted therapies. *Nat Rev Neurol*. 14: 22-39 *Invited review*.
2. #Joensuu M, #**Martínez-Mármol R**, Padmanabhan P, Glass NR, Durisic N, Pelekanos M, Mollazade M, Balistreri G, Amor R, Cooper-White JJ, Goodhill GJ, Meunier FA. (2017) Visualizing endocytic recycling and trafficking in live neurons by subdiffractional tracking of internalized molecules. *Nat Protoc*. 12: 2590-2622 # equal contribution
3. **Martínez-Mármol R**, Styrzewska K, Pérez-Verdaguer M, Vallejo-Gracia A, Comes N, Sorkin A, Felipe A. (2017) Ubiquitination mediates Kv1.3 endocytosis as a mechanism for protein kinase C-dependent modulation. *Sci Rep*. 10: 42395
4. #**Martínez-Mármol R**, #Barneda-Zahonero B, Soto D, Andrés RM, Coccia E, Gasull X, Planells-Ferrer L, Moubarak RS, Soriano E, Comella JX. (2016) FAIM-L regulation of XIAP degradation modulates synaptic long-term depression and axon degeneration. *Sci Rep*. 6: 35775 # equal contribution
5. **Martínez-Mármol R**, Comes N, Styrzewska K, Pérez-Verdaguer M, Vicente R, Pujadas L, Soriano E, Sorkin A, Felipe A. (2016) Unconventional EGF-induced ERK1/2-mediated Kv1.3 endocytosis. *Cell Mol Life Sci*. 73: 1515-28

Actin in dendritic spines: connecting dynamics to function

Pirta Hotulainen

*Minerva Foundation Institute for Medical Research,
Helsinki, Finland*

ANS member type: Will become ordinary member in the case of successful symposium proposal

Early career scientist: No

Summary:

Dendritic spines are small protrusions from neuronal dendrites where the postsynaptic components of most excitatory synapses reside. Precise control of dendritic spine morphology and density is critical for normal brain function. Accordingly, aberrant spine morphology is linked to many neurological diseases. The actin cytoskeleton is a structural element underlying the proper morphology of dendritic spines. Consequently, defects in the regulation of the actin cytoskeleton in neurons have been implicated in neurological diseases. In my talk, I will discuss how regulation of actin cytoskeleton and changes in dendritic spine morphology will contribute to functional changes in synapses and changes in behavior. I will also discuss how defective actin regulation in dendritic spines may contribute to differently functioning brain of patients having autism spectrum disorder.

5 relevant papers from last 5 years

1. Saarikangas, J., Kourdougli, N., Senju, Y., Chazal, G., Segerstråle M., Kuurne, J., Minkeviciene, R., Mattila, P.K., Garrett, L., Höltér, S.M., Becker, L., Racz, I., Hans, W., Klopstock, T., Wurst, W., Zimmer, A., Fuchs, H., Gailus-Durner, V., Hrabě de Angelis, M., von Ossowski, L., Taira, T., Lappalainen, P., Rivera, C. and **Hotulainen, P.** (2015) MIM-Induced Membrane Bending Promotes Dendritic Spine Initiation. *Dev. Cell.* 33: 644-659
2. Bertling, E., Englund, J., Minkeviciene, R., Koskinen, M., Segerstråle, M., Castren, E., Taira, T. and **Hotulainen, P.** (2016) Actin Tyrosine-53-Phosphorylation in Neuronal Maturation and Synaptic Plasticity. *J. Neuroscience.* 36: 5299-5313
3. Koskinen, M., Bertling E., Hotulainen, R., Tanhuanpää, K. and **Hotulainen, P.** (2014) Myosin IIb controls actin dynamics underlying the dendritic spine maturation. *Mol. Cell. Neurosci.* 61C: 6-64
4. Joensuu M, Lanoue V, and **Hotulainen P.** (2017) Dendritic spine actin cytoskeleton in autism spectrum disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* 84: 362-381
5. Hlushchenko I, Koskinen M, **Hotulainen P.** (2016) Dendritic spine actin dynamics in neuronal maturation and synaptic plasticity. *Cytoskeleton* 73: 435-41

Proposal Number: 9

Theme: Clinical disorders and injury of the nervous system

Title: Roads less travelled: recent ideas on the cause of age-related dementia (Alzheimers disease)

Michael Lardelli¹, Estela Area-Gomez², Jonathan Stone³, Robert Richards¹

1. *University of Adelaide, Adelaide, SOUTH AUSTRALIA, Australia*
2. *Department of Neurology, Columbia University Medical Center, New York, NY, USA*
3. *Department of Physiology, University of Sydney, Sydney, NSW, Australia*

Over 100,000 original research papers have addressed the subject of Alzheimer's disease (AD) but we still have no clear idea what causes this age-related dementia. Despite recent admissions from leaders in this research field that the pattern of accumulation of the supposed pathogenic agent, the amyloid beta (Abeta) peptide, is inconsistent with the progression of the late-onset form of the disease, as well as the failure of Abeta-based therapeutic strategies (drugs), and a host of other inconsistent data, the idea that Abeta accumulation is the cause of the disease still holds sway over the majority of researchers. The ageing of our population means that interest in age-related dementia is increasing and young researchers are being encouraged to devote themselves to this field. But their introduction to AD research is most likely through an Abeta-focussed research group or an Abeta-focussed literature review from one of the established leaders in the field and it may take some time before they become aware of the heated internal debate over the validity of the Amyloid Cascade Hypothesis and of the data that support alternative views of this disease. This proposal seeks to redress the imbalance and expose young ANS members to a wider diversity of views on age-related dementia. The internationally competitive strength of Australia's AD research enterprise means that excellent domestic speakers are available, but we have also invited a young up-and-coming international speaker from Columbia University, Dr Estela Area-Gomez, currently an Assistant Professor in the Department of Neurology at Columbia Medical Center in New York. Estela's recent research suggests that it may be the "C99" fragment of the APP protein, (rather than its Abeta fragment), that is critical to development of the disease. (Indeed, this may be more consistent with what we know of mutations in APP that cause the early onset form of AD.) Dr Michael Lardelli of the University of Adelaide has constructed the world's first zebrafish models of familial AD mutations and has evidence that these accelerate the ageing of the brain towards a transcriptional "inversion" event that may represent the zebrafish equivalent of AD. Prof Jonathan Stone of the University of Sydney will describe how the ageing of the body's vasculature allows the pulse to destroy the ageing brain, while Prof Robert Richards of the University of Adelaide will present a case for the importance of inflammation, not only in driving the cell death that characterises later stages of many neurodegenerative diseases including AD, but also as a proximal cause of disease in expanded repeat neurodegenerative diseases. The presentations will reflect on less appreciated, but very important, data regarding age-related dementia and suggest productive ways forward for exploration of Alzheimer's disease.

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ANS member type

International invited speaker – not a member

Early Career Researcher/HDR student?

Assistant Professor (currently striving for tenure)

Title and summary of talk (no more than 200 words)

Old players in a new game: A role for C99 in early stages of AD

Alterations in the maintenance of a membrane's lipid composition can result in cellular dysfunction and disease. In order to maintain lipid homeostasis, the cell has evolved interconnected enzymatic reactions that regulate lipid pathways in specific areas of the cell, so that they can be easily co-regulated. One such cellular area is located in a subregion of the endoplasmic reticulum (ER) in apposition to mitochondria, called MAM (mitochondria-associated ER membranes). MAMs are involved in many metabolic functions, including the regulation of lipid metabolism. Therefore, alteration of MAM results in the loss of lipid homeostasis, changes in the composition of membranes, and thus, cellular dysfunction.

We and others have shown that γ -secretase activity is enriched in MAM, and that MAM function is upregulated in AD. Our recent data shows that in cellular and animal models of AD and cells from AD patients, the C-terminal fragment of the amyloid precursor protein (APP-C99) accumulates above normal levels in MAM, resulting in the deregulation of lipid homeostasis and the membrane's lipid composition.

Taken together, our data shows that these alterations of MAM-localized functions can help explain some of the early metabolic alterations seen in AD, including lipid deregulation and mitochondrial dysfunction.

List citations of up to 5 relevant papers published in the past 5 years.

Area-Gomez E, de Groof AJC, Boldogh I, Bird TD, Gibson GE, Koehler CM, Yu WH, Duff KE, Yaffe MP, Pon LA, Schon EA (2009). **Presenilins are enriched in endoplasmic reticulum membranes associated with mitochondria.** *Am. J. Pathol.* 175, 1810-1816. PMID: 1983406.

Area-Gomez E, Lara Castillo MdC, Tambini MD, de Groof AJC, Madra M, Ikenouchi J, Umeda M, Bird TD, Sturley SL, Schon EA (2012). **Upregulated function of mitochondria-associated ER membranes in Alzheimer disease.** *EMBO J.* 31, 4106-4123. PMID: 22892566

Guardia-Laguarta C, **Area-Gomez E.**, Rub C., Liu Y., Magrane J., Becker D., Voos W., Schon EA., Przedborski S. (2014). **α -Synuclein is localized to mitochondria-associated ER membranes.** *J Neurosci.* 2014 Jan 1;34(1):249-59. PMID: 24381286

Pera, M., Larrea. D., Guardia-Laguarta C., Montesinos J., Velasco K. R, Agrawal R. R. Xu Y., Chan R. B., Di Paolo G., Mehler M.F., Perumal G.S., Macaluso F.P., Freyberg Z.Z., Acin-Perez R., Enriquez J.A., Schon E.A., **Area-Gomez, E.A.** **Increased localization of APP-C99 in mitochondria-associated ER membranes causes mitochondrial dysfunction in Alzheimer disease** (2017). *EMBO J.* Nov 15;36(22):3356-3371. PMID: 29018038

Area-Gomez, E; deGroof, Ad., Bonilla, E., Montesinos, J., Tanji, K., Boldogh, I., Pon, L., Schon, E.A. **A key role for MAM in mediating mitochondrial dysfunction in Alzheimer disease.** (2018) *Cell Death and Disease*, 9. 335 (2018). Doi: 10.1038/s41419-017-0215-0

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ANS member type

Ordinary member

Early Career Researcher/HDR student?

No

Title and summary of talk (no more than 200 words)

Zebrafish “knock-in” models of familial Alzheimer’s disease mutation show accelerated aging, transcriptional “inversion” and an age-dependent inability to respond to hypoxia

The zebrafish possesses a number of characteristics advantageous for analysis of human disease mutations. It is a vertebrate, it has an established genome editing technology, and its large family sizes and dense stocking rates facilitate reduction of genetic and environmental noise in ‘omics analyses. We exploited these advantages to make transcriptomic analyses of “knock-in” of familial Alzheimer’s-like mutations. Our zebrafish mutants are similar to the knock-in mouse mutants that were created two decades ago but were never analysed using ‘omics approaches. Despite the lack of an apparent neurodegenerative pathology in our models (similar to what was seen for the knock-in mouse models) we found evidence that the mutations are accelerating the aging of the brain and that the transcriptional changes seen “invert” when the mutant brains become old. We also found that transcriptional responses to hypoxia invert in aged mutant fish and in extremely aged wild type fish. Our data are consistent

with Alzheimer's disease being an inevitable consequence of aging (explaining why age is the greatest risk factor for this disease) and suggest the possibility that the disease is a distinct molecular brain state that precedes overt histological neurodegeneration.

List citations of up to 5 relevant papers published in the past 5 years.

Nhi Hin, Morgan Newman, Jan Kaslin, Alon M. Douek, Amanda Lumsden, Xin-Fu Zhou, Noralyn B. Mañucat-Tan, Alastair Ludington, David L. Adelson, Stephen Pederson, **Michael Lardelli**. (submitted) **Accelerated brain aging towards transcriptional inversion in a zebrafish model of familial Alzheimer's disease.**

bioRxiv 262162; doi: <https://doi.org/10.1101/262162>

Jayne, T., Newman, M., Verdile, G., Sutherland, G., Münch, G., Musgrave, I., Moussavi Nik, S.H. and **Lardelli, M.** (2016) **Evidence for and against a pathogenic role of reduced γ -secretase activity in familial Alzheimer's disease.**

Journal of Alzheimer's Disease 52: 781–799.

Ebrahimie, E., Moussavi Nik, S.H., Newman, M., Van Der Hoek, M. and **Lardelli, M.** (2016) **The zebrafish equivalent of Alzheimer's disease-associated PRESENILIN isoform PS2V regulates inflammatory and other responses to hypoxic stress.**

Journal of Alzheimer's Disease 52: 581–608.

Moussavi Nik, S.H., Newman, M., Wilson, L., Ebrahimie, E., Wells, S., Musgrave, I., Verdile, G., Martins, R.N. and **Lardelli, M.** (2015) **Alzheimer's disease-related peptide PS2V plays ancient, conserved roles in suppression of the unfolded protein response under hypoxia and stimulation of γ -secretase activity.**

Human Molecular Genetics 24:3662-78.

Newman, M., Wilson, L., Verdile, G., Lim, A., Khan, I., Moussavi Nik, S.H., Pursglove, S., Chapman, G., Martins, R.N. and **Lardelli, M.** (2014) **Differential, dominant activation and inhibition of Notch signalling and APP cleavage by truncations of PSEN1 in human disease.**

Human Molecular Genetics 23: 602-17.

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ANS member type

Is, or will become, an ordinary member before the symposium

Early Career Researcher/HDR student?

No

Title and summary of talk (no more than 200 words)

The ageing pulse destroys the ageing brain: age-related dementia is a small-vessel vascular dementia

The cause of age-related dementia has proved elusive. Competing ideas include proteinopathies (of A β , tau), prion-like infections, inflammation and various ideas of vascular dysfunction. By including understanding of the ageing pulse (pulse pressure increases as the great arteries harden), and of the normal function of A β , we have been able to bring bodies of data that seem to conflict, or at least be unrelated, into a simple concept: The ageing pulse destroys the ageing brain. The pulse becomes destructive with age because pulse pressure increases with age; and the brain is vulnerable (the kidney too) because its circulation is low resistance, to meet the brain's high metabolic requirements. The result is the insidious onset, relentless, age-related dementia long known as Alzheimer's disease.

The implications of the idea are both sombre (*if I am 70 then if my heart stops suddenly I will die suddenly; if I keep going I will die slowly as my pulse beats my brain into mush*). And full of therapeutic possibilities – anything that protects one's cardiovascular system (*controlling blood pressure and cholesterol,*

preventing atherosclerosis, exercise, weight control, and more) should delay the dementia. Indeed there is already much literature showing this broad protective effect. This 'dementia is fate' idea may be less welcome than a curative pill; but it may be the reality from which effective prevention and treatment must be built.

List citations of up to 5 relevant papers published in the past 5 years.

Kim, B., A. Brandli, J. Mitrofanis, **J. Stone**, S. Purushothuman and J. DM. (2017). **Remote tissue conditioning – an emerging approach for inducing body-wide protection against diseases of ageing.**
Ageing Research Reviews Accepted 18/5/17.

Stone, J., D. Johnstone, J. Mitrofanis and M. O'Rourke (2015). The mechanical cause of age-related dementia: the brain is destroyed by the pulse.
J Alz Dis 44 (355-373).

Stone, J. (2015). A tale of two organ's - Ockham's Razor.
Ockham's Razor. R. Williams. Australian Broadcasting Commission.

Purushothuman, S. and **J. Stone** (2015). **The reaction of cerebral cortex to a nearby lesion: damage, survival, self-protection.**
Brain Res 1601: 52-63.

Purushothuman, S., D. M. Johnstone, C. Nandasena, J. Eersel, L. M. Ittner, J. Mitrofanis and **J. Stone** (2015). **Near infrared light mitigates cerebellar pathology in transgenic mouse models of dementia.**
Neurosci Lett 591: 155-159.

Name and Affiliation

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ANS member type

Will become an ordinary member before the symposium

Early Career Researcher/HDR student?

No

Title and summary of talk (no more than 200 words)

'Non-self' Mutation: Double-stranded RNA elicits antiviral cell death response in a *Drosophila* model of expanded CAG repeat neurodegenerative diseases

Inflammation is activated prior to symptoms in neurodegenerative diseases, providing a plausible pathogenic mechanism for cell death. Indeed genetic and pharmacological ablation studies in animal models of several neurodegenerative diseases demonstrate that inflammation is required for pathology. However, while there is growing evidence that inflammation-mediated cell death may be the common mechanism underlying neurodegenerative diseases, including those due to dominantly inherited expanded repeats, the proximal causal agent is unknown. Expanded CAG.CUG repeat double stranded RNA causes inflammation-mediated cell death when expressed in *Drosophila*. Repeat dsRNA is recognised by *Dicer2* as a foreign or 'non-self' molecule triggering both antiviral RNA and RNAi pathways. Neither of the RNAi pathway cofactors *R2D2* nor *loquacious* are necessary, indicating antiviral activation. RNA modification enables avoidance of recognition as 'non-self' by the innate inflammatory surveillance system. Human

ADAR1 edits RNA conferring 'self' status and when co-expressed with expanded CAG.CUG dsRNA in *Drosophila* the toxicity is lost. Cricket Paralysis Virus protein CrPV-1A is a known antagonist of *Argonaute2* in *Drosophila* antiviral defence. CrPV-1A co-expression also rescues pathogenesis, confirming anti-viral-RNA response. Repeat expansion mutation therefore confers 'non-self' recognition of endogenous RNA, thereby providing a proximal, autoinflammatory trigger for expanded repeat neurodegenerative diseases.

List citations of up to 5 relevant papers published in the past 5 years.

Richards, R.I., Robertson, S.A., Kastner, D.L. (2018) Neurodegenerative diseases have genetic hallmarks of autoinflammatory disease

Human Molecular Genetics (in press – July Review issue)

Webber, D.L., Choo, A., Hewson, L.J., Trim, P.J., Snel, M.F., Hopwood, J.J., **Richards, R.I.**, Hemsley, K.M., O'Keefe, L.V. (2018) **Neuronal-specific impairment of heparan sulfate degradation in *Drosophila* reveals pathogenic mechanisms for Mucopolysaccharidosis Type IIIA.**

Experimental Neurology 303:38-47. doi: 10.1016/j.expneurol.2018.01.020.

Richards, R.I., Robertson, S.A., O'Keefe, L.V., Fornarino, D., Scott, A., Lardelli, M., Baune, B.T. (2016) The Enemy Within: Innate Surveillance-mediated Cell Death, the common mechanism of neurodegenerative disease.

Front. Neurosci. Doi: 10.3389/fnins.2016.00193

Samaraweera, S.E., O'Keefe, L.V., Price, G.R., Venter D.J. and **Richards, R. I. (2013) Distinct roles for Toll and autophagy pathways in double-stranded RNA toxicity in a *Drosophila* model of expanded repeat neurodegenerative diseases.**

Human Molecular Genetics 22: 2811-2819. PMID: 23719916

Lawlor, K.T., O'Keefe, L.V., Samaraweera, S., van Eyk, C., McLeod, C.J., Maloney, C., Dang, T., Suter C. and **Richards, R.I. (2011) Double stranded RNA is pathogenic in *Drosophila* models of expanded repeat neurodegenerative diseases.**

Human Molecular Genetics 20: 3757–3768.

Proposal Number: 12

Theme: Cognition/learning and behaviour

Title: Emotional modulation of (Un)Conscious experience

Marta Garrido ¹ , Jessica McFadyen ¹ , Hakwan Lau ² , Bruno van Swinderen ¹ , Jakob Hohwy ³

1. *The University of Queensland, Brisbane, QLD, Australia*

2. *University California Los Angeles, Los Angeles*

3. *Monash University, Melbourne*

Our conscious experience of the world is strongly influenced by subtle, ongoing emotional reactions to behavioural relevant stimuli. We quite literally “see what we want to see”, such that we are quicker to become aware of rewarding or threatening stimuli, and are better at interpreting these stimuli under ambiguous circumstances. We can even be fear conditioned to stimuli that we have no awareness of, critically demonstrating that unconscious emotional processing is a powerful modulator of our conscious experience of the world.

This symposium will draw together research from humans and animals to present different perspectives of the emotional modulation of conscious awareness. We will present novel research findings for how visual stimuli processed outside of awareness can influence subsequent conscious processing. Specifically, we will discuss the influences of prior expectations, fear conditioning, and bodily interoception. We will present results from sophisticated decoding techniques applied to non-invasive human neuroimaging data, as well as measurements of both neural and physiological signals, to create a comprehensive neurobiological account for how emotion and consciousness interact. We will extend this even further by presenting electrophysiological data from flies in different stages of sleep that illustrate the role that sleep, as an unconscious neural state, has on reward circuits in the brain. Thus, the research presented in this symposium has the potential to further our understanding of, and have treatment implications for, emotion-related neuropsychological disorders, such as post-traumatic stress disorder, phobias, or gambling behaviour.

Overall, this symposium discusses findings from a wide variety of neuroscientific research in an integrative manner – bridging human neuroimaging, animal recordings, and philosophy – that will appeal to the broad ANS community. This proposal benefits from an international recognised consciousness researcher, as well as good gender balance (across chair and speakers), geographical representation (across Australia). Moreover, it showcases the work done by researchers at different career stages (PhD student, postdoc, A/Prof and Professor).

Speaker #1

Jessica McFadyen

Queensland Brain Institute, The University of Queensland

j.mcfadyen@uq.edu.au

HDR student

Talk Title: Expecting the unexpected: Emotional modulation of prediction and conscious awareness

Summary: Our survival depends on how well we can rapidly detect threats in our environment. To facilitate this, the brain is faster to bring behavioural relevant information (such as threatening or rewarding stimuli) into conscious awareness than neutral (or irrelevant) stimuli. Unexpected events may indicate a potential threat, and yet we tend to respond slower to unexpected than expected stimuli. It is unclear if or how these effects of emotion and expectation might interfere with one's conscious experience. Would we become aware of threats faster if they were expected, unexpected, or either? To answer this question, we conducted a series of breaking continuous flash suppression (bCFS) experiments using neutral and fearful faces. We found that expectation quickened response time (indicating time of breakthrough into conscious awareness) to neutral faces, while expectation had little to no effect on fearful faces, which overall reached consciousness faster than neutral faces. This suggests that prior expectations have a greater effect on neutral compared with threat-related stimuli during unconscious processing. Our analysis of electroencephalography data suggested a faster rate of evidence accumulation for fear than neutral faces. Overall, these results suggest a dominance of emotion over expectation during preconscious processing that influences transitions into awareness.

Publications:

Baumann O, Vromen JMG, Cheung A, **McFadyen J**, Ren Y, & Guo CC (2018) Neural correlates of temporal complexity and synchrony during audiovisual correspondence detection. *eNeuro*

Bret A, Beffara B, **McFadyen J**, & Mermillod M (2017) Right wing authoritarianism is associated with race bias in face detection. *PLoS One*, 12(7)

McFadyen J, Mermillod M, Mattingley JB, Halasz V, & Garrido, MI (2017) A Rapid Subcortical Amygdala Route for Faces Irrespective of Spatial Frequency and Emotion. *Journal of Neuroscience*, 37(14), p. 3864-3874

Bednark JG, Poonian SK, Palghat K, **McFadyen J**, & Cunnington R. (2015) Identity-specific predictions and implicit measures of agency. *Psychology of Consciousness: Theory, Research, and Practice*, 2(3), p.253-268

Cao Y, Contreras-Huerta LS, **McFadyen J**, & Cunnington R (2015) Racial bias in neural response to others' pain is reduced with other-race contact. *Cortex*, 70, p. 68-78

Speaker #2

Hawkan Lau

UCLA

hlau@psych.ucla.edu

Talk Title: Towards an unconscious multi-voxel neural reinforcement treatment for common fears

Summary: Can “hardwired” physiological fear responses (e.g., for spiders and snakes) be reprogrammed unconsciously in the human brain? Currently, exposure psychotherapy is among the most effective treatments for anxiety disorders, but the associating subjective aversiveness causes many to drop out of treatment prematurely. Here we introduce a method to reduce fear by directly pairing monetary reward with unconscious occurrences of decoded representations of naturally feared animals in the brain. To decode representations of feared objects without triggering aversive reactions, we capitalized on recent advancements in neuroimaging decoding techniques, to infer the relevant representations of feared animals for a designated participant based on data from other “surrogate” participants. In this way, the procedure completely bypassed the need for conscious encounter with the feared objects. We demonstrated that our method can lead to reliable reductions in physiological fear responses. This created a rare opportunity to rigorously test a psychological intervention of this nature in a double-blind, placebo-controlled fashion. We also discuss how these findings may also pave the way for a new approach combining the appealing rationale and proven efficacy of conventional psychotherapy with the rigor and leverage of clinical neuroscience, for a variety of disorders of emotion.

Publications:

Taschereau-Dumouchel V, Cortese A, Chiba T, Knotts JD, Kawato M, **Lau H** (2018) Towards an Unconscious Neural-Reinforcement Intervention for Common Fears. *PNAS*

Dehaene S, **Lau H**, Kouider S (2017) What is consciousness, and could machines have it? *Science*

Odegaard B, Knight R, **Lau H** (2017) Should a few null findings falsify prefrontal theories of consciousness? *Journal of Neuroscience*

Koizumi A, Amano K, Cortese A, Shibata K, Yoshida W, Seymour B, Kawato M, **Lau H** (2016) Fear reduction without fear through reinforcement of neural activity that bypasses conscious exposure. *Nature Human Behavior*

Cortese A, Amano K, Koizumi A, Kawato M, **Lau H** (2016) Multivoxel neurofeedback selectively modulates confidence without changing perceptual performance. *Nature Communications*

Speaker #3

Bruno van Swinderen

Queensland Brain Institute, The University of Queensland

b.vanswinderen@uq.edu.au

Talk Title: A role for sleep in maintaining value systems in the fly brain

Summary: The diverse functions of sleep, and how or why they might be distributed among different sleep stages, remain unresolved. Our recent discovery that even flies display different sleep stages suggests conserved evolutionary functions for both deep sleep and wake-like, or 'paradoxical', sleep. Here, we test the hypothesis that one of the functions of paradoxical sleep is to maintain a capacity for surprise, to thereby enable more effective attention processes and learning. We address this in insects with visual selective attention and oddball paradigms inspired from human experiments. We use behavioural paradigms, electrophysiology, and whole-brain imaging of genetically modified flies to investigate the relationship between sleep quality and these attention-like readouts. We focus on a specific neuropeptide reward circuit that modulates attentional gain, to investigate how sleep quality might help maintain emotion-like responses in flies. The likelihood that sleep stages and attention processes co-evolved in the first animal brain suggests an alternative approach to understanding the role of complex phenomena such as paradoxical sleep.

Publications:

van Alphen, B, Yap, MH, Kirszenblat, L, Kottler, B, & **van Swinderen, B** (2013) A dynamic deep sleep stage in *Drosophila*. *The Journal of Neuroscience* 33, 6917-6927

Yap, MHW, Grabowska, MJ, Rohrscheib, C, Jeans, R, Troup, M, Paulk, AC, van Alphen, B, Shaw, PJ, & **van Swinderen, B** (2017) Oscillatory brain activity in spontaneous and induced sleep stages in flies. *Nature Communications* 8, 1815

Paulk, AC, Kirszenblat, L, Zhou, Y, & **van Swinderen, B** (2015) Closed-Loop Behavioral Control Increases Coherence in the Fly Brain. *The Journal of Neuroscience* 35, 10304-10315

Paulk, AC, Stacey, JA, Pearson, TW, Taylor, GJ, Moore, RJ, Srinivasan, MV, & **van Swinderen, B** (2014) Selective attention in the honeybee optic lobes precedes behavioral choices. *Proceedings of the National Academy of Sciences of the United States of America* 111, 5006-5011

Kirszenblat, L, & **van Swinderen, B** (2015) The Yin and Yang of Sleep and Attention. *Trends in Neurosciences* 38, 776-786

Speaker #4

Jakob Hohwy

University of Melbourne

jakob.hohwy@monash.edu

Talk Title: Consciousness, interoception and allostasis

Summary: Conscious experience is tightly related to emotion and affect, mediated through interoception and bodily states. We explain the basic notions of consciousness and emotion and lay out a framework for thinking about them in the context of creatures seeking to maintain their homeostatic states through allostatic regulation. We consider the implications for our understanding of consciousness, and present experimental findings from studies exploring coupling between body and brain in the setting of consciousness science.

Publications:

Carter, OJ, **Hohwy J**, van Boxtel J, Lamme V, Block N, Koch C, & Tsuchiya N (2018). Conscious machines: Defining questions. *Science* 359(6374): 400-400

Bayne T, **Hohwy J**, Owen A (2017). Reforming the Taxonomy in Disorders of Consciousness. *Annals of Neurology* 82(6): 866-872. DOI: 10.1002/ana.25088

Gordon N, Koenig-Robert R, Tsuchiya N, van Boxtel JJA, **Hohwy J** (2017) Neural markers of predictive coding under perceptual uncertainty revealed with Hierarchical Frequency Tagging. *eLife* 2017;10.7554/eLife.2274

Hohwy J. (2016) The self-evidencing brain. *Noûs* 50(2): 259–285

Hohwy J (2013) The Predictive Mind. *Oxford University Press*.

Proposal Number: 21

Theme: Glia

Title: Oligodendrocytes in health and disease

Jessica Fletcher ¹ , Shane Liddelow ² , David Gonsalvez ¹ , Kaylene Young ³ , Steven Petratos ⁴

1. *The University of Melbourne, Melbourne, VIC, Australia*
2. *New York University Neuroscience Institute, New York, United States of America*
3. *The University of Tasmania, Hobart, TAS, Australia*
4. *Monash University, Melbourne, VIC, Australia*

Oligodendroglia generate and maintain myelin, the electrical insulating material in the vertebrate central nervous system (CNS). Myelin is absolutely essential for normal nervous system function, with damage to myelin and oligodendrocytes resulting in irreversible functional loss and progressive neural degeneration characteristic of demyelinating diseases. In addition, despite our knowledge that aberrant proliferation of oligodendroglia can result in oligodendroglioma, one of the most aggressive forms of brain cancer in adults and children, little is actually known about the rates of oligodendroglia production *in vivo*, or how these cells interact with other glia in complex responses to injury. This symposium aims to highlight novel developments that are changing our understanding of how oligodendrocytes are produced in development and throughout life, how they contribute to and respond in disease, and reveal novel insights on oligodendrocyte and astrocyte interactions that are of great potential therapeutic interest to many neurological conditions.

Our invited speakers will present an overview of how oligodendrocytes are integral to healthy brain function. They will reveal exciting new data on the interactions between oligodendrocytes and reactive astrocytes following injury and disease (Dr Liddelow), detail a novel mode as to how oligodendrocyte production occurs over a lifespan (Dr Gonsalvez), provide insights into the molecular mechanisms that result in aberrant oligodendrocyte proliferation that contribute to brain cancers (Dr Young), and show how targeted molecular manipulation of axons and oligodendrocytes can support neuroregeneration (Dr Petratos).

It is anticipated that this symposium will be of significant interest to the ANS membership and is highly relevant to the conference research themes of 'glia,' 'development and regeneration,' and 'clinical disorders and injury of the nervous system.' It will cover the role of oligodendrocytes in the contexts of healthy brain development, oncology, as well as numerous neurologic conditions including multiple sclerosis, neurodegenerative dementias (eg. Alzheimer's and Parkinson's disease), and acute brain ischemia. Our speakers will also present on a diverse range of methodologies for investigating neuroscience ranging from mathematical modelling, and novel imaging techniques to the implementation of *in vivo* cell therapies. Overall, our symposium will be an excellent addition to the ANS conference proceedings, able to ignite discussion across multiple disciplines of the Australian neuroscience community.

Symposium: Oligodendrocytes in Health and Disease

Proposal by: Dr Jessica Fletcher and Dr David Gonsalvez (University of Melbourne, VIC)

Speaker 1: Dr Shane Liddelow

Contact details: shane.liddelow@med.nyu.edu

Affiliation: New York University Neuroscience Institute, New York, USA

ANS membership type: N/A – overseas invited speaker

Early Career Researcher/HDR student: No

Title: *What do reactive astrocytes do?*

Abstract: Reactive astrocytes are rapidly generated following brain injuries and neurodegenerative diseases, however their role in trauma and disease states is poorly understood. Previously we distinguished two reactive astrocyte subclasses dependent on the type of inducing injury. We named these classes “A1” and “A2”. Based on gene profiles we hypothesized they were harmful and helpful respectively. We have shown that harmful A1 reactive astrocytes are induced by neuroinflammatory microglia. Specifically, activated microglia induce A1s by secreting IL-1 α , TNF α , and C1q – factors necessary and sufficient to induce A1s *in vitro* and *in vivo*. A1s have little ability to promote neuronal survival, outgrowth, synaptogenesis or phagocytosis and instead are powerfully toxic to neurons and oligodendrocytes. Additionally, A1s inhibit proliferation and maturation of OPCs into mature oligodendrocytes. We further showed A1s are present in multiple human neurodegenerative diseases including MS, AD, PD, HD, and ALS, and that death of CNS neurons and oligodendrocytes is prevented when A1 formation is blocked. We now show roles of A1 astrocytes in the context of neurodegeneration in both acute (ischemia) and chronic (glaucoma) mouse models. Together our findings strongly suggest A1s drive death of neurons and oligodendrocytes in disease and point the way forward for developing new treatments.

Top 5 publications (chronologically, last 5 years)

1. Clarke LE, **Liddelow SA**, ..., Barres BA (2018) Characterization of the gaining mouse astrocyte transcriptome. *Proc Natl Acad Sci USA* 115(8): E1896-E1905. PMID: 29437957. *First study to show aged reactivity in astrocytes in brain regions most susceptible to neurodegeneration.*
2. **Liddelow SA**, ..., Barres BA (2017) Activated microglia induce neurotoxic reactive astrocytes via IL-1 α , TNF α , and C1q. *Nature* 541:481-487. PMID: 28099414. *This landmark study provided new methods for investigating diseased astrocytes and showing their presence in a range of neurodegenerative disease.*
274 citations
3. Shi Y, ..., **Liddelow SA**, ..., Holtzman D (2017) ApolipoproteinE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature* 549:523-527. PMID: 28959956. *Demonstrates that astrocyte reactivity is contingent on both age and genetic predisposition for AD. Also developed a new mouse model for AD that properly recapitulates the astrocyte dysfunction seen in human patients.*
22 citations.
4. Bennett ML, ..., **Liddelow SA**, ..., Barres BA (2016) New tools for studying microglia in the mouse and human CNS. *Proc Natl Acad Sci USA* 113(12):E1738-1746. PMID: 26884166. *First in field paper that identifies a new toolset for the purification, culture, and imaging of microglia.*
178 citations
5. Zhang Y, ..., **Liddelow SA**, ..., Wu JQ (2014) An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J Neurosci* 34(36):11929-41197. PMID: 25186741. *Demonstrating commitment to providing tools for the research community, this manuscript provides a searchable database of cell-type specific transcriptomes from the mouse brain*
911 citations.

Speaker 2: Dr David Gonsalvez

Contact details: david.gonsalvez@unimelb.edu.au; (03) 9035 7611

Affiliation: Department of Anatomy and Neuroscience, The University of Melbourne, VIC

ANS membership type: Ordinary member

Early Career Researcher/HDR student: Yes (NHMRC ECF)

Title: *Novel insights into the mode of oligodendrocyte production during development*

Abstract: Combining innovative cell cycle assays with designed-based stereology and mathematical modelling, we have identified a novel mode of OPC proliferation that contrasts previous observations. We revise the traditional view that oligodendrocytes lengthen their cell division times with aging and show that aging does not significantly influence an OPCs capacity for fast cell division or DNA synthesis. On postnatal day(s) 5 (P5), P7, P15, P60 and P90, both cortical and callosal OPCs displayed consistent cell cycle times of 40hrs \pm 9hrs and S-phase lengths of 13hrs \pm 5hrs (min. n=3/developmental stage). Our data provides critical new evidence that oligodendrocyte production is not regulated by changes in cell division times, rather, it is regulated by OPC's proliferative growth fraction (GF - the percentage of dividing OPCs in the population) in a spatially and temporally distinct manner. We also provide the first account of oligodendrocyte production rates in terms of absolute number over a lifespan for the cortex and corpus callosum revealing surprising insights, for example 35% of oligodendrocytes after postnatal day 90 in the corpus callosum. Our initial analysis of OPC proliferative responses to injury, reveals a recapitulation with developmental processes, that oligodendrocyte production depends primarily on changes to the proliferative GF as opposed to dramatic changes in OPC division time, and that canonical Wnt signalling influences OPCs behaviour during remyelination *in vivo*.

Top 5 publications (chronologically, last 5 years):

1. **Gonsalvez DG**, Tran G, Fletcher JL, Hughes RA, Hodgkinson S, Wood RJ, Yoo SW, De Silva M, Wong AW, McLean C, Kennedy P, Kilpatrick TJ, Murray SS, Xiao J. (2017). A brain-derived neurotrophic factor-based p75NTR peptide mimetic ameliorates experimental autoimmune neuritis induced axonal pathology and demyelination. *eNeuro*, 4: ENEURO.0142-17.2017. *Demonstrates for the first time that in vivo stimulation of neurotrophin receptor, p75NTR has protective effects in peripheral demyelinating neuropathy.* 1 citation
2. **Gonsalvez DG**, Ferner AH, Peckham H, Murray SS, Xiao K. (2016) The roles of extracellular related-kinases 1 and 2 signaling in CNS myelination. *Neuropharmacology*, 11: 586-593. *Highlights the intracellular signalling cascades involving Erk1/2 that regulate oligodendrocyte behaviour.* 19 citations
3. **Gonsalvez DG**, Li-Yuen-Fong M, Cane KN, Stamp LA, Young HM, Anderson CR. (2015). Different neural crest populations exhibit diverse proliferative behaviours. *Dev Neurobiol*, 75: 287-301. *Demonstrates that neural crest-derived neuronal populations have tissue-specific patterns of proliferation.* 6 citations
4. Wong AW, Giuffrida L, Wood R, Peckham H, **Gonsalvez D**, Murray SS, Xiao J. (2014) TDP6, a brain-derived neurotrophic factor-based trkB peptide mimetic, promotes oligodendrocyte myelination. *Mol Cell Neurosci*, 63: 132-140. *Shows for the first time that a structural peptide mimic of BDNF can promote oligodendrocyte myelination in vitro.* 11 citations
5. **Gonsalvez DG**, Cane KN, Landman KA, Enomoto H, Young HM, Anderson CR. (2013) Proliferation and cell cycle dynamics in the developing stellate ganglion. *J Neurosci*, 33: 5969-5979. *First study to identify in vivo production rates for neural crest cells, and the neural progenitors that give rise to the sympathetic nervous system.* 25 citations

Speaker 3: Dr Kaylene Young

Affiliation: Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS

Contact details: kaylene.young@utas.edu.au; (03) 6226 7700

ANS membership type: Ordinary member

Early Career Researcher/HDR student: No

Title: *The role of non-clustered protocadherins in the development of oligodendroglioma*

Abstract: Oligodendrocyte progenitor cells (OPCs) comprise the largest proliferating cell population in the healthy adult brain, and their dysregulation is associated with formation of paediatric and adult gliomas. This research aims to understand how non-clustered protocadherins allow OPCs to maintain an even distribution throughout the brain, undergoing controlled proliferation to generate new oligodendrocytes (OLs) throughout life, and how dysregulated proliferation contributes to gliomagenesis. Protocadherin-15 (PCDH15) is a member of the cadherin superfamily of transmembrane proteins that mediate calcium-dependent cell adhesion. Microarray and RNA sequencing data show that *Pcdh15* mRNA is highly expressed by OPCs in the healthy CNS and its expression within gliomas can be predictive of tumor aggression, however the role of *Pcdh15* within the normal CNS or in glioma formation is unknown. Using shRNA-mediated gene knockdown, we determined that decreased *Pcdh15* expression is accompanied by a significant increase in OPC proliferation *in vitro*, which is dependent on increased activation of ERK. Importantly, reducing *Pcdh15* expression significantly alters interactions between adjacent OPCs; *Pcdh15* knockdown affects actin polymerization at OPC processes - increasing filopodial contact time and reducing the frequency of lamellipodial extrusion and retraction, while also markedly reducing the number of lamellipodia-like processes produced by each OPC. This phenotype was not affected by ERK activation, indicating that *Pcdh15* suppresses proliferation and promotes self-repulsion through signaling distinct downstream pathways.

Top 5 Publications (chronologically, last 5 years):

1. Cullen CL, **Young KM.** (2016). How does transcranial magnetic stimulation influence glial cells in the central nervous system? *Front Neural Circuits* 10: 26. *Explores potential molecular mechanisms of action of transcranial magnetic stimulation on glial cells and how they contribute to improved outcomes in multiple sclerosis, mental health conditions and ischemia.* 15 citations
2. Pitman KA, **Young KM.** (2016). Activity-dependent calcium signalling in oligodendrocyte generation. *Int J Biochem Cell Biol* 77: 30-34. *Summarises the current understanding of how neuronal activity influences oligodendrocyte myelination and proposes novel hypotheses in how calcium signalling modulates these effects.* 2 citations
3. Auderset L, Cullen CL, **Young KM.** (2016). Low density lipoprotein-receptor related protein 1 is differentially expressed by neuronal and glial populations in the developing and mature mouse central nervous system. *PLoS One*, 11: e0155878. *Demonstrates that LDRP1 plays an important role in glial cell development including of OPCs.* 5 citations
4. O'Rourke M, Gasperini R, **Young KM.** (2014). Adult myelination: wrapping up neuronal plasticity. *Neural Regen Res* 9: 1261-1264. *Examines the contribution of neuronal activity and neurogenesis in driving OPC proliferation and myelin formation in the adult CNS.* 14 citations
5. **Young KM,** Psachoulia K, Tripathi RB, Dunn SJ, Cossell L, Attwell D, Tohyama K, Richardson WD. (2013) Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodelling. *Neuron* 77: 873-885. *First study to demonstrate that oligodendrocyte precursor cell proliferation was dynamic in the adult central nervous system and actively contributed to myelin remodelling.* 341 citations

Speaker 4: Dr Steven Petratos

Contact details: steven.petratos@monash.edu; (03) 9902 0191

Affiliation: Department of Medicine, Central Clinical School, Monash University, VIC.

ANS membership type: Ordinary member

Early Career Researcher/HDR student: No

Title: *Targeting EAE-Induced Demyelination and Axonal Pathology By Transplanting Haematopoietic Stem Cells That Overexpress NgR(310)Ecto-Fc Fusion Protein*

Abstract: Multiple Sclerosis (MS) is an immune-mediated neurodegenerative disorder. Nogo receptor 1 (NgR1) is a high affinity receptor for myelin-associated inhibitory factors (MAIFs) to abrogate neurite outgrowth and may promote axonal degeneration in an animal model of MS, experimental autoimmune encephalomyelitis (EAE). HSCs can be utilised as carriers of the therapeutic NgR(310)ecto-Fc decoy protein for specific delivery into EAE lesions and can potentiate neurological recovery. As MS and EAE exhibit large numbers of inflammatory cell infiltrates to potentiate oligodendrocyte dystrophy and central nervous system (CNS) demyelinating lesions, we utilised transplantable HSCs as a cellular delivery method of the NgR(310)ecto-Fc fusion protein. We show that we can deliver NgR(310)ecto-Fc to sites of EAE pathology following the transplantation of lentivirus (LV)-transduced HSCs that encode the fusion protein. We identified infiltrating macrophages expressing NgR-Fc localised to areas of inflammation and demyelination ($2.0 \times 10^3 \pm 0.5 \times 10^3$ cells/mm², $p < 0.0001$), at the peak of neurological disability. Importantly, mice transplanted with HSCs overexpressing the therapeutic NgR(310)ecto-Fc protein, recovered from symptoms associated with EAE demonstrating axonal regrowth and remyelination. Our results suggest that HSCs can be utilised as carriers of the therapeutic NgR-Fc protein delivered to EAE lesions and can potentiate neurological recovery through neurorepair.

Top 5 Publications (chronologically, last 5 years):

1. Lee JY, Kim MJ, Li L, Velumian AA, Aui PM, Fehlings MG, **Petratos S.** (2017). Nogo receptor 1 regulates Caspr distribution at axo-glial units in the central nervous system. *Sci Rep*, 7: 8958. *Demonstrates for the first time that global reduction in Nogo receptor-1 expression dysregulates myelin ultrastructure negatively affecting neurotransmission throughout the CNS.*
2. Lee JY, **Petratos S.** (2016) Thyroid hormone signalling in oligodendrocytes: from extracellular transport to intracellular signal. *Mol Neurobiol* 53: 6568-6583. *Explores the molecular mechanisms behind the influence of thyroid hormone on oligodendrocyte myelination and how they may be targeted for therapy development.* 9 citations
3. Dahl LC, Nasa Z, Chung J, Niego B, Tarlac V, Ho H, Galle A, **Petratos S**, Lee JY, Alderuccio F, Medcalf RL. (2016) The influence of differentially expressed tissue-type plasminogen activator in experimental autoimmune encephalomyelitis: implications for multiple sclerosis. *PLoS One*, 11: e0158653. *Demonstrates that altered levels of molecules regulating blood-brain barrier integrity can increase disease severity of a preclinical model of multiple sclerosis.* 2 citations
4. Lee JY, Taghian K, **Petratos S.** (2014) Axonal degeneration in multiple sclerosis: can we predict and prevent permanent disability? *Acta Neuropathol Commun*, 2: 97. *Summarises the mechanisms of axonal degeneration in multiple sclerosis and how clinical imaging and molecular markers can be used to improve prognosis.* 18 citations
5. Alsanie WF, Niclis JC, **Petratos S.** (2013) Human embryonic stem cell-derived oligodendrocytes: protocols and perspectives. *Stem Cells Dev*, 22: 2459-2476. *Highlights the advantages and limitations of using embryonic stem cell-derived oligodendrocytes for cellular therapies to promote remyelination.* 32 citations

Proposal Number: 29

Theme: New techniques in neuroscience

Title: Understanding protein synthesis and translational control in neurobiology and disease

Harrison T Evans¹, Jurgen Gotz¹, Erin Schuman², Timothy Bredy¹, Joanna Williams³

1. *Queensland Brain Institute, St Lucia, QLD, Australia*
2. *The Max Planck Institute for Brain Research, Frankfurt, Germany*
3. *The University of Otago, Dunedin, New Zealand*

The essential cellular processes of protein synthesis and translational control are fundamental to a plethora of neurological phenomena, both physiological and pathological. Neuronal activities such as synaptic plasticity and memory formation are dependent upon dynamic and regulated control of the proteome. Perturbance of this control has also been implicated in a range of disease pathologies, such as Alzheimer's disease, Huntington's disease and, motor neuron disease.

Recent advancements in the field have enabled researchers to examine how the proteome is altered in response to both physiological and pathological stimuli, and by doing so has allowed them to gain a greater understanding of the mechanisms underpinning these complex neurological phenomena. Novel techniques such as non-canonical amino acid (NCAA) tagging to examine *de novo* protein synthesis have had a large impact upon the field by enabling a deeper analysis of the dynamic and complex proteome both *in vitro* and *in vivo*.

This symposium will include talks from researchers both developing and using these techniques in order to examine learning and memory, Alzheimer's disease, long-term potentiation and Parkinson's disease. This symposium will focus on the current applications of these techniques, examine how these techniques may be used to answer a wide variety of different research questions, and explore the future development of these techniques.

It is the hope of the proposer of this symposium that those attending will gain a greater understanding of the importance of alterations in protein synthesis and translational control in neurobiology and be able to apply this knowledge in their own fields.

Professor Erin Schuman

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Title of Talk: Local Translation at Synapses.

Abstract:

The complex morphology of neurons, with synapses located 100's of microns from the cell body, necessitates the localization of important cell biological machines and processes within dendrites and axons. We have discovered thousands of mRNAs within dendrites that are endowed with unique regulatory features in their 3' untranslated regions. Using expansion microscopy together with metabolic labelling we have discovered that both postsynaptic spines and presynaptic terminals exhibit rapid translation, which exhibits differential sensitivity to different neurotransmitters and neuromodulators. These data suggest that selective translation of mRNAs in response to different extracellular cues can give rise to plasticity phenotypes at both sides of the synapse.

Citations:

Tushev, G., Glock, C., Heumueller, M., Biever, A., Jovanovic, M. and Schuman, E.M. (2018). Alternative 3'UTRs modify the localization, regulatory potential, stability, and plasticity of mRNAs in neuronal compartments. **Neuron**, in press.

Schanzenbaecher, C.T., Langer, J.D., and Schuman, E.M. (2018). Time- and polarity-dependent proteomic changes associated with homeostatic scaling at central synapses. *eLife* 2018;7:e33322. doi: <https://doi.org/10.7554/eLife.33322>

Alvarez-Castelao, B., Schanzenbaecher, C.T., Hanus, C., Glock, C., tom Dieck, S., Dörrbaum, A.R., Bartnik, I., Nassim-Assir, B., Ciirdaeva, E., Mueller, A., Dieterich D.C., Tirrell, D.A., Langer, J.D., Schuman, E.M. (2017). Cell-type-specific metabolic labeling of nascent proteomes *in vivo*. *Nature Biotechnology*, 35: 1196-1201. doi:10.1038/nbt.4016

Sambandan, S., Akbalik, G., Kochen, L., Rinne, J., Kahlstatt, J., Glock, C., Tushev, G., Alvarez-Castelao, B., Heckel, A., and Schuman, E.M. (2017). Activity-dependent spatially localized miRNA maturation in neuronal dendrites. *Science*, 355 (6325), 634-637.

Tom Dieck, S., Kochen, L., Hanus, C., Bartnik, I., Nassim-Assir, B., Merk, K., Mosler, T., Garg, S., Bunse, S., Tirrell, D.A. and Schuman, E.M. (2015). Direct visualization of identified and newly synthesized proteins in situ. *Nature Methods*, 12: 411-414, doi:10.1038/NMETH.3319.

Associate Professor Timothy Bredy

Affiliation: The Queensland Brain Institute

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ANS Membership: Ordinary

Title of Talk: RNA modification in the brain

Abstract:

In this talk, I will highlight recent findings in the emerging field of epitranscriptomic mechanisms and discuss their potential role in neural plasticity, learning and memory. These include the influence of RNA modifications on activity-induced RNA structure states, RNA editing and RNA localization, and how qualitative state changes in RNA increase the functional diversity and information-carrying capacity of RNA molecules by ultimately influencing translation.

Citations:

Leighton, L. J., Ke, K., Zajackowski, E. L., Edmunds, J., Spitale, R. C., & Bredy, T. W. (2017). Experience-dependent neural plasticity, learning, and memory in the era of epitranscriptomics. *Genes, Brain and Behavior*, e12426. <https://doi.org/10.1111/gbb.12426>

Nainar, S., Marshall, P. R., Tyler, C. R., Spitale, R. C., & Bredy, T. W. (2016). Evolving insights into RNA modifications and their functional diversity in the brain. *Nature Neuroscience*. <https://doi.org/10.1038/nn.4378>

Widagdo, J., Zhao, Q.-Y., Kempen, M.-J., Tan, M. C., Ratnu, V. S., Wei, W., ... Bredy, T. W. (2016). Experience-Dependent Accumulation of N6-Methyladenosine in the Prefrontal Cortex Is Associated with Memory Processes in Mice. *Journal of Neuroscience*, 36(25), 6771–6777. <https://doi.org/10.1523/JNEUROSCI.4053-15.2016>

Mr Harrison Evans

Affiliation: The Queensland Brain Institute

Email: h.evans@uq.edu.au

ANS Membership: Student

HDR student

Title of Talk: Decreased *de novo* protein synthesis observed in mouse models of tauopathy

Abstract:

De novo protein synthesis has been robustly demonstrated to be required for many neurological processes. Recently, it has been suggested that the dynamics of protein synthesis is altered in tauopathy, with pathological tau being shown to interact with RNA-binding and ribosomal proteins (Li & Götz, 2017; Calve et al., 2016). It is however, unclear how these interactions alter the de novo proteome.

We therefore sought to examine how the presence of pathological tau affects the de novo proteome *in vivo*. To achieve this, we used the novel techniques of fluorescent non-canonical amino acid tagging (FUNCAT) to visual protein synthesis *in vivo* and bio-orthogonal non-canonical amino acid tagging (BONCAT) to purify the *de novo* proteome and perform quantitative proteomics.

We were able to demonstrate that in the K3 and rTg4510 mouse models of tauopathy, there is a significant decrease in *de novo* protein synthesis in the presence of pathological phosphorylated tau. These data suggest that the interaction between tau and RNA-binding proteins may perturb protein synthesis, which further opens novel research possibilities for the field.

Citations:

Bodea, L. G., Evans, H. T., Van der Jeugd, A., Ittner, L. M., Delerue, F., Kril, J., ... Götz, J. (2017).

Accelerated aging exacerbates a pre-existing pathology in a tau transgenic mouse model. *Aging Cell*, 16(2), 377–386.

<https://doi.org/10.1111/acer.12565>

Nisbet, R. M., Van Der Jeugd, A., Leinenga, G., Evans, H. T., Janowicz, P. W., & Götz, J. (2017).

Combined effects of scanning ultrasound and a tau-specific single chain antibody in a tau transgenic mouse model. *Brain*, 140(5), 1220–1230.

<https://doi.org/10.1093/brain/awx052>

Dr Joanna Williams

Affiliation: The University of Otago

Email: joanna.williams@otago.ac.nz

ANS membership: Ordinary

Title of Talk: Secreted amyloid precursor protein alpha regulates glutamate receptor trafficking and plasticity-related protein synthesis.

Abstract:

Secreted amyloid precursor protein- α (sAPP α) mediates neuroprotection, neurogenesis and long-term potentiation (LTP), however, the underlying molecular mechanisms employed by sAPP α are not well elucidated. Since LTP is dependent on synthesis and regulated trafficking of AMPA glutamate receptors (AMPA α s) we hypothesized that sAPP α may harness these mechanisms to promote synaptic plasticity. Using FUNCAT-PLA to specifically label newly synthesized proteins in primary hippocampal neurons, we discovered that sAPP α (1 nM, 2 h), increased GluA1 synthesis three-fold ($p < 0.0001$), while GluA2 synthesis was unaffected. Moreover, there was a significant increase in the surface expression of pre-existing GluA1-containing AMPA α s ($p = 0.0003$) but, curiously, there was no difference in the surface expression of the *de novo* synthesized GluA1 at the time-point investigated. These data suggest that enhanced synthesis and trafficking of GluA1-containing AMPA α s, by increasing the pool of available AMPA α s, may contribute to the LTP-enhancing properties of sAPP α .

Citations:

Claasen AM, Guévremont D, Mason-Parker SE, Bourne K, Tate WP, Abraham WC, Williams JM (2009). Secreted amyloid precursor protein-alpha upregulates synaptic protein synthesis by a protein kinase G-dependent mechanism. *Neurosci Lett*. 460(1):92-6. doi: 10.1016/j.neulet.2009.05.040.

Ryan MM, Morris GP, Mockett BG, Bourne K, Abraham WC, Tate WP, Williams JM (2013). Time-dependent changes in gene expression induced by secreted amyloid precursor protein-alpha in the rat hippocampus. *BMC Genomics*. 14:376. doi: 10.1186/1471-2164-14-376.

Williams JM, Guévremont D, Mason-Parker SE, Luxmanan C, Tate WP, Abraham WC (2007). Differential trafficking of AMPA and NMDA receptors during long-term potentiation in awake adult animals. *J Neurosci*. 27(51):14171-8.

Proposal Number: 37

Theme: Sensory systems

Title: Sensory and motor processing in cortical circuits in vivo

Malinda L S Tantirigama ¹ , Juliette E Cheyne ² , John M Bekkers ¹ , Elizabeth Zavitz ³ , Mehdi Adibi ^{4 5} , Ruth M Empson ⁶

1. *Eccles Institute of Neuroscience, The Australian National University, Canberra, ACT, Australia*
2. *Centre for Brain Research, The University of Auckland, Auckland, New Zealand*
3. *Department of Physiology, Monash University , Clayton, VIC, Australia*
4. *School of Psychology, University of New South Wales, Sydney, NSW, Australia*
5. *Department of Cognitive Neuroscience, International School for Advanced Studies , Trieste, Italy*
6. *Department of Physiology, University of Otago, Dunedin, New Zealand*

The cerebral cortex is the largest part of the mammalian brain. The basic structure of cortical circuits is similar in different cortical areas ('canonical' circuit) and in different species. However, cortical processing generates vastly different mental functions like perception, voluntary movement and memory. With its large variety of cell types, elaborate connectivity, computational complexity, and its ability to undergo plastic changes, how the cortex processes information continues to drive interest in neuroscience research.

To gain a basic understanding of how the cerebral cortex works it is essential to study active information processing in live animals, while they are responding to natural stimuli or during movement tasks. Since recent technological advances in the ability to record from a large number of identified cells in the intact brain, we have made tremendous progress in understanding basic principles that govern cortical sensorimotor processing *in vivo*. *In vivo* imaging and multiunit recording are now the gold standard for understanding sensory processing and motor function in cortical circuits.

This symposium proposal aims to highlight the cutting-edge *in vivo* cortical research undertaken in Australia and New Zealand. The proposal gathers speakers and chairs across Australia, New Zealand and Italy, and achieves 50:50 balance in both gender and career status of speakers. The techniques covered are multielectrode arrays, optogenetics, and voltage and calcium imaging, all of which are conducted *in vivo*.

Prof. John Bekkers (ANU, Canberra) will present how NMDA receptors, a critical component of memory processes, can modulate odour processing in the mouse piriform cortex, the oldest part of the cerebral cortex. Dr. Elizabeth Zavitz (Monash, Melbourne) will present how the nature of the stimulus can modulate visual processing in a higher-order animal model, the marmoset monkey. Dr. Mehdi Adibi (UNSW, Sydney and SISSA, Italy) will present cortical processing underlying sensory adaptation in the rodent somatosensory cortex. Finally, Prof. Ruth Empson (Otago, NZ) will present how information represented in motor maps undergoes plasticity during motor learning.

Currently, *in vivo* cortical sensorimotor research is a hot topic in many international neuroscience meetings. This proposal aims to bring this topic to ANS 2018 and attract the many ANS members studying sensorimotor-related brain structures, including the large population of visual neuroscientists in Australia. We also hope this symposium proposal will invigorate interest in researchers wanting to incorporate *in vivo* imaging or multiunit recording in to their research,

or foster collaborations with those who do. There is still a large gap in basic understanding between how brain processes operate and the resultant high-level behaviour, and the ultimate goal of this proposal is to stimulate more research on this fascinating topic in Australia and New Zealand.

Name and contact details:

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ANS member type: Ordinary
Early Career Researcher: No

Title of talk:

NMDA receptors and olfactory learning in the piriform cortex

Summary:

The primary olfactory (or piriform) cortex is the first cortical destination of olfactory information and is essential for recognising and remembering odours. I will present our new work that reveals unexpected roles for NMDA (N-methyl-D-aspartate) receptors in the operation of the piriform cortex *in vivo*. Using 2-photon Ca^{2+} imaging in mice, we made two key findings about the importance of NMDA receptors for odour learning. First, we found that NMDA receptors are required for the expression of a form of experience-dependent change in the representation of odours in the piriform cortex. This form of learning seemed to involve cell type-specific synaptic plasticity. Second, we discovered that the dendrites of principal neurons in the piriform cortex support both spontaneous and odour-evoked backpropagating action potentials (bAPs). These bAPs were completely suppressed by NMDA receptor antagonists, implying a major role for NMDA receptors in dendritic excitability. We suggest that bAPs in the piriform cortex, as in other cortical regions, are important for spike timing-dependent synaptic plasticity and memory. In summary, both of our findings underline the key contribution of NMDA receptors to olfactory learning, and demonstrate that the 'primitive' piriform cortex shares a number of essential features with other, more complex, sensory cortices.

Papers in last 5 years:

1. **Bekkers, J. M.** & Suzuki, N. (2013) Neurons and circuits for odor processing in the piriform cortex. *Trends Neurosci.* **36**, 429-438.
2. Suzuki, N., Tang, C. S.-M. & **Bekkers, J. M.** (2014) Persistent barrage firing in cortical interneurons can be induced *in vivo* and may be important for the suppression of epileptiform activity. *Front. Cell. Neurosci.* **8**, 76-86.
3. Choy, J. M. C., Suzuki, N., Shima, Y., Budisantoso, T., Nelson, S. B., & **Bekkers, J. M.** (2017) Optogenetic mapping of intracortical circuits originating from semilunar cells in the piriform cortex. *Cereb. Cortex* **27**, 589-601.
4. Tantirigama, M. L. S., Huang, H. H.-Y. & **Bekkers J. M.** (2017) Spontaneous activity in the piriform cortex extends the dynamic range of cortical odor coding. *Proc. Natl. Acad. Sci. USA* **114**, 2407-2412.
5. Gerrard, L., Tantirigama, M. L. S. & **Bekkers J. M.** (2018) Pre- and postsynaptic activation of GABA_B receptors modulates principal cell excitation in the piriform cortex. *Front. Cell. Neurosci.* **12**, Article 28, 1-11.

Name and contact details:

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26 Innovation Walk
Department of Physiology
Monash University
Clayton, VIC 3800
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ANS member type: Ordinary
Early Career Researcher: Yes

Title of talk:

Population codes in primate visual cortex are optimised for the structure of natural images

Summary:

Visual perception is informed by the pattern of activation across a broad population of neurons. To understand how information is represented in cortical circuits, it is important to understand how it is distributed across members of the population. However, most studies explore neural activity in visual cortex using only gratings or dots. In the natural visual world, there is information at a range of spatial scales, and this information is often sparse and phase aligned. Visual information with this structure will recruit a systematically distinct population of neurons, and these neurons will modulate one another in ways that cannot be detected using simpler stimuli. Here, we examine how the structure of visual information impacts the way it is encoded with multielectrode arrays implanted in V1, V2, and/or MT of anaesthetised marmoset monkeys. We recorded neuronal responses simultaneously from dozens of neurons while presenting visual stimuli with a variety of spatial structures. We show that naturalistic patterns of stimulation modulate network activity to reduce correlated variability. This suggests that visual cortical networks operate most efficiently when they represent information with a natural stimulus structure.

Papers in last 5 years:

1. **Zavitz, Elizabeth**, Hsin-Hao Yu, Marcello G. P. Rosa, and Nicholas S. C. Price. (accepted). "Correlated Variability in the Neurons With the Strongest Tuning Improves Direction Coding." *Cerebral Cortex*, *in press*. <https://doi.org/10.1093/cercor/bhx344>.
2. **Zavitz, Elizabeth**, Hsin-Hao Yu, Elise G. Rowe, Marcello G. P. Rosa, and Nicholas S. C. Price. 2016. "Rapid Adaptation Induces Persistent Biases in Population Codes for Visual Motion." *The Journal of Neuroscience* 36 (16): 4579–90.
3. **Zavitz, Elizabeth**, and Curtis L. Baker. 2014. "Higher Order Image Structure Enables Boundary Segmentation in the Absence of Luminance or Contrast Cues." *Journal of Vision* 14 (4). <https://doi.org/10.1167/14.4.14>.
4. **Zavitz, Elizabeth**, and Curtis L. Baker. 2013. "Texture Sparseness, but Not Local Phase Structure, Impairs Second-Order Segmentation." *Vision Research* 91: 45–55.

Name and contact details:

Mehdi Adibi

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Department of Cognitive Neuroscience, International School for Advanced Studies (SISSA), Trieste, Italy

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ANS member type: Ordinary

Early Career Researcher: Yes

Title of talk:

Neural computations underlying sensory adaptation in rodent somatosensory cortex

Summary :

In the natural environment, animals are constantly exposed to a continuous stream of dynamic sensory stimulation. A key question in systems neuroscience is how attributes of the sensory stimulus are encoded in the activity of neurons, and in turn, how these attributes can be read out from the activity of neuronal populations. We address this question in the whisker-mediated touch system of rodents due to its well-established anatomy and exquisite functionality. The whisker system is one of the major channels through which rodents acquire information about their surrounding environment. The response properties of neurons dynamically adjust to the prevailing diet of sensory stimulation, a process known as sensory adaptation. Adaptation is a common phenomenon across all sensory modalities and occurs at various stages of processing. In a combination of electrophysiological, functional optogenetic and computational approaches at single cell level and at population level, we characterise the dynamics of neuronal responses in primary somatosensory cortex of rodents. Our findings reveal adaptation enhances information processing efficiency with reduced metabolic cost. Additionally, the ability to decode sensory information based on a linear readout mechanism improves with adaptation. Interestingly, a decoder that does not adjust to the state of adaptation can perform remarkably well.

Papers in last 5 years:

1. E. Kheradpezhoh, **M. Adibi**, E. Arabzadeh (2017) "Response Dynamics of Rat Barrel Cortex Neurons to Repeated Sensory Stimulation" *Scientific Reports*, 7, doi:10.1038/s41598-017-114477-6.
2. M.M. Sabri, **M. Adibi**, E. Arabzadeh (2016) "Dynamics of Population Activity in Rat Sensory Cortex: Network Correlations Predict Anatomical Arrangement and information Content" *Frontiers in Neural Circuits*, 10(49), doi:10.3389/fncir.2016.00049.
3. **M. Adibi**, J.S. McDonald, C.W.G. Clifford, E. Arabzadeh, (2014) "Population Coding in rat Barrel Cortex: Optimizing the Linear Readout of Correlated Population Responses," *PLoS Computational Biology*, 10(1): e1003415. doi:10.1371/journal.pcbi.1003415.
4. **M. Adibi**, C.W.G. Clifford, E. Arabzadeh, (2013) "Informational Basis of Sensory Adaptation: Entropy and Single Spike Efficiency in Rat Barrel Cortex," *Journal of Neuroscience*, 33(37): 14921–14926.
5. **M. Adibi**, J.S. McDonald, C.W.G. Clifford, E. Arabzadeh, (2013) "Adaptation Improves Neural Coding Efficiency despite Increasing Correlations in Variability," *Journal of Neuroscience*, 33(5):2108-2120.

Name and contact details:

Prof Ruth Empson,
Department of Physiology
University of Otago, NZ
Email: ruth.empson@otago.ac.nz

ANS member type: Ordinary
Early Career Researcher: No

Title of talk:

Visualising Motor Map Dynamics

Summary:

Motor maps in the motor cortex have traditionally been viewed as static, perhaps because old methods precluded time-dependent measurements. However, during motor learning we predict that dynamic changes to the maps take place and that these are underpinned by altered cortical circuit connectivity. Here, we use a genetically encoded fluorescent voltage sensor expressed exclusively in layer 2/3 cortical neurons and through-skull mesoscopic imaging *in vivo* to reveal dynamic changes in motor maps during motor learning. Our results have the potential to shift perceptions of motor maps from being static to being dynamic, and to enhance understanding of how synaptic connections underpin motor map expansion to enable learning. This knowledge will ultimately translate into refining brain controlled prosthetic limbs so that they learn to move more like natural limbs, and also to inform rehabilitation and treatment of a diversity of movement disorders.

Papers in last 5 years:

1. Motor and Cerebellar Architectural Abnormalities during the Early Progression of Ataxia in a Mouse Model of SCA1 and How Early Prevention Leads to a Better Outcome Later in Life. Ibrahim MF, Power EM, Potapov K, **Empson RM**. Front Cell Neurosci. **2017** 11:292
2. Prolonged type 1 metabotropic glutamate receptor dependent synaptic signaling contributes to spino-cerebellar ataxia type 1 Power, EM, Morales, A, **Empson, RM**. Journal of Neuroscience May 4 36 (18) **(2016)**
3. Voltage imaging to understand connections and functions of neuronal circuits. Antic SD, **Empson RM**, Knopfel T. (equal contributions) Journal of Neurophysiol. Apr 13:jn.00226.2016. doi: 10.1152/jn.00226.2016. **(2016)**
4. Transgenic mice for intersectional targeting of neural sensors and effectors with high specificity and performance. Linda Madisen, Aleena R. Garner, Daisuke Shimaoka, Amy S. Chuong, Nathan C. Klapoetke, Lu Li, Alexander van der Bourg, Yusuke Niino, Ladan Egolf, Claudio Monetti, Hong Gu, Maya Mills, Adrian Cheng, Bosiljka Tasic, Thuc Nghi Nguyen, Susan M. Sunkin, Andrea Benucci, Andras Nagy, Atsushi Miyawaki, Fritjof Helmchen, **Ruth M. Empson**, Thomas Knöpfel, Edward S. Boyden, R. Clay Reid, Matteo Carandini, Hongkui Zeng Neuron 85(5):942-58. doi: 10.1016/j.neuron.2015.02.022. **(2015)**.
5. Expression of the developmental transcription factor *Fezf2* identifies a distinct subpopulation of layer 5 intratelencephalic-projection neurons in mature mouse motor cortex. Tantirigama ML, Oswald MJ, Duynstee C, Hughes SM, **Empson RM**. Journal of Neuroscience Mar 19;34(12):4303-8 **(2014)**.

Proposal Number: 17

Theme: Development and regeneration

Title: Degeneration or Regeneration, Choice After Axon Injury

Tong Wang¹, Anna E King², Brent Neumann³, Tobias J Merson⁴

1. *Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia*
2. *Wicking Dementia Research and Education Centre, The University of Tasmania, Hobart, Tasmania, Australia*
3. *Monash Biomedicine Discovery Institute, Monash University, Melbourne, Victoria, Australia*
4. *Australian Regenerative Medicine Institute, Monash University, Melbourne, Victoria, Australia*

Symposium topic

The topic of the proposed symposium is to discuss the factors that determine the fate of axons after injury, and how regenerative or degenerative responses are induced in different types of neurons. It comprises talks from 4 speakers covering different areas of axon regeneration and degeneration, and adaptation to injury and pathology in the nervous system of both mammalian and *C. elegans*, with an emphasis on interventions that promote the regrowth of damaged axons. From attending the session the attendees will gain knowledge from the following four subtopics:

1. Cytoskeletal machinery that controls the innate axon repair capacity. For this part, Dr. Brent Neumann will share his lab's recent works on cytoskeletal mechanism underlying axon regeneration or degeneration after nerve injury in *C. elegans*, in which they have identified MEC-17 as a central component in preserving synaptic integrity, and in repairing the nervous system after injury.
2. How to achieve axon regeneration by activating the axon trafficking machinery in mammalian CNS axons. For this part, Dr. Tong Wang will share her recent findings of how long-range axonal trafficking promotes the regenerative growth of injured rat hippocampal axons, in which they have identified Lgl1/aPKC as key pathway to promote axon regeneration after injury.
3. Regeneration of the axon integrity after injury. The remyelination of axons i.e. the regeneration of a functional axon-myelin unit, is of great importance for the full recovery of axon integrity. Dr. Tobias Merson will share recent findings of his lab in identifying intrinsic and extrinsic cues that influence myelin production during CNS remyelination, which will provides insights to restoration of signal conduction following demyelinating injury of the CNS axons.
4. How the CNS axons degenerate in different types of neurodegenerative diseases. For this part, A/Prof. Anna King will talk the recent works of her lab in exploring the axon-soma singling process underlying CNS axon degeneration. Using a number of *in vitro* and *in vivo* models, they separately probed axon and somatodendritic compartments, and found failure of axon-soma singling and axonal caspase activation underlie axon degeneration.

Scientific impact

The axons in human central nervous system (CNS) fail to regenerate and their further degeneration leads to permanent deficiencies in patients ^{1,2}. As generally accepted, two major factors limit the regeneration of injured CNS axons: (1) the extremely low intrinsic growing capacity of axons *per se* ³, and (2) the inhibitory effects exerted by the myelin-associated molecules, which are produced by the wrapping oligodendrocytes⁴. In contrast, axons in peripheral nervous system (PNS) or CNS of lower organism readily regenerate after damage ^{5,6}. Therefore in different types of axons, dissecting the molecular pathways that determine the degenerative or regenerative fates after injury, will provide invaluable insights for the development of regenerative medicines for human CNS damages.

Relevance to the ANS membership

All speakers/chair of this symposium are current ANS members.

1. Liu, K., Tedeschi, A., Park, K. K. & He, Z. Neuronal intrinsic mechanisms of axon regeneration. *Annu Rev Neurosci* 34, 131-152, doi:10.1146/annurev-neuro-061010-113723 (2011).
2. Wang, J. T., Medress, Z. A. & Barres, B. A. Axon degeneration: molecular mechanisms of a self-destruction pathway. *J Cell Biol* 196, 7-18, doi:10.1083/jcb.201108111 (2012).
3. He, Z. & Jin, Y. Intrinsic Control of Axon Regeneration. *Neuron* 90, 437-451, doi:10.1016/j.neuron.2016.04.022 (2016).
4. Yiu, G. & He, Z. Glial inhibition of CNS axon regeneration. *Nat Rev Neurosci* 7, 617-627, doi:10.1038/nrn1956 (2006).
5. Silver, J. & Miller, J. H. Regeneration beyond the glial scar. *Nat Rev Neurosci* 5, 146-156, doi:10.1038/nrn1326 (2004).
6. Neumann, B., Nguyen, K. C., Hall, D. H., Ben-Yakar, A. & Hilliard, M. A. Axonal regeneration proceeds through specific axonal fusion in transected *C. elegans* neurons. *Dev Dyn* 240, 1365-1372, doi:10.1002/dvdy.22606 (2011).

- **Name and Affiliation**

Dr. Brent Neumann

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- **Contact details**

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- **ANS member type**

Ordinary member

- **Early Career Researcher/HDR student?**

No

- **Title and summary of talk**

Title: MEC-17/ATAT1 is essential for preserving synaptic integrity, and for nervous system repair after injury

Summary: Microtubules are key elements of the eukaryotic cytoskeleton formed through the dynamic assembly of α - and β -tubulin heterodimers. In the nervous system, and particularly within axons, microtubules serve as vital structural and functional components necessary for axonal transport. MEC-17/ATAT1 post-translationally modifies α -tubulin, imparting both stability and flexibility to the microtubule network. However, the functions of MEC-17 in microtubule dynamics and how this impacts nervous system structure, remains poorly defined. We previously demonstrated that loss-of-function mutations in *mec-17* cause spontaneous axonal degeneration in *C. elegans* neurons. We now report that correct regulation of MEC-17 is essential for both synaptic integrity and for an effective regenerative response after injury. Despite synapses forming normally during development in animals overexpressing *mec-17*, they are specifically lost in older animals due to disrupted microtubule dynamics. Furthermore, animals lacking MEC-17 display a two-fold reduction in regrowth length after injury, largely as a result of growth cone instability. Through analysis of the genetic pathways known to function in synaptic integrity and axonal regeneration, we have identified MEC-17 as a central component for these cellular mechanisms. Overall, we have found that MEC-17 plays a crucial role in preserving synaptic integrity, and in repairing the nervous system after injury.

- **List citations of up to 5 relevant papers published in the past 5 years**

1. Abay ZC, Wong MYY, Teoh JS, Vijayaraghavan T, Hilliard MA, and Neumann B (2017). Phosphatidylserine 'save-me' signals drive functional recovery of severed axons in *Caenorhabditis elegans*. *Proceedings of the National Academy of Sciences USA* 114(47): E10196–E10205.
2. Ritchie FK, Knable R, Chaplin J, Gursansky R, Gallegos M, Neumann B, and Hilliard MA (2017). The heterochronic gene *lin-14* controls axonal degeneration in *C. elegans* neurons. *Cell Reports* 20(12): 2955-2965.
3. Nichols ALA, Meelkop E, Linton C, Giordano-Santini R, Sullivan RK, Donato A, Nolan C, Hall DH, Xue D, Neumann B*, and Hilliard MA* (2016). The apoptotic engulfment machinery regulates axonal degeneration in *C. elegans* neurons. *Cell Reports* 14(7): 1673–1683. *Corresponding authors.

4. Neumann B, Coakley S, Giordano-Santini R, Linton C, Lee ES, Nakagawa A, Xue D, and Hilliard MA (2015). EFF-1-mediated regenerative axonal fusion requires components of the apoptotic pathway. *Nature* 517(7533): 219-222.
5. Neumann B, and Hilliard MA (2014). Loss of MEC-17 leads to microtubule instability and axonal degeneration. *Cell Reports* 6(1): 93-103.

- **Name and Affiliation**

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- **ANS member type**

Ordinary member

- **Early Career Researcher/HDR student?**

No

- **Title and summary of talk**

Title: The tumor suppressor Lethal Giant Larve 1 promotes the axon regeneration through enhancing growthcone recovery in central neurons.

Summary: In the mammalian central nervous system, neurons have extremely low capability to recover from axon injury, which usually leads to the retraction and degeneration of lesioned axon even though the neuronal soma survives. The main underlying reason that impedes its recovery is because the axon have diminished intrinsic capability to regenerate following injury. This prompted us to investigate key molecules that are able to boost the wound healing and regrowth of injured axons. Here, we report a role of Lgl1, the mammalian homolog of Drosophila tumor suppressor Lethal giant larvae, in promoting axon regeneration by enhancing the growth cone recovery. We found that Lgl1 was enriched in the growth cones and was critical for the rapid axon extension after injury. Lgl1 overexpression promoted axon regrowth, whereas its down-regulation attenuated the process. Furthermore, Lgl1 phosphorylation by the atypical protein kinase C (aPKC) inactivated and removed Lgl1 from the growth cone, thereby inhibiting axon regrowth. Consistently, the expression of phospho-mimetic Lgl1 abolished its ability to promote axon regrowth. In contrast, Lgl1 phosphomutant that blocks phosphorylation by aPKC promoted axon regrowth after injury. Finally, Lgl1 expression increased both the formation and dynamics of growth cones initiated from the sites of lesion, an effect that was abolished by aPKC phosphorylation. Thus, Lgl1 under the regulation of aPKC, promotes the dynamic recovery of growth cones from injured axons, a key step for axonal regeneration.

- **List citations of up to 5 relevant papers published in the past 5 years**

1. **Wang T**, Martin S, Nguyen TH, Harper CB, Gormal RS, Martinez-Marmol R, Karunanithi S, Coulson EJ, Glass NR, Cooper-White JJ, van Swinderen B, Meunier FA (2016) Flux of signalling endosomes undergoing axonal retrograde transport is encoded by presynaptic activity and TrkB. *Nature Communications*. **7**: p. 12976.
2. Harper CB, Papadopoulos A, Martin S, Matthews DR, Morgan GP, Nguyen TH, **Wang T**, Nair D, Choquet D, Meunier FA (2016) Botulinum neurotoxin type-A enters a non-recycling pool of synaptic vesicles. *Scientific Reports*. **6**: p. 19654.

3. Narayana VK, Tomatis VM, **Wang T**, Kvaskoff D, Meunier FA (2015) Profiling of free fatty acids using stable isotope tagging uncovers a role for saturated fatty acids in neuroexocytosis. *Cell Chemical Biology*. **22**: p. 1552-61.
4. **Wang T**, Martin S, Papadopulos A, Harper CB, Mavlyutov TA, Niranjana D, Glass NR, Cooper-White JJ, Sibarita JB, Choquet D, Davletov B, Meunier FA (2015) Control of autophagosome axonal retrograde flux by presynaptic activity unveiled using botulinum neurotoxin type A. *Journal of Neuroscience*. **35**: p. 6179-94.
5. Xu XH, Deng CY, Liu Y, He M, Peng J, **Wang T**, Yuan L, Zheng ZS, Blackshear PJ, Luo ZG (2014) MARCKS regulates membrane targeting of Rab10 vesicles to promote axon development. *Cell Research*. **24**: p. 576-94.

- **Name and Affiliation**

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- **ANS member type**

Ordinary member

- **Early Career Researcher/HDR student?**

No

- **Title and summary of talk**

Title: Regulation of myelin morphology during CNS remyelination

Summary: Following demyelination, the adult central nervous system can regenerate myelin-forming oligodendrocytes from either parenchymal oligodendrocyte progenitor cells (OPCs) or neural progenitor cells (NPCs) residing in the subventricular zone. We demonstrate that progenitor identity and the severity of demyelination have marked influences on the morphology of myelin produced by adult-born oligodendrocytes. Whereas adult-born OPCs produce myelin internodes that are thinner, shorter and more numerous than those generated during development, the myelin regenerated by NPCs is of normal thickness and restores orderly nodal structures. Further, we find that both the length and thickness of myelin segments produced by OPCs correlate with the degree of demyelination. Our findings demonstrate that progenitor identity, postnatal age and the degree of local pathology are critical determinants of myelin structure during CNS remyelination.

Significance: Multiple aspects of myelin morphology influence signal conduction along myelinated axons, yet the mechanisms regulating myelin structure remain poorly defined. Our analyses identify intrinsic and extrinsic cues that influence the morphology of myelin produced during CNS remyelination. Modulating these parameters could enable more faithful restoration of signal conduction following demyelinating injury.

- **List citations of up to 5 relevant papers published in the past 5 years**

Mitew S, Gobius I, Fenlon LR, McDougall SJ, Hawkes D, Xing YL, Bujalka H, Gundlach AL, Richards LJ, Kilpatrick TJ, Merson TD*, Emery B* (2018) Pharmacogenetic stimulation of neuronal activity increases myelination in an axon-specific manner. Nat Commun 9:306. *co-senior authors

Walsh DA, Röth PT, Holmes WR, Landman KA, Merson TD, Hughes BD. (2016) Is cell migration or proliferation dominant in the formation of linear arrays of oligodendrocytes? *J Theor Biol* 406:17-30.

Mitew S, Xing YL, Merson TD. (2016) Axonal activity-dependent myelination in development: insights for myelin repair. *J Chem Neuroanat* pii: S0891-0618(16)30029-1.

Xing YL, Röth PT, Stratton JA, Chuang BHA, Danne J, Ellis SL, Ng SW, Kilpatrick TJ, Merson TD. (2014) Adult neural precursor cells from the subventricular zone contribute significantly to oligodendrocyte regeneration and remyelination. *J Neurosci* 34:14128–46.

Merson TD, Castelletto S, Aharonovich I, Turbic A, Kilpatrick TJ, Turnley AM (2013) Nanodiamonds with silicon vacancy defects for nontoxic photostable fluorescent labeling of neural precursor cells. *Opt Lett* 38:4170-3..

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- **ANS member type**

Ordinary member

- **Early Career Researcher/HDR student?**

No

- **Title and summary of talk**

Title: How do Axons degenerate in disease and Injury?

Summary: The degeneration of axons is a key feature of a number of neurodegenerative diseases and injury and a likely cause of the clinical symptoms. The landmark finding that axons can initiate their own self destruction and remodelling pathways has opened up new potential targets for therapeutic intervention in these neurodegenerative conditions. While the mechanisms involved in Wallerian degeneration, which occurs following axon severing, are beginning to be elucidated, the links to axon degeneration in neurodegenerative disease and injury are unclear. The focus of our research is to determine how axons degenerate in disease, the relationship to described forms of axon degeneration and the involvement of axon-soma signaling in this degeneration. To investigate these questions we have developed a number of *in vitro* and *in vivo* models that allow us to separately probe axon and somatodendritic compartments including compartmented microfluidic primary cell culture models and a model using the visual system to separate out somal and axon effects in retinal ganglion cells. Our data indicate that specific insults can differentially affect axon resulting in degeneration by a number of mechanisms including activation of SARM1, failure of axon-soma signaling and axonal caspase activation. Understanding disease specific insults to axons will lead to therapeutic protection in neurological disease.

- **List citations of up to 5 relevant papers published in the past 5 years**

1. Yap YC, **King AE**, Guijt RM, Jiang T, Blizzard CA, Breadmore MC, Dickson TC. (2017). Mild and repetitive very mild axonal stretch injury triggers cytoskeletal mislocalization and growth cone collapse. *PLoS One*, 12(5), e0176997.
2. Farg MA, Sundaramoorthy V, Sultana JM, Yang S, Atkinson RAK, Levina V, Halloran MA, Gleeson P, Blair IP, Soo KY, **King AE**, Atkin JD (2014) C9ORF72, implicated in ALS and FTD, regulates endosomal trafficking. *Hum Mol Genet.* 23:3579-3595
3. **King AE**, Southam K, Dittmann J, Vickers JC (2013). Excitotoxin-induced caspase-3 activation and microtubule disintegration in axons is inhibited by taxol. *Acta Neuropathologica Communications* 1:59.

4. Hosie KA*, **King AE***, Blizzard, CA, Vickers, JC, and Dickson, TC. (2012) Chronic excitotoxin-induced axon degeneration in a compartmented neuronal culture model. *ASN Neuro*. Feb 23;4(1) (* equal contribution)
5. **King AE**, Dickson TC, Blizzard CA, Woodhouse A, Foster SS, Chung RS, Vickers JC. (2011) Neuron-glia interactions underlie ALS-like axonal cytoskeletal pathology. *Neurobiology of Aging*. Mar;32(3):459-69

Proposal Number: 4

Theme: Clinical disorders and injury of the nervous system

Title: New frontiers in gene therapy for neurological disorders

Bradley Turner , Yoshitsugu Aoki , Sue Fletcher , Mary-Louise Rogers , Kara Perrow

A new era has dawned for children diagnosed with spinal muscular atrophy (SMA) with the recent approval of Spinraza®, the first and only gene therapy approved for neurodegenerative disease. The recent triumph of gene therapy for SMA has emboldened the pursuit of gene therapies for other neurological disorders. This Symposium features 4 outstanding speakers who will present their latest advances in the development and application of diverse gene therapy approaches spanning antisense oligonucleotides, immunogenes to lipid nanoparticles for tackling pediatric and adult motor neuron diseases and frontotemporal dementia. Prof. Yoshitsugu (National Center of Neurology and Psychiatry, Japan) will present his ground-breaking research developing novel oligonucleotide-based therapy for targeting toxic *C9orf72* tandem repeat expansions in amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD) using patient-derived stem cell models. He will outline mechanisms of efficacy and challenges in implementing RNA therapy for the brain. Prof. Sue Fletcher (Murdoch University, WA) who pioneered the recently approved gene therapy for Duchenne's muscular dystrophy will provide an authoritative overview of Spinraza® in SMA, from basic science to translation. She will also outline her innovative approaches using antisense oligomers to further improve *SMN2* splicing in SMA using combinatorial gene therapy to silence associated RNA binding proteins in patient-derived cell models. Next, Dr. Mary-Louise Rogers (Flinders University, SA) will showcase the latest advances in immunogene technology to deliver therapeutic genes to target neurons in the CNS. She will demonstrate the efficacy of immunogenes to deliver potent neurotrophic factors to the spinal cord for motor neuron injury and disorders in mouse models. Lastly, Dr. Kara Vine-Perrow (University of Wollongong, NSW) will close the Symposium by presenting her findings on application of novel lipid nanoparticles for therapeutic gene knockdown in the CNS with a focus on zebrafish models. Given the recent approval of gene therapy for SMA, this Symposium is very timely and these 4 speakers will deliver fascinating insights into gene therapies from bench-to-beside for neurological disorders focussing on the spectrum of motor neuron disease to dementia. The recent approval of Spinraza® provides a unique opportunity to showcase approved, developing and upcoming gene therapies for neurology that we believe will be of broad interest to the ANS community.

Speaker 1. Associate Professor Yoshitsugu Aoki, MD, PhD

Laboratory Chief /Associate Professor

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Targeting RNA to treat neuromuscular disease: mechanism and clinical application

The recent discovery of a hexanucleotide repeat expansion in the C9orf72 gene as the causative agent of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) gives rise to the opportunity to develop novel therapies directed at this mutation, which is responsible for a significant proportion of FTD and/or ALS cases. Antisense oligonucleotides are now becoming more widespread in use as gene therapies, and the possibility of chemical modifications that can enhance their properties makes them excellent candidates for drug development. The recent advances in the development of oligonucleotide-based therapies for diseases including Duchenne muscular dystrophy highlight the potential of this approach for targeting the C9orf72 repeat expansion in FTD/ALS. Here I would like to discuss the potential mechanisms and the challenges for developing an oligonucleotide-based therapy for FTD/ALS caused by the C9orf72 repeat expansion.

Key publications in the last 5 years

1. Komaki H, Aoki Y, et al. Systemic administration of the morpholino antisense NS-065/NCNP-01 for exon-53 skipping in Duchenne muscular dystrophy: A phase I study. *Sci. Transl. Med.* Accepted. (IF 16.796)
2. Aoki Y (corresponding), Manzano R, et al. C9orf72 and RAB7L1 regulate vesicle trafficking in amyotrophic lateral sclerosis and frontotemporal dementia. *Brain*. 2017;140:887-897. (IF 10.767)
3. Echigoya Y, Aoki Y, et al. Effects of systemic multiexon skipping with peptide-conjugated morpholinos in the heart of a dog model of Duchenne muscular dystrophy. *Proc Natl Acad Sci U S A*. 2017;114:4213-4218. (IF 9.661)
4. Aoki Y, Ezzat K, et al. Self-Assembly into Nanoparticles Is Essential for Receptor Mediated Uptake of Therapeutic Antisense Oligonucleotides. *Nano Lett*. 2015; 15: 4364-73. (IF 12.712)
5. Aoki Y, Nagata T, Yokota T, Nakamura A, Wood MJ, Partridge T, Takeda S. Highly Efficient in vivo delivery of PMO into regenerating myotubes and rescue in laminin $\alpha 2$ chain-null congenital muscular dystrophy mice. *Hum Mol Genet*. 2013;22:4914-4928. (IF 5.689)

Speaker 2. Professor Sue Fletcher

Deputy Director and Principal Research Fellow

Centre for Comparative Genomics, Murdoch University, Perth, Western Australia

Email: sfletcher@cgc.murdoch.edu.au

Antisense oligomer interventions to reduce the severity of spinal muscular atrophy

Proximal spinal muscular atrophy is a neurodegenerative disease that is the leading genetic cause of infant death, with a pan-ethnic incidence of 1 in 11,000 live births, and is commonly caused by homozygous loss of *SMN1*, the telomeric copy of the gene encoding SMN. *SMN1* and *SMN2* are part of a 500 kb inverted duplication on chromosome 5q13, however, a single nucleotide change in *SMN2* exon 7 creates a splice silencer, leading to production of truncated mRNA transcripts missing exon 7, and a non-functional SMN protein. Antisense oligonucleotide-mediated *SMN2* exon 7 inclusion has shown promise, and the patient community has welcomed regulatory approval of the splice modifying drug *Spinraza*[®]. *SMN2* exon 7 selection is modulated by numerous RNA-binding proteins, including SAM68 and hnRNP A1. Phosphorodiamidate morpholino oligomers designed to induce a frame-shift and knockdown of *SAM68* and *hnRNP A1*, and *SMN2* exon 7 inclusion were evaluated in patient cells. RNA, imaging and functional protein analysis showed both SAM68 and hnRNP A1 knockdown and an increase in functional SMN production. There is therefore potential for antisense oligomers targeting SAM68 and hnRNP A1 to be used in combinatorial therapies for reducing the severity of spinal muscular atrophy.

Key publications in the last 5 years

1. Flynn LL, Mitrapant C, Pitout IL, Fletcher S, and Wilton SD, Antisense oligonucleotide mediated terminal intron retention of the *SMN2* transcript. *Mol Ther Nucleic Acids*, 2018. (in press).
2. Le BT, Adams AM, Fletcher S, Wilton SD, and Veedu RN, Rational Design of Short Locked Nucleic Acid-Modified 2'-O-Methyl Antisense Oligonucleotides for Efficient Exon-Skipping In Vitro. *Mol Ther Nucleic Acids*, 2017. 9: p. 155-161.
3. Fletcher S, Bellgard MI, Price L, Akkari AP, and Wilton SD, Translational development of splice-modifying antisense oligomers. *Expert Opin Biol Ther*, 2017. 17(1): p. 15-30.
4. Toh ZY, Thandar Aung-Htut M, Pinniger G, Adams AM, Krishnaswamy S, Wong BL, Fletcher S, and Wilton SD, Deletion of Dystrophin In-Frame Exon 5 Leads to a Severe Phenotype: Guidance for Exon Skipping Strategies. *PLoS One*, 2016. 11(1): p. e0145620.
5. Wilton SD, Veedu RN, and Fletcher S, The emperor's new dystrophin: finding sense in the noise. *Trends Mol Med*, 2015. 21(7): p. 417-26.

Speaker 3. Dr Mary-Louise Rogers

Lab Head and Senior Research Fellow

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Immunogenes for targeted neurotrophin gene delivery to motor neurons

Neurotrophic factor therapy showed promise in pre-clinical animal trials for ALS/MND. Human trials, however, have been unsuccessful, mostly due to lack of targeting of the treatment to the motor neuron. Our group is developing a non-viral gene delivery system (immunogenes) capable of targeted gene delivery to motor neurons. These comprise monoclonal antibodies to p75 or TrkC receptors on motor neurons (MLR2 and 2B7) conjugated to a cationic co-polymer (PEI-PEG12), capable of binding plasmid DNA (pVIVO2). Initial experimentation with the immunogenes, demonstrated the capability of MLR2 immunogene to deliver pVIVO2 carrying a reporter gene (GFP) specifically to motor neurons from the circulation in neonatal mice. More recent work demonstrates the delivery of genes coding for human insulin-like growth factor 1 (hIGF-1) and human glial cell-derived neurotrophic factor (hGDNF) to motor neurons of neonatal mice and adult SOD1G93A (MND) mice. Following intraperitoneal injection of immunogenes carrying hIGF-1 or hGDNF plasmids, we have used immunohistochemistry or RT-PCR analysis to indicate the presence of these genes in the spinal cord of neonatal mice. We are also investigating p75 and TrkC immunogenes in adult SOD1G93A mice, to determine their efficiency of transfecting motor neurons. Immunogenes have clear potential as MND/ALS treatment and further experimentation, including quantifying the delivery of neurotrophins delivered by immunogenes are currently underway.

Key publications in the last 5 years

1. Shephard S, Wu J, Wiklendt L, Dinning P.G, Chataway T, Schultz D, Benatar M, Rogers M-L. 2017. Urinary p75ECD: A prognostic, disease progression, and pharmacodynamic biomarker in ALS. *Neurology* 88: 1137-1143; Cites 7
2. Delalat B, Sheppard V, Rasi Ghaemi S, Rao S, Prestidge C, McPhee G, Rogers M-L, Donoghue J, Johns T, Kröger K, Voelcker NH. 2015. Targeted drug delivery using genetically engineered diatom biosilica. *Nature Communications* 6:879 Cites 74
3. Rogers, M.-L., Smith, K.S., Matusica, D., Fenech, M., Hoffman, L., Rush, R.A., and Voelcker, N.H. 2014. Non-viral gene therapy that targets motor neurons in vivo. *Frontiers in Molecular Neuroscience* 780. doi: 10.3389/fnmol.2014.00080. Cites 15
4. Shephard, S; Chataway T; Schultz D; Rush R.A, and Rogers M.-L 2014. The Extracellular Domain of Neurotrophin Receptor p75 As a Candidate Biomarker For ALS. *PLOS One*. 9 (1) e87398 doi:10.1371/journal.pone.0087398 Cites 18
5. Secret E, Smith K, Dubljevic V, Moore E, Macardle P, Delalat B, Rogers M-L, Johns T-G, Durand J-O, Cunin F, Voelcker N.H. 2013. Antibody-Functionalized Porous Silicon Nanoparticles for Vectorization of Hydrophobic Drugs. *Advanced Healthcare Materials*. 2(5): 718-27 Cites 85

Speaker 4. Dr Kara Vine-Perrow

Research Fellow and Group Leader Targeted Cancer Therapeutics Laboratory

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Improving the delivery of antisense oligonucleotides to motor neurons using calcium phosphate-lipid nanoparticles

Abnormal accumulation of mutant superoxide dismutase 1 (SOD1) in motor neurons is a pathological hallmark of some forms of ALS. Considering that SOD1 can propagate from cell-to-cell in a prion-like fashion, potentially contributing to the orderly progression of the disease, reducing levels of SOD1 is a promising therapeutic approach. Antisense oligonucleotides (ASOs) can efficiently silence proteins with gain-of-function mutations. However, naked ASOs have a short circulation half-life and are unable to cross the blood brain barrier (BBB) warranting the use of a drug carrier for effective delivery. To improve the delivery of gene therapies to motor neurons in the context of ALS, we have developed calcium phosphate lipid-coated nanoparticles (CaP-lipid NPs) to encapsulate an ASO directed to SOD1. We found the delivery of CaP-lipid NPs is efficacious in a motor-neuron-like established cell line (NSC-34) and in primary motor neuron cultures isolated from murine spinal cords. Significant down-regulation of SOD1 protein expression was confirmed by immunoblotting following the delivery of SOD1 ASO-loaded CaP-lipid NPs. We also describe nanoparticle distribution in the brain, spinal cord and blood circulation of zebrafish, a powerful experimental vertebrate model for studying ALS. Our results suggest that CaP-lipid NPs could be an effective and safe system for the improved delivery of SOD1 ASOs to affected motor neurons in ALS.

Key publications in the last 5 years

1. Belfiore, L.; Spenkelink, L. M.; Ranson, M.; van Oijen, A. M.; Vine, K. L., Quantification of ligand density and stoichiometry on the surface of liposomes using single-molecule fluorescence imaging. *J Control Release* 2018, In press <https://doi.org/10.1016/j.jconrel.2018.03.022>
2. Belfiore, L.; Saunders, D. N.; Ranson, M.; Thurecht, K. J.; Storm, G.; Vine, K. L., Towards clinical translation of ligand-functionalized liposomes in targeted cancer therapy: Challenges and opportunities. *J Control Release* 2018, 277, 1-13.
3. Chen, L.; Watson, C.; Morsch, M.; Cole, N. J.; Chung, R. S.; Saunders, D. N.; Yerbury, J. J.; Vine, K. L., Improving the Delivery of SOD1 Antisense Oligonucleotides to Motor Neurons Using Calcium Phosphate-Lipid Nanoparticles. *Front Neurosci* 2017, 11, 476.
4. Zeineddine, R.; Pundavela, J. F.; Corcoran, L.; Stewart, E. M.; Do-Ha, D.; Bax, M.; Guillemain, G.; Vine, K. L.; Hatters, D. M.; Ecroyd, H.; Dobson, C. M.; Turner, B. J.; Ooi, L.; Wilson, M. R.; Cashman, N. R.; Yerbury, J. J., SOD1 protein aggregates stimulate macropinocytosis in neurons to facilitate their propagation. *Mol Neurodegener* 2015, 10, 57.
5. Vine, K. L.; Lobov, S.; Indira Chandran, V.; Harris, N. L.; Ranson, M., Improved pharmacokinetic and biodistribution properties of the selective urokinase inhibitor PAI-2 (SerpB2) by site-specific PEGylation: implications for drug delivery. *Pharm Res* 2015, 32 (3), 1045-54.

Proposal Number: 36

Theme: Sensory systems

Title: Auditory system: From sound transduction to hearing loss and tinnitus

Srdjan Vlajkovic ¹ , Gary D Housley ² , Wilhelmina Mulders ³ , Peter R Thorne ⁴ , Bryony Nayagam ⁵

1. *Department of Physiology, The University of Auckland, Auckland, New Zealand*
2. *Department of Physiology & Translational Neuroscience Facility, University of New South Wales, Sydney, NSW, Australia*
3. *School of Human Sciences, University of Western Australia, Perth, WA, Australia*
4. *Department of Physiology, The University of Auckland, Auckland, New Zealand*
5. *Departments of Audiology and Speech Pathology and Medical Bionics, The University of Melbourne, Melbourne, Victoria, Australia*

The focus of the symposium is on auditory neuroscience. People with hearing loss represent one of the largest disability groups worldwide, and the prevalence of hearing loss is predicted to rise with an ageing population. This symposium will present recent progress towards understanding some of the biological processes involved in the development of hearing impairment and tinnitus, as well as novel therapeutic ways to mitigate or reverse hearing loss. The topics include feedback control of sound transduction in the cochlea (Prof. Gary Housley), dysfunctional sensory gating in development of tinnitus (A/Prof. Helmy Mulders), preservation of residual hearing after cochlear implantation (Prof. Peter Thorne) and the application of stem cells for regeneration of auditory sensory cells (A/Prof. Bryony Nayagam).

Speakers:

Professor Gary Housley holds the Chair of Physiology and is director of the Translational Neuroscience Facility, School of Medical Sciences, UNSW (Sydney, Australia). His research program is broadly within molecular, cellular and systems physiology in the nervous system, particularly around neuroprotection in the auditory system and CNS. He has contributed prominently to understanding how hearing adapts to noise and ageing. His research has an applied arm with respect to bionics such as the cochlear implant which has led to development of an innovative gene therapy platform for auditory nerve regeneration.

Assoc. Prof. Wilhelmina Mulders holds an academic appointment at the School of Human Sciences at the University of Western Australia. Her research into the auditory system is focused on the plasticity of the auditory system which occurs after hearing loss and is thought to be involved in the generation of tinnitus. This research uses single neuron recordings to investigate increased spontaneous activity following hearing loss and behavioural and gene expression studies in animal models. The second arm of her studies is related to efferent pathways in the auditory system, which modulates afferent activity at every stage from cochlea to the cortex.

Professor Peter Thorne holds a joint appointment in the Section of Audiology and in the Department of Physiology at the University of Auckland. He has recently established the Eisdell Moore Centre for hearing and balance research in NZ and has been appointed as a co-director of Brain Research New Zealand, a national Centre of Research Excellence focussed on the ageing brain. His key current areas of research include role of extracellular purines in the regulation of cochlear function, development of auditory synapses, inflammation and its role in inner ear disease and relationship between hearing loss and cognitive decline.

Assoc. Prof. Bryony Nayagam currently holds a teaching and research position at the University of Melbourne where she heads the Auditory Neuroscience Unit. Her primary research interest is in developing regenerative therapies for hearing loss. Dr Nayagam's laboratory uses a range of experimental techniques including cell and tissue culture and transplantation, confocal imaging, electron microscopy, in vitro and in vivo electrophysiology to study human pluripotent stem cells. Bryony is independently funded by several major funding agencies including NHMRC and The Garnett Passe and Rodney Williams Memorial Foundation.

Professor Gary Housley

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Title: Feedback control of sound transduction in the cochlea

The hearing organ operates across the largest dynamic range of our sensory systems (120 dB) and does so for a lifetime using a finite pool of sensory hair cells as the sound transducer elements. Each of the 4,000 inner hair cells in the organ of Corti are uniquely innervated by type I spiral ganglion afferent neurons, whereas three rows of opposing outer hair cells (OHCs), which function as 'cochlear amplifier' are broadly innervated by a sub-population of type II spiral ganglion neurons. The OHCs are also innervated by cholinergic medial olivocochlear efferent fibres which provide dynamic neural feedback control of the cochlear amplifier. The role of the type II afferent fibres in this efferent feedback loop is emerging and our evidence based on the absence of contralateral suppression in a peripherin knockout mouse model supports a principal role of the afferent input to this reflex. Data from the P2X₂ receptor knockout mouse has revealed an adaptation mechanism that provides sustained and slowly reversible suppression of hearing sensitivity during sustained elevation of the noise floor above the dynamic range of the cochlear amplifier. P2X₂ receptor knockout mice lack temporary threshold shifts during sustained loud noise exposure which makes these mice (and people with mutated P2X₂ receptors) vulnerable to noise-induced hearing loss.

Relevant publications:

- Froud KE, Wong ACY, Cederholm JME, Klugmann M, Sandow SL, Julien J-P, Ryan AF, Housley GD (2015). Type II spiral ganglion afferent neurons drive medial olivocochlear reflex suppression of the cochlear amplifier. *Nature Communications* 6:7115 doi: 10.1038/ncomms8115.
- Housley GD, Morton-Jones R., Vlajkovic SM, Telang RS, Paramananthasivam V, Tadros SF, Wong ACY, Froud KE, Cederholm JME, Sivakumaran Y, Snguanwongchai P, Khakh BS, Cockayne DA, Thorne PR., Ryan AF (2013). ATP-gated ion channels mediate adaptation to elevated sound levels. *Proceedings of the National Academy of Sciences of the U.S.A.* 110, 18:7494-7499.
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- Morton-Jones RT, Vlajkovic SM, Thorne PR Dockayne DA, Ryan AF, Housley GD (2015) Properties of ATP-gated ion channels assembled from P2X₂ subunits in mouse cochlear Reissner's membrane epithelial cells. *Purinergic Signalling* 11(4):551-60.

Assoc. Prof. Wilhelmina Mulders

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Title: Investigations of the mechanisms of tinnitus: Dysfunctional sensory gating

Tinnitus is a common phantom auditory perception that can result in severe stress and depression. However, the neural mechanisms are still unresolved which is hampering the search for a cure. Tinnitus is strongly associated with cochlear trauma, which evokes plasticity in the central auditory system, resulting in altered levels and patterns of spontaneous activity. It has been proposed that tinnitus is generated from these alterations in neural activity in combination with dysfunctional sensory gating at the level of the auditory thalamus. This would allow the altered neural signals reaching the cortex, leading to perception. In our laboratory, we use animal models of cochlear trauma and tinnitus to investigate the underlying neural circuitry of sensory gating. Electrophysiological recordings in auditory thalamus in animals with and without tinnitus were combined with chronic and acute stimulation of prefrontal cortex, which is thought to be an element in sensory gating circuitry. Stimulation was achieved by focal electrodes or by repetitive transcranial magnetic stimulation. Our results demonstrate that prefrontal cortex stimulation can modulate the altered patterns of activity in auditory thalamus and that these effects are different between animals with and without tinnitus. Our data support the notion that sensory gating is involved in tinnitus generation and open up avenues for treatment.

Relevant publications:

- Mulders, W.H.A.M., Vooys, V., Makowiecki, K., Tang, A., Rodger, J. (2016) The effects of repetitive transcranial magnetic stimulation in an animal model of tinnitus, *Sci. Rep.* 6: 38234.
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- Norena A.J., Mulders W.H.A.M. and Robertson D. (2015) Suppression of putative tinnitus-related activity by extra-cochlear electrical stimulation. *J. Neurophysiol.* 113(1):132-43.
- Mulders, W.H.A.M., Barry, K.M., Robertson, D. (2014) Effects of furosemide on central neural hyperactivity and tinnitus after cochlear trauma in guinea pig *PLOS One* 16;9(5):e97948.

Professor Peter Thorne

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Title: Preventing loss of residual hearing and fibrosis following cochlear implantation.

Cochlear implants (CIs) are an important intervention for people with severe to profound sensorineural deafness. The criteria for implantation are changing as more people with residual acoustic hearing in the low frequencies are being implanted with hybrid systems that include acoustic and electrical stimulation. The implant, however, can cause tissue injury resulting in fibrosis and loss of residual cochlear function. This presentation will describe our research to understand the mechanisms of the loss of residual hearing and the fibrosis using a guinea-pig CI model. It will describe our research into the inflammatory changes in the cochlea during implantation and show how fibrosis develops around the electrode and may interact with the basilar membrane leading to loss of acoustic conduction to sensory cells. It will further show the impact of various therapeutic strategies to reduce the fibrosis and protect loss of residual hearing.

Relevant publications:

- Yan D, et al. (2013). Mutation of the ATP-gated P2X2 receptor leads to progressive hearing loss and increased susceptibility to noise. PNAS, www.pnas.org/cgi/doi/10.1073/pnas.1222285110
- Le Floc'h J, et al. (2013) Markers of cochlear inflammation using magnetic resonance imaging. Journal of Magnetic Resonance Imaging doi: 10.1002/jmri.24144
- Housley GD, et al. (2013). ATP-gated ion channels mediate cochlear adaptation to noise. PNAS, 110 (18):7494–7499. doi: 10.1073/pnas.1222295110. (* shared senior authorship).
- Barclay M, et al. (2016) Onset of Sensory Stimulation in the Developing Cochlea Affects the Molecular Make-up of the Excitatory Synapses. Neuroscience 325:50-62
- Vlajkovic SM, et al. (2017) Adenosine receptors regulate susceptibility to noise-induced neural injury in the mouse cochlea and hearing loss Hearing Research 345: 43-51.

Assoc. Prof. Bryony Nayagam

Departments of Audiology and Speech Pathology and Medical Bionics, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Australia, email: b.nayagam@unimelb.edu.au

Title: The application of stem cells for regeneration of auditory sensory cells

The cochlear sensory hair cells and auditory neurons are susceptible to a range of insults which causes their irreversible damage and loss, resulting in hearing loss. We are interested in the application of human pluripotent stem cells to reverse damage to these cell types and thus preserve or restore hearing. This paper will describe two of our key research projects involving *in vitro* hair cell differentiation for disease modelling and *in vivo* application of stem cell-derived neurons to the deaf cochlea. Recent experimentation deriving inner ear hair cells from organoids has illustrated that functional inner ear phenotypes can be produced *in vitro*. We have characterised these hair cell phenotypes using micro-CT, helium microscopy and patch clamp electrophysiology. The described model can be utilised to further interrogate normal hair cell development and differentiation, but also pathological hair cell function for disease modelling applications. In addition, we have developed a novel *in vivo* model to better quantify functional improvements when stem cell-derived sensory neurons are combined with cochlear implantation in the deaf mammalian cochlea. This new focal lesion model allows us to test the functional and tonotopic integration of stem cell-derived neurons into existing circuitry, thus addressing a critical step for all neural stem cell therapy more generally. Whilst currently in the basic research phase, our experimentation is designed to be directly applicable in the clinic, with an emphasis on providing patient-matched stem cells for either disease modelling or surgical transplantation.

Relevant publications:

- Mattei, C., Alshawaf, A.J., D'Abaco, G., **Nayagam, B.A.**, Dottori, M. (2018) Generation of neural organoids from human embryonic stem cells using the rotary cell culture system: effects of microgravity on neural progenitor cell fate. *Stem Cells and Development*. Accepted 16th March 2018: <https://doi.org/10.1089/scd.2018.0012>
- Alshawaf, A.J., Qiu, W., Viventi, S., D'Abaco, G., **Nayagam, B.A.**, Erlichster, M., Chana, G., Overall, I., Ivanusic, J., Skafidas, E., and Dottori, M. (2018) Phenotypic and Functional Characterization of Peripheral Sensory Neurons derived from Human Embryonic Stem Cells. *Scientific Reports*, 8(1):603. doi: 10.1038/s41598-017-19093-0
- Gunewardene, N., Van Bergen, N., Crombie, D., Needham, K., Dottori, M. and **Nayagam, B.A.** (2014). Directing human induced pluripotent stem cells into a neurosensory lineage for auditory neuron replacement. *BioResearch Open Access* 3(4):162-175
- Needham, K., Hyakumura, T., Gunewardene, N., Dottori, M. and **Nayagam, B.A.** (2014). Electrophysiological properties of neurosensory progenitors derived from human embryonic stem cells. *Stem Cell Research*. 12(1):241-249.
- **Nayagam, B. A.**, Edge, A.S., Needham, K., Leung, J., Nayagam, D.A.X., Dottori, M. (2013) An *in vitro* model of developmental synaptogenesis using cocultures of stem cells and cochlear explants. *Stem Cells and Development*, 22:901-912

Proposal Number: 24

Theme: Motor systems

Title: Adaptive learning and plasticity in the motor system

Li-Ann Leow¹, Ann-Maree Vallence, Reza Shadmehr², Jenny Rodger³, Siobhan Schabrun⁴

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2. *Johns Hopkins University, Baltimore*
3. *School of Biological Sciences, The University of Western Australia, Crawley, Western Australia, Australia*
4. *School of Science and Health, Western Sydney University, Penrith, NSW, Australia*

Despite a long history of work on learning and plasticity in the motor system (e.g., Bonnet 1779-1783), we do not yet have a full mechanistic understanding of how motor learning occurs, and what mechanisms drive learning. For example, even apparently trivial actions, such as reaching for an object, require the capacity to adapt movements to delayed, noisy sensory feedback, and to changes in the dynamics of motion. How does the brain accomplish this learning? What drives this learning, and is learning always adaptive? How can we leverage advances in learning and neuroplasticity to improve clinical outcomes in motor impairments?

This symposium highlights recent empirical work from multidisciplinary perspectives, promising fresh insights into the problem of learning and plasticity in the motor system. Shadmehr will first showcase recent breakthroughs in understanding the role of a critical brain region, the cerebellum, in learning to control movements. This work focuses on what cerebellar Purkinje cells encode during adaptive learning, and how Purkinje cells learn to alter their encoding in response to error information. The purpose of adaptive learning is ostensibly to serve adaptive functions (e.g., obtaining rewards and avoiding punishments). Leow will present evidence that shows how adaptive learning is affected by a drive to attain rewards and avoid punishments, but also highlight instances where learning is re-expressed despite serving no adaptive purpose. Maladaptive learning is most evident in chronic musculoskeletal pain, where the re-expression of previous learning often exacerbates the persistence of pain. Schabrun will present neurophysiological work that shines light on homeostatic plasticity mechanisms that could contribute to the persistence of pain. Motor learning is required for successful rehabilitation of movement. Brain stimulation techniques are fast becoming a crucial method of enhancing clinical outcomes in neurological populations that respond poorly to conventional treatments, but the mechanisms through which brain stimulation improves outcomes is poorly understood. Rodger leverages experimental and pre-clinical animal models of disease to investigate how brain stimulation affects synaptic and non-synaptic plasticity during learning, impacting not only on the learning process but also on the motivation and effort exerted to obtain rewards thus providing a mechanistic understanding of how these treatments improve outcomes.

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ANS membership to be obtained prior to commencement of the conference. Non-ECR.

Title: Neural basis of motor learning in the cerebellum

Behavioral studies have long suggested that the ability to make accurate movements depends largely on the cerebellum. Current theories suggest that the cerebellum monitors motor commands and makes predictions about their sensory consequences. These predictions are then updated when sensory errors are experienced, resulting in learning. A central question, however, is with regard to the link between behavioral observations and the neural activity in the cerebellum. How does the cerebellum make predictions? How are these predictions updated following experience of error? Here, I focus on the principal cells of the cerebellum, Purkinje cells, in non-human primates. Firing rates of individual P-cells appear to be poorly related to behavior. However, when P-cells are organized into populations that share the same preference for error, their ensemble neural activity precisely predicts motion of the body part. Following experience of error, the neural activity of the ensemble changes, resulting in trial-to-trial change in the predictions of that population. This suggests that the fundamental unit of computation in the cerebellum is a group of P-cells that share the same preference for sensory error. Our results provide a link between behavioral changes during learning and the neural basis of those changes in the cerebellum.

1. D.J. Herzfeld, Y. Kojima, R. Soetedjo, R. Shadmehr. Encoding of error and learning to correct that error by the Purkinje cells of the cerebellum. *Nature Neuroscience*, in press.
2. S.T. Albert, R. Shadmehr. The neural feedback response to error as a teaching signal for the motor learning system. *Journal of Neuroscience*, 36 (2016) 4832-4845.
3. D.J. Herzfeld, Y. Kojima, R. Soetedjo, R. Shadmehr. Encoding of action by the Purkinje cells of the cerebellum. *Nature*, 526 (2015) 439-442.
4. D.J. Herzfeld, D. Pastor, A.M. Haith, Y. Rossetti, R. Shadmehr, J. O'Shea. Contributions of the cerebellum and the motor cortex to acquisition and retention of motor memories. *Neuroimage*, 98 (2014) 147-158.
5. D.J. Herzfeld, P.A. Vaswani, M.K. Marko, R. Shadmehr. A memory of errors in sensorimotor learning. *Science*, 345 (2014) 1349-1353.

Dr Li-Ann Leow, UQ Development Fellow, Centre for Sensorimotor Performance, The School of Human Movement & Nutrition Sciences, The University of Queensland.

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Presentation title: The role of reward prediction errors in motor learning

Sensorimotor adaptation (i.e., the capacity to adapt movements to unexpected perturbations of sensory feedback) is crucial for our survival. Retention of this learning is evident in faster relearning after returning behaviour to the naive state, a phenomenon known as savings. Evidence shows that savings occurs because we recognize previously encountered errors, however, as perturbations evoke both sensory prediction errors (discrepancies between predicted and actual sensory outcomes of movements), as well as reward prediction errors (unexpected failures to attain a reward), the contributions of these distinct errors to savings remain unclear. Here, we investigate the role of reward prediction errors in learning, by manipulating reward prediction errors independently of sensory prediction errors. Results suggest that a memory of reward prediction errors is both necessary and sufficient for savings during sensorimotor adaptation. This memory of reward prediction errors is triggered by contextual cues, even when this memory is unnecessary to obtain reward. Finally, we show that the memory of reward prediction errors is consolidated by the passage of time, shedding light upon previous controversies surrounding the existence of consolidation in sensorimotor adaptation.

1. L.-A. Leow, W. Marinovic, T.J. Carroll, S. Riek, Cerebellar anodal tDCS increases implicit learning when strategic re-aiming is suppressed in sensorimotor adaptation, PLOS One, DOI (2017).
2. L.A. Leow, R. Gunn, W. Marinovic, T.J. Carroll, Estimating the implicit component of visuomotor rotation learning by constraining movement preparation time, J Neurophysiol, DOI 10.1152/jn.00834.2016(2017) jn 00834 02016.
3. L.-A. Leow, A. De Rugy, W. Marinovic, S. Riek, T.J. Carroll, Savings for visuomotor adaptation require prior history of error, not prior repetition of successful actions, Journal of Neurophysiology, 116 (2016) 1603-1614.
4. L.A. Leow, G. Hammond, A. de Rugy, Anodal motor cortex stimulation paired with movement repetition increases anterograde interference but not savings, Eur J Neurosci, 40 (2014) 3243-3252.
5. L.A. Leow, A. de Rugy, A.M. Loftus, G. Hammond, Different mechanisms contributing to savings and anterograde interference are impaired in Parkinson's disease, Front Hum Neurosci, 7 (2013) 55.

Dr Siobhan Schabrun, National Health and Medical Research Council (NHMRC) Career Development Fellow. Group leader of the Brain Rehabilitation and Neuroplasticity Unit (BRAiN-U) at Western Sydney University.

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ANS membership: ordinary. Non-ECR.

Title: Altered homeostatic plasticity and implications for learning in the presence of pain

Human learning is underpinned by a number of functional and structural mechanisms, including the dynamic expression of long-term potentiation (LTP) and long-term depression (LTD)-like changes in synaptic efficacy. However, in addition to plasticity mechanisms that promote neural ‘changeability’, human learning is governed by plasticity mechanisms that promote stability. These mechanisms, termed homeostatic plasticity, prevent overexpression of LTP and LTD based on the principle of a ‘sliding synaptic threshold’, such that high post-synaptic activity biases the synaptic threshold towards LTD, and low post-synaptic activity biases the synaptic threshold towards LTP. When the brain is exposed to extended periods of afferent input (as occurs during learning), studies have shown the threshold for the induction of LTP and LTD is modulated according to homeostatic principles. Extending this concept, we have shown that sustained periods of nociceptive input, induced by repeated injection of nerve-growth factor into the elbow extensor muscles in humans, disturbs homeostatic plasticity. Altered homeostatic plasticity in response to sustained pain could represent an adaptive response that prevents memory encoding of pain-driven synaptic patterns of activity. Indeed, high levels of LTP, as would be expected if homeostatic mechanisms fail to bias synaptic thresholds toward LTD, is known to impair subsequent learning.

1. Thapa T, Graven-Nielsen T, Chipchase L, Schabrun SM (2018). Disruption of cortical synaptic homeostasis in individuals with chronic low back pain. Clin Neurophys 129:1090-1096.
2. Schabrun SM, Christensen SW, Mrachacz-Kersting N, Graven-Nielsen T (2016). Motor cortex reorganization and impaired function in the transition to sustained muscle pain. Cerebral Cortex 26: 1878-90.
3. Schabrun SM, Elgueta-Cancino E, Hodges PW (2017). Smudging of the motor cortex is related to the severity of low back pain. Spine 42(15):1172-78.
4. Schabrun SM, Weise D, Ridding MC, Classen J (2013). A new temporal window for inducing depressant associative plasticity in human primary motor cortex. Clin Neurophys 124: 1196-203.

Associate Professor Jennifer Rodger. Associate Professor and Senior Research Fellow at the School of Biological Sciences, The University of Western Australia.

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ANS membership: ordinary. Non-ECR.

Using brain stimulation to enhance learning: before, during or after the task?

Repetitive transcranial magnetic stimulation (rTMS) induces plasticity in neural circuits, an effect that interacts with intrinsic brain activity, and has potential to improve performance in healthy individuals and in patients. Here we studied behavioural effects of low-intensity rTMS (LI-rTMS) applied as a priming, concurrent or consolidating intervention during learning tasks in mice.

Using a motor learning task, we delivered daily intermittent theta burst stimulation as a priming or consolidating stimulus to mice completing 10 consecutive days of skilled reaching training. Relative to sham, priming LI-rTMS significantly increased skill accuracy but did not alter the rate of learning over time. In contrast, consolidating LI-rTMS increased the rate of learning but did not alter skill accuracy.

To study the effects of concurrent LI-rTMS, ephrin-A2A5^{-/-} mice were affixed a detachable coil and underwent 2 weeks of 10 minutes daily training in a visual discrimination task with concurrent LI-rTMS. Unexpectedly, task+LI-rTMS mice completed significantly more trials compared to sham, and comparison with wildtypes revealed that ephrin-A2A5^{-/-} mice had reduced accuracy and response rates, suggesting a goal-directed behavioural deficit, which was improved by LI-rTMS.

These results suggest that LI-rTMS can alter specific aspects of learning in a manner dependent on the timing of intervention.

1. Poh E, Makowiecki K, Harvey AR, Rodger J. (2018) Online LI-rTMS during a visual learning task: differential impacts on visual circuit and behavioural plasticity in adult ephrin-A2A5^{-/-} mice. E-neuro accepted 31/01/2018
2. Heath E, Lindberg DR, Makowiecki K, Gray A, Asp AJ, Rodger J*, Choi DS*, Croarkin PE*. Medium- and High-Intensity rTMS Reduces Psychomotor Agitation with Distinct Neurobiologic Mechanisms. Translational Psychiatry Accepted 19/02/2018. * indicates equal contribution.
3. Tang A, Bennett W, Hadrill C, Collins J, Fulopova B, Wills K, Bindoff A, Puri R, Garry M, Hinder M, Summers J, Rodger J. Cauty A. (2018) Low intensity repetitive transcranial magnetic stimulation modulates skilled motor learning in adult mice. Scientific Report, Accepted 22/2/2018
4. Seewoo BJ, Feindel KW, Etherington SJ, Rodger J. (2018) Resting-state fMRI study of brain activation using low-intensity repetitive transcranial magnetic stimulation in rats. Scientific Reports accepted 12/04/2018

Proposal Number: 27

Theme: New techniques in neuroscience

Title: Computational neuroscience and neuroimaging approaches to investigate Integrative Brain Function

Gary F. Egan^{1 2 3}, N. Jon Shah^{2 4}, James Roberts⁵, Paula Sanz-Leon^{6 7}, Phillip G. D. Ward^{1 2 3}, Marta Garrido^{1 8}

1. *ARC Centre of Excellence for Integrative Brain Function, Clayton, Australia*
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3. *Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Clayton, Australia*
4. *Institute of Neuroscience and Medicine, Research Centre Jülich, Jülich, Germany*
5. *QIMR Berghofer Medical Research Institute, Brisbane, Australia*
6. *ARC Centre of Excellence for Integrative Brain Function, Sydney, Australia*
7. *Complex Systems Group, School of Physics, University of Sydney, Sydney, Australia*
8. *Queensland Brain Institute, University of Queensland, Brisbane, Qld, Australia*

Brain function arises from the cohesion of metabolic, vascular, and neuronal systems. It is through the study of these integrated systems in health and disease that we advance our understanding of their complex inter-dependencies and coupling mechanisms. Such investigation requires a diverse array of equipment and expertise, and is undergoing rapid advancement with recent developments in technology. In this symposium, we will cover four areas within this domain: 1) trimodal functional imaging, 2) connectome geometry, 3) functional dynamics, and 4) metabolic imaging.

Prof Jon Shah will present his simultaneous MR-PET-EEG analysis techniques (magnetic resonance imaging – positron emission tomography – electroencephalography). This work is a truly revolutionary integration of neuroimaging methods. The novel trimodal approach has revealed complementary fingerprints that depict energy metabolism, inhibition/excitation balance of neuronal activation, functional connectivity, and electrophysiological signatures. In his talk, Prof Shah will describe his team's findings characterising the default mode network using this approach.

The second presentation will focus upon the connectivity of the brain and its topological complexity. Dr James Roberts has been investigating the spatial characteristics of the human connectome using tractography data in an effort to understand the origin and advantages of structural hubs. He has developed new computational tools for perturbing topology and analysing the resultant connectivity. Dr Roberts analysis has identified particularly fragile regions of the human connectome in which perturbations may underpin neurological and psychiatric disorders.

The third presentation will focus upon computational tools for modelling brain dynamics. Dr Paula Sanz-Leon is an expert on brain simulators and models for predicting the spatiotemporal dynamics of the brain. In her talk, she will describe two mean-field models for predicting dynamics and introduce two brain simulators, namely The Virtual Brain and NFTsim. These approaches allow multiple scales of brain dynamics to be investigated, ranging from single brain areas to the whole brain. With these tools, Dr Sanz-Leon has been developing a comprehensive understanding of brain functional dynamics.

The final presentation will focus upon advanced approaches to measuring simultaneous metabolic and haemodynamic responses. Dr Phillip Ward will present his latest work towards a comprehensive approach to mapping the dynamics of cerebral physiology. Dr Ward has focused upon advancing PET techniques to capture the dynamics of glucose uptake with a temporal resolution of seconds. With MR-PET hardware, he has simultaneously measured metabolic responses (fPET) and blood-oxygen level dependent responses (fMRI) at multi-second resolution. Dr Ward will share his latest findings investigating the integration, coupling and disparity in metabolic and haemodynamic responses in the visual cortex.

Symposium Title: Computational neuroscience and neuroimaging approaches to investigate Integrative Brain Function

Speaker Details:

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ANS member type: None

Early Career Researcher/HDR student? No

Title and summary of talk (no more than 200 words)

Multimodal imaging fingerprints using simultaneous MR-PET-EEG

Simultaneous MR-PET-EEG (magnetic resonance imaging - positron emission tomography electroencephalography), a new tool for the investigation of neuronal networks in the human brain, is a very powerful tool and it will be presented. MRI and PET enable the assessment of molecular metabolic information with high spatial resolution in a given brain simultaneously. EEG provides exquisite access to the temporal dimension at the millisecond level. All three of these methods are being routinely performed at 3T. By way of example, results from the characterization of the brain's default mode network in healthy male subjects using multimodal fingerprinting will be presented. Energy metabolism was quantified via 2- [18F]fluoro-2-deoxy-D-glucose PET, the inhibition – excitation balance of neuronal activation via magnetic resonance spectroscopy (MRS), its functional connectivity via fMRI and its electrophysiological signature via EEG.

The trimodal approach reveals a complementary fingerprint.

In addition to basic neuroscience questions addressing neurovascular- metabolic coupling, this new methodology lays the foundation for individual physiological and pathological fingerprints for a wide research field addressing healthy aging, gender effects, plasticity and different psychiatric and neurological diseases.

Advances to 7T and beyond will also be discussed.

List citations of up to 5 relevant papers published in the past 5 years.

1. Shah NJ. Multimodal neuroimaging in humans at 9.4 T: a technological breakthrough towards an advanced metabolic imaging scanner. *Brain Struct Funct.* 220(4):1867-84, 2015
2. Shah NJ, Oros-Peusquens AM, Arrubla J, Zhang K, Warbrick T, Mauler J, Vahedipour K, Romanzetti S, Felder J, Celik A, Rota-Kops E, Iida H, Langen KJ, Herzog H, Neuner I. Advances in multimodal neuroimaging: hybrid MR-PET and MR-PET-EEG at 3 T and 9.4 T. *J Magn Reson.* 229:101-15, 2013
3. Langen KJ, Galldiks N, Hattingen E, Shah NJ. Advances in neuro-oncology imaging. *Nat Rev Neurol.* 13(5):279-289, 2017
4. Shah NJ, Arrubla J, Rajkumar R, Farrher E, Mauler J, Rota Kops E, Tellmann L, Scheins J, Boers F, Dammers J, Sripad P, Lerche C, Langen KJ, Herzog H, Neuner I. Multimodal Fingerprints of Resting State Networks as assessed by Simultaneous Trimodal MR-PET-EEG Imaging. *Sci Rep.* 7(1):6452, 2017
5. Neuner I, Arrubla J, Felder J, Shah NJ. Simultaneous EEG-fMRI acquisition at low, high and ultra-high magnetic fields up to 9.4 T: perspectives and challenges. *Neuroimage.* 102 Pt 1:71-9, 2014

Symposium Title: Computational neuroscience and neuroimaging approaches to investigate Integrative Brain Function

Speaker Details:

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ANS member type:

Ordinary Member

Early Career Researcher/HDR student?

No

Title and summary of talk (no more than 200 words)

Geometry and fragility of the human connectome

The human connectome is a topologically complex, spatially embedded network. While its topological properties have been richly characterized, the constraints imposed by its spatial embedding are poorly understood. In this talk I will present a recent novel resampling method that enables randomisation of a network while preserving its spatial embedding. Applying this method to tractography data reveals that the brain's spatial embedding – its geometry – makes a major contribution to the topology of the human connectome. For example, geometry accounts for much of the brain's modularity. But geometry is not the sole determinant: the brain's structural hubs would be positioned closer to the geometric centre of the brain if geometry was the only source of topology. Closer analysis of the brain's hubs under weaker randomisation reveals that the brain sits at a local minimum in wiring cost, and that progressive randomisation leads to a topologically unstable regime consistent with a phase transition. Moreover, prefrontal hubs are particularly fragile to perturbations, correlating with the pattern of acceleration of grey matter loss in schizophrenia. This suggests that fragile prefrontal hub connections and topological volatility act as evolutionary influences on complex brain networks, whose set point may be perturbed in neurological and psychiatric disorders.

List citations of up to 5 relevant papers published in the past 5 years.

Roberts JA, Perry A, Lord AR, Roberts G, Mitchell PB, Smith RE, Calamante F, Breakspear M (2016). The contribution of geometry to the human connectome. *NeuroImage* 124:379-393.

Roberts JA, Perry A, Roberts G, Mitchell PB, Breakspear M (2017). Consistency-based thresholding of the human connectome. *NeuroImage* 145:118-129.

Gollo LL , Roberts JA, Cropley VL, Di Biase MA, Pantelis C, Zalesky A, Breakspear M (2018). Fragility and volatility of structural hubs in the human connectome. (in revision)

Symposium Title: Computational neuroscience and neuroimaging approaches to investigate Integrative Brain Function

Speaker Details:

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ANS member type:

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Early Career Researcher/HDR student?

ECR

Title and summary of talk (no more than 200 words)

Computational tools for modelling generalized and subject-specific multiscale brain dynamics.

Abstract:

Robust scientific software is a key neurotechnology to bridge the gap between experiments and theory. When mathematical models and analytic methods become intractable, the use of numerical simulations is essential, if not the only solution, to get a deeper understanding of brain activity in health and disease.

In this talk I will briefly explain the two large families of mean-field models known as neural masses and neural fields which are used to predict the spatiotemporal dynamics of the brain (e.g., like the brain rhythms recorded from electroencephalography, or the responses recorded in fMRI).

Then, I will introduce two open-source brain simulators, The Virtual Brain and NFTsim, which allow for the modelling and simulation of one single brain area (or tissue), to a few interconnected areas to the whole brain. Both TVB and NFTsim handle time delays and complex networks and spatial-temporal propagation, which are crucial features to obtain a complete understanding of brain functional dynamics.

I'll then present published examples of what researchers from diverse backgrounds have achieved (and can achieve) by using these computational tools. Lastly, I will show you that getting started with brain simulations may be just a few clicks away.

List citations of up to 5 relevant papers published in the past 5 years.

1. The Virtual Brain: a simulator of primate brain network dynamics

Sanz-Leon P, Knock SA, Woodman MM, Domide L, Mersmann J, McIntosh AR and Jirsa VK.

Citations: [104] Year: 2013. Frontiers in Neuroinformatics.

NOTE: This paper is one of the top 10 most viewed articles (+25k views) of the journal since the beginning of the journal in 2007.

2. Mathematical framework for large-scale brain network modelling in The Virtual Brain

Sanz-Leon P, Knock SA, Spiegler A and Jirsa VK.

Citations: [65] Year: 2015. Neuroimage.

NOTE: In 2017 Neuroimage was the 4th most cited journal in Neurosciences.

3. Motion clouds: model-based stimulus synthesis of natural-like random textures for the study of motion perception

Leon PS, Vanzetta V, Masson GS and Perrinet LU.

Citations: [23] Year: 2012. Journal of Neurophysiology.

NOTE: This paper lists me as **Leon PS** due to problems handling double family names during the editorial process.

4. Multistability in the corticothalamic system

Sanz-Leon P and Robinson PA. Year: 2017. Journal of Theoretical Biology.

5. NFTsim: Theory and Simulation of Multiscale Neural Field Dynamics

Sanz-Leon P, Robinson PA, Knock SA, Drysdale PD, Abey Suriya RG, Fung F, Rennie CJ, Zhao X.

Year: 2018. PLoS Computational Biology (under review). Available from bioRxiv: doi:

<https://doi.org/10.1101/237032>

Symposium Title: Computational neuroscience and neuroimaging approaches to investigate Integrative Brain Function

Speaker Details:

Name and Affiliation:

Phillip G. D. Ward

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Monash Biomedical Imaging, Monash University, Clayton, Australia

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ANS member type:

Ordinary member

Early Career Researcher/HDR student?

ECR

Title and summary of talk (no more than 200 words)

High temporal resolution measurement of brain function and metabolism using simultaneous dynamic PET and functional MRI.

In this talk, I will describe a novel method of measuring task-evoked metabolic and haemodynamic responses with a temporal resolution of seconds. This approach has immense potential for studying the complex systems underlying energy production and brain function. A reliable and responsive supply of glucose and oxygen is paramount to maintaining brain health, and impairments contribute to the structural and functional neural changes that underlie age-related cognitive decline and neurodegenerative illnesses.

As glucose consumption primarily reflects synaptic transmission, [18F]-fluodeoxyglucose positron emission tomography (PET) brain imaging has long been used as a proxy for studying human neuronal function. However, standard PET has a limited temporal resolution (tens of minutes), rendering studies of dynamic metabolism impractical. In contrast, blood oxygenation level dependent functional magnetic resonance imaging (fMRI) is a measure of neural activity based on the haemodynamic response that provides a temporal resolution of seconds. Recent technological advances in MR-PET scanners allow simultaneous acquisition of fMRI and PET. In response to these developments, we have advanced PET protocols to provide a 'functional' PET (fPET) measure that is temporally consistent with fMRI. With this simultaneous fPET-fMRI approach, the metabolic and haemodynamic behaviour of the brain can be investigated and their relationship probed.

List citations of up to 5 relevant papers published in the past 5 years.

1. S. D. Jamadar, F. Sforazzini, S. Li, **P. G. D. Ward**, J. Baran, Z. Chen, and G. F. Egan. "Fusion analysis of task-based BOLD-fMRI and [18-F] FDG functional PET (fPET) for simultaneous measurement of neuronal metabolism in the visual cortex," *PNAS*, [under review].
2. **P. G. D. Ward**, N.J. Ferris, P. Raniga, D.L. Dowe, A.C.L. Ng, D.G. Barnes, G.F. Egan. "Combining images and anatomical knowledge to improve automated vein segmentation in MRI," *NeuroImage*, 165, **2018**, 294-305.
doi:10.1016/j.neuroimage.2017.10.049.
3. **P. G. D. Ward**, N. J. Ferris, P. Raniga, A. C. L. Ng, D. G. Barnes, D. L. Dowe, and G. F. Egan, "Improved quantification of cerebral vein oxygenation using partial volume correction," *Frontiers in Neuroscience*, 11, **2017**.
doi:10.3389/fnins.2017.00089.
4. **P. G. D. Ward**, A. P. Fan, P. Raniga, A. C. L. Ng, D. G. Barnes, D. L. Dowe, and G. F. Egan, "Improved quantification of cerebral vein oxygenation using partial volume correction," in *14th IEEE International Symposium on Biomedical Imaging*, 14, **2017**, 1133-1136.
doi:10.1109/ISBI.2017.7950716.

Proposal Number: 23

Theme: Limbic and other systems

Title: Novel therapeutic approaches for modulating behavioural responses to stress and reward: Transdiagnostic implications for psychiatry

Susannah J Tye¹, Andrea Gogos², Jennifer L Cornish³, Adam J Walker⁴, Sophie Erhardt⁵

1. *Queensland Brain Institute, The University of Queensland, St Lucia, Queensland, Australia*
2. *Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, VIC, Australia*
3. *Psychology, Macquarie University, North Ryde, NSW, Australia*
4. *IMPACT Strategic Research Centre, Deakin University, Geelong, VIC, Australia*
5. *Physiology & Pharmacology, Karolinska Institutet, Stockholm, Sweden*

Dysregulation of behavioural responses to stress and reward are observed across a large proportion of psychiatric disorders, including mood disorders, drug addiction, and schizophrenia. Available therapeutics remain ineffective for a significant proportion of patients, and novel treatments are urgently needed. The integration of neuroscience and psychiatry can help fast track effective translation of novel treatments. However, critical for this, established neurobiological processes and behavioural outcomes must be the focus, rather than traditional diagnostic categories. Core deficits in stress coping and reward processing represent such well-established neurobiological and behavioural constructs that are observed across a range of psychiatric and neurological disorders. Novel treatments targeting these mechanisms may thus have broad scope for therapeutic potential if focused towards these discrete pathophysiological processes rather than broader and more heterogeneous diagnostic categories. Our potential, as a field, to effectively translate basic neuroscience discoveries from bench to bedside may be limited by the disconnect between basic and clinical science.

This symposium will include presentations by 4 researchers representing 3 Australian states (QLD, NSW and VIC), as well as an international visitor from the Karolinska Institutet in Sweden. Speaker experience ranges from early-career researcher to professor. This symposium will describe the most current neuroscience research into novel and emerging treatment approaches for depression, drug addiction, and schizophrenia, with a focus on animal models. Jennifer Cornish (Macquarie University, NSW) will discuss the therapeutic potential of oxytocin and medicinal cannabinoids for addiction. Adam Walker (Deakin University, VIC) will describe the rapid antidepressant actions of ketamine in a subset of antidepressant resistant animals, and metabolic factors associated with response and non-response therein. Susannah Tye (Queensland Brain Institute, QLD) will discuss the circuit, cellular, and synaptic mechanisms of deep brain stimulation and their role in mediating depression-, mania- and anxiety-like behaviours. Dr Sophie Erhardt (Karolinska Institutet, Sweden), will describe the potential for targeting the kynurenine pathway within the central nervous system in schizophrenia. The symposium will be chaired by Dr Andrea Gogos who has extensive expertise in rodent behavioural studies of neuroendocrine dysfunction and novel endocrine treatment targets. The overlapping impact of each of these treatments on neural mechanisms regulating stress coping and reward processing will be discussed.

The aim of this symposium is to highlight the diversity of emerging treatments for psychiatric illnesses not responsive to other available interventions, while also discussing areas for improvement in the translational pipeline. The important role of basic and translational

neuroscience research aimed at improving treatment options and outcomes for patients with treatment-refractory psychiatric disorders will be discussed, together with the need to strengthen the alignment of preclinical and clinical research protocols. This symposium will be of interest to many Society members, not only those interested in psychiatry, because of the range of molecular substrates and neural systems described as well as the various methodologies used to identify and examine novel treatments.

A/Professor Jennifer L. Cornish, Head Behavioural Neuropharmacology Laboratory

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ANS Member: Full Academic

Novel Therapeutics for Methamphetamine Addiction and Psychosis

The abuse of “ice” (methamphetamine, “METH”) continues to destroy families, careers and lives of users, with current treatments (pharmacological or psychological) inadequate for curing addiction and the associated mental health disorders that develop with repeated METH abuse (psychoses, depression, anxiety). Our aim, using rodent models, is to discover the neurobiological underpinnings of METH abuse and addiction to develop effective pharmacotherapies. One of the most promising pharmacological leads for reducing METH abuse and addiction comes from our work using the neuropeptide oxytocin. Using the model of intravenous METH self-administration in rats we have demonstrated that the systemic administration of oxytocin significantly reduced the relapse potential of re-exposure to METH (1mg/kg, i.p.). We have also shown that the direct administration of oxytocin into reward-related brain areas, such as the nucleus accumbens (NA), significantly reduced METH-seeking behaviour, however these effects of oxytocin are independent of oxytocin receptor activation. More recently we have also investigated the effect of medicinal cannabinoids (cannabidiol) on METH-induced behaviours to show that systemic pretreatment with cannabidiol significantly reduced behavioural sensitization to METH and METH-seeking behaviours. Together these data provide promising avenues for future pharmacotherapy development for METH addicted individuals.

Relevant publications in last 5 years

1. Everett N.A., McGregor I.S., Baracz S.J., **Cornish J.L.** (2018). The role of the vasopressin V1A receptor in oxytocin modulation of methamphetamine primed reinstatement. *Neuropharmacology* 133:1-11.
2. Baracz, S. J., & **Cornish, J. L.** (2013). Oxytocin modulates dopamine-related reward in the rat subthalamic nucleus. *Hormones and Behavior*, 63(2), 370-375.
3. Baracz, S. J., Everett, N. A., McGregor, I. S., & **Cornish, J. L.** (2016). Oxytocin in the nucleus accumbens core reduces reinstatement of methamphetamine-seeking behaviour in rats. *Addiction Biology*, 21(2), 316-325.
4. Hicks, C., **Cornish, J. L.**, Baracz, S. J., Suraev, A., & McGregor, I. S. (2016). Adolescent pretreatment with oxytocin protects against adult methamphetamine-seeking behavior in female rats. *Addiction Biology*, 21(2), 304-315.
5. Baracz, S. J., & **Cornish, J.L.** (2016). The neurocircuitry involved in oxytocin modulation by methamphetamine addiction. *Frontiers in Neuroendocrinology*, 43, 1-18.

Dr Adam J. Walker

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ANS Member: Ordinary Member; Early Career Researcher

Insulin-mediated mTOR signalling differentially correlates with antidepressant effects of ketamine in a rodent model of tricyclic antidepressant resistance

Sub-anaesthetic ketamine elicits rapid antidepressant effects in approximately 50% of patients with treatment-resistant depression (TRD). Animal studies have shown that activation of mammalian target of rapamycin (mTOR), a key mediator of insulin signalling, is critical for ketamine's antidepressant effects at the behavioural and cellular level. To investigate the role of insulin in moderating ketamine activation of mTOR signalling and antidepressant response, we characterised the antidepressant-like effect of ketamine (10mg/kg) in a rodent model of antidepressant resistance induced via chronic pre-treatment with adrenocorticotrophic hormone (ACTH 100µg/d;14d). We found that ketamine elicited an antidepressant-like response in 50% of animals, which was associated with activation of mTOR signalling in the infralimbic cortex and peripheral white blood cells (mean increase). Using *ex vivo* brain cell cultures from ACTH-treated animals, we demonstrated that ketamine application elicited local insulin release and concurrently stimulated mTOR signalling and glucose uptake. Facilitation of insulin signalling in response to the combined administration of ketamine (10mg/kg) with metformin (200mg/kg) improved antidepressant-like response rates in ACTH-treated animals (90% response rate). Taken together, these data suggest that ketamine-mediated insulin signalling may be an important and targetable moderator of mTOR activation and antidepressant efficacy in treatment-resistant individuals.

Relevant publications in last 5 years

1. **Walker AJ**, Foley BM, Sutor SL, McGillivray JA, Frye MA, Tye SJ. Peripheral proinflammatory markers associated with ketamine response in a preclinical model of antidepressant-resistance. *Behav Brain Res*. 2015 Oct 15;293:198-202.
2. **Walker AJ**, Kim Y, Price JB, Kale RP, McGillivray JA, Berk M, Tye SJ. Stress, Inflammation, and Cellular Vulnerability during Early Stages of Affective Disorders: Biomarker Strategies and Opportunities for Prevention and Intervention. *Front Psychiatry*. 2014 Apr 9;5:34.
3. **Walker AJ**, Burnett SA, Hasebe K, McGillivray JA, Gray LJ, McGee SL, Walder K, Berk M, Tye SJ. Chronic adrenocorticotrophic hormone treatment alters tricyclic antidepressant efficacy and prefrontal monoamine tissue levels. *Behav Brain Res*. 2013 Apr 1;242:76-83.
4. Morris G, **Walker AJ**, Berk M, Maes M, Puri BK. Cell Death Pathways: a Novel Therapeutic Approach for Neuroscientists. *Mol Neurobiol*. 2017 Oct 19. doi: 10.1007/s12035-017-0793-y. [Epub ahead of print]
5. Gómez-Coronado N, **Walker AJ**, Berk M, Dodd S. Current and Emerging Pharmacotherapies for Cessation of Tobacco Smoking. *Pharmacotherapy*. 2018

Feb;38(2):235-258.

Dr Susannah J. Tye, Head Functional Neuromodulation & Novel Therapeutics Laboratory

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ANS Member: Ordinary Member

Modulating stress- and reward-related behaviour with Deep Brain Stimulation of the mesoaccumbens dopamine system: Targeting circuit, cellular, and synaptic dysfunction.

Psychiatric illnesses that are refractory to treatment are a source of severe, long-term suffering for millions of patients. For decades, deep brain stimulation (DBS) has been used as an effective treatment for late-stage movement disorders, and more recently it has been trialled in refractory psychiatric disorders, with some success. DBS is thought to be effective primarily because it selectively targets dysfunctional brain circuits that contribute to persistent disease states. Through chronic stimulation, DBS modulates the local target region as well as the broader neural network. Using animal models of depression, mania and anxiety, we have explored the cellular, synaptic and network-level effects of mesoaccumbens DBS. Across these models we have observed that DBS, of either the infralimbic cortex, lateral habenula, nucleus accumbens or ventral tegmental area, functions to normalise aberrant nucleus accumbens dopamine neurotransmission and cellular metabolism to promote synaptic plasticity. This has important implications for acute modulation of responses to stress- or reward-related cues, as well as longer-term neuroadaptive therapeutic consequences. To optimise clinical outcomes, we must align the disease modifying actions of DBS with circuit- and cell-specific pathophysiological processes. The importance of obtaining transdiagnostic metrics of stress- and/or reward-related behaviours in the laboratory and clinic will be discussed.

Relevant publications in last 5 years

1. Kim Y, McGee S, Cieczor JK, Walker AJ, Kale RP, Kouzani AZ, Walder K, Berk M, **Tye SJ**. Nucleus accumbens deep-brain stimulation efficacy in ACTH-pretreated rats: alterations in mitochondrial function relate to antidepressant-like effects. *Transl Psychiatry*. 2016 Jun 21;6(6):e842. doi: 10.1038/tp.2016.84.
2. Kim Y, Morath B, Hu C, Byrne LK, Sutor SL, Frye MA, **Tye SJ**. Antidepressant actions of lateral habenula deep brain stimulation differentially correlate with CaMKII/GSK3/AMPK signaling locally and in the infralimbic cortex. *Behav Brain Res*. 2016 Jun 1;306:170-7. doi: 10.1016/j.bbr.2016.02.039.
3. **Tye SJ**, Miller AD, Blaha CD Ventral tegmental ionotropic glutamate receptor stimulation of nucleus accumbens tonic dopamine efflux blunts hindbrain-evoked phasic neurotransmission: implications for dopamine dysregulation disorders. *Neuroscience*. 2013 Nov 12;252:337-45. doi: 10.1016/j.neuroscience.2013.08.01
4. Adams SD, Kouzani AZ, **Tye SJ**, Bennet KE, Berk M. An investigation into closed-loop treatment of neurological disorders based on sensing mitochondrial dysfunction. *J Neuroeng Rehabil*. 2018 Feb 13;15(1):8. doi: 10.1186/s12984-018-0349-z
5. Kouzani AZ, Kale RP, Zarate-Garza PP, Berk M, Walder K, Tye SJ. Validation of a

Portable Low-Power Deep Brain Stimulation Device Through Anxiolytic Effects in a Laboratory Rat Model. *IEEE Trans Neural Syst Rehabil Eng.* 2017 Sep;25(9):1365-1374. doi: 10.1109/TNSRE.2016.2628760.

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Enhanced production of kynurenic acid associates to increased dopaminergic activity – relation to psychosis and cognitive deficits

The essential amino acid tryptophan is degraded primarily by the kynurenine pathway, a cascade of enzymatic steps leading to the generation of several neuroactive compounds. Of those, kynurenic acid, being an antagonist at N-methyl-D-aspartate (NMDA) and $\alpha 7$ nicotinic receptors, has gained much attention in research related to schizophrenia. In this presentation, data showing elevated kynurenic acid concentration in patients with schizophrenia and how kynurenic acid controls dopaminergic, cholinergic, glutamatergic and GABAergic neurotransmission will be discussed. We will show that elevated brain levels of kynurenic acid relates to psychotic symptoms and cognitive impairments and furthermore, how the kynurenine pathway is highly inducible by immune activation. Another mechanism accounting for the abnormally high central kynurenine and kynurenic acid levels seen in schizophrenia, i.e. reduced expression and activity of the enzyme kynurenine 3-monooxygenase (KMO), hereby shunting the synthesis of kynurenine towards kynurenic acid, will be discussed. Indeed, expression and enzyme activity of KMO is reduced in schizophrenia. Pre-clinical results suggest that reduced synthesis of kynurenic acid by inhibition of kynurenine aminotransferase (KAT) II is a novel target for psychosis and may improve cognitive performance in schizophrenia. Here, we show that blockade of KAT II also decreases rat midbrain dopamine firing.

Relevant publications in last 5 years

- **Erhardt S**, Pocivavsek A, Repici M, Liu XC, Imbeault S, Maddison DC, Thomas MA, Smalley JL, Larsson MK, Muchowski PJ, Giorgini F, Schwarcz R. Adaptive and Behavioral Changes in Kynurenine 3-Monooxygenase Knockout Mice: Relevance to Psychotic Disorders. *Biol Psychiatry*. 2016 Dec 16. pii: S0006-3223(16)33112-2. doi: 10.1016/j.biopsych.2016.12.011. [Epub ahead of print] PMID: 28187857
- Sellgren C, Kegel ME, Ekman CJ, Bergen SE, Sullivan PF, Sklar P, Purcell S, Smoller JW, Magnusson PKE, Hultman CM, Olsson S, Walther-Jallow L, Larsson MK, Svensson CI, Lichtenstein P, Engberg G, **Erhardt S**, Landén M. A genome-wide association study of kynurenic acid in cerebrospinal fluid: implications for psychosis and cognitive impairment in bipolar disorder. *Molecular Psychiatry*, online 15 December 2015, doi of 10.1038/MP.2015.186
- Linderholm KR, Tufvesson-Asp M, Olsson SK, Larsson MK, Gojny M, Hajos M, **Erhardt S**, Engberg G. Reduction in firing of rat dopamine neurons by inhibition of kynurenine aminotransferase II. *Neuropharmacology*, 2015, 102:42-47. PMID: 26514401

- Schwieler L, Larsson MK, Skogh E, Kegel ME, Orhan F, Abdelmoaty S, Finn A, Bhat M, Samuelsson M, Lundberg K, Dahl ML, Sellgren C, Schuppe-Koistinen I, Svensson C, **Erhardt S**, Engberg G. Increased central levels of IL-6 in chronic patients with schizophrenia. *J Neurosci Psychiatry*, 2015, 40(2):126-33. PMID: 25455350
- Lavebratt C, Olsson, S, Backlund S, Frisé L, Sellgren C, Priebe L, Nikamo, P, Träskman-Bendz L, Cichon S, Vawter MP, Ösby U, Engberg G, Landén M, **Erhardt S**, Schalling M. The KMO allele encoding Arg452 is associated with psychotic features in bipolar disorder type 1, and with increased CSF KYNA level and KMO expression. *Mol Psychiatry*. 2014; 19(3):334-41. PMID: 23459468



**Karolinska
Institutet**

I hereby confirm my participation in the Australasian Neuroscience Society meeting in Brisbane, December 2018 if the submitted symposia is accepted.

Sincerely,

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