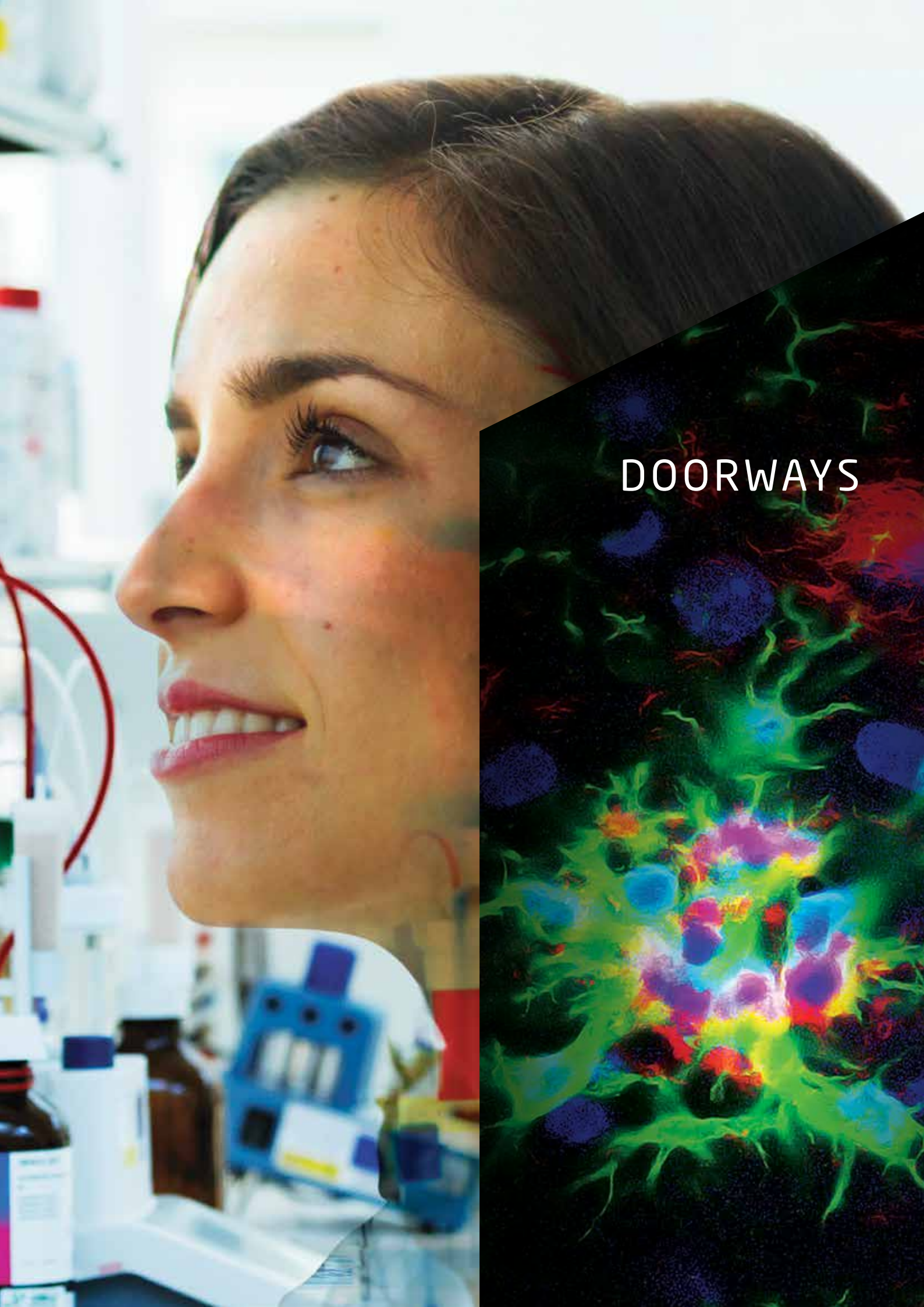
NeuRA

Discover. Conquer. Cure.

Profile 2015

Opening laboratory doors of neuroscience research at NeuRA

Cover Image Jessica Patti, Research Assistant & General Psychologist


DOORWAYS

Doorways to discovery
the search for cures to illness and disease

NeuRA

Advances in neuroscience are unfolding at a breathtaking pace as we seek to transform medical research into real-world improvements in human health. We're excited to open our laboratory doors and share some of our most significant clinical and translational research in the pages that follow.

Our vision is to prevent and cure disease and disability of the brain and nervous system through leadership, excellence and innovation in neuroscience research.

Prof Peter R Schofield

Paul V Brassil

Welcome

Opening laboratory doors to neuroscience research at NeuRA

Medical research is intrinsic to improving health. It enhances our lives with new knowledge and so many new possibilities. It provides rich potential to discover mechanisms that cause disease, previously undiscovered treatment options and, ultimately, ways to protect and improve our health. Without the application of advanced scientific knowledge, it would be difficult to have an efficient and effective public health system which safeguards our health and wellbeing.

In the following pages, you will read about the focus of our research and how we are opening a diverse range of doorways to develop new ideas and make important discoveries. It's always inspiring when, from out of nowhere, there comes a 'eureka moment'. One that puts our research into perspective, solves a longstanding problem, and signifies that we've crossed the threshold from the unknown, to the known.

It is pleasing to report that, through the generous financial support of philanthropist and benefactor Mrs Margarete Ainsworth, we have embarked on the final phase of development of our research facilities. In March, the government announced an investment of $10 million, matching that of Mrs Ainsworth's, to complete the fit-out of the Margarete Ainsworth Building.

In May, the government committed $2.5 million to support the merger of NeuRA and the Schizophrenia Research Institute. Both organisations already have a common focus on schizophrenia research and the merger will allow researchers to fast track the early stages of discovery in the laboratory, to widespread translational and clinical research and clinical trials which will together unlock new treatments and possible cures.

> “Medical research is intrinsic to improving health. It enhances our lives with new knowledge and so many new possibilities.”

We are committed to providing opportunities for the next generation of scientists and clinicians to develop their research ideas – the 'new talent' whose intelligence and dedication will help address the health challenges of today and tomorrow. Some of their research is profiled in the New Horizons section of this publication.

As always, we are indebted to those who support our research financially. Your practical advocacy is instrumental in giving us the capacity to develop innovative health outcomes that arise from our many discoveries.

Paul V Brassil **Prof Peter R Schofield, *FAAHMS PhD DSc***

Dr Leonora Long – ensuring environmental enrichment in animal model research including housing conditions that facilitate enhanced sensory, cognitive and motor stimulation

Blue skies

challenging accepted scientific paradigms and opening doorways to new fields of thinking and study

Medical marijuana

Cannabis, or marijuana, has been used medicinally for millennia.

Assoc Prof Tim Karl is assessing the safety and efficacy of cannabis compounds for treating disease

Research into the medicinal effects of cannabis has recently gained traction. There are over 70 plant constituents, called cannabinoids, expressed in the cannabis plant. One ingredient, $\triangle^9$-tetrahydrocannabinol or THC, has detrimental effects on cognition and schizophrenia. Another component, cannabidiol or CBD, has been found to block some of the negative effects of THC. It also appears to have antipsychotic-like potential.

Studies by Assoc Prof Tim Karl and colleagues show that CBD can block the behavioural effects of psychosis-inducing drugs in humans and also reverse aspects of schizophrenia-like behaviour in a mouse model.

Assoc Prof Karl's research is also focused on CBD's effect on dementia – specifically Alzheimer's disease, or AD. CBD may not only reduce the symptoms of AD but also prevent its development. Preliminary studies found that CBD can counteract some pathological changes in cell models of AD.

In a collaboration with Prof Brett Garner at the University of Wollongong, AD or healthy mice were treated with CBD or a control substance. The AD mice treated with CBD showed robust improvements in tests related to recognising and remembering objects and other mice.

This study is the first of its kind and demonstrates that CBD not only exerts neuroprotective, anti-oxidant and anti-inflammatory effects in cell models, but that CBD actually reverses memory deficits in AD mice.

> A randomised controlled trial is focused on a new treatment.

Conquering low back pain

Low back pain is responsible for the greatest disability burden in Australia – four million Australians suffer from low back pain at any time.

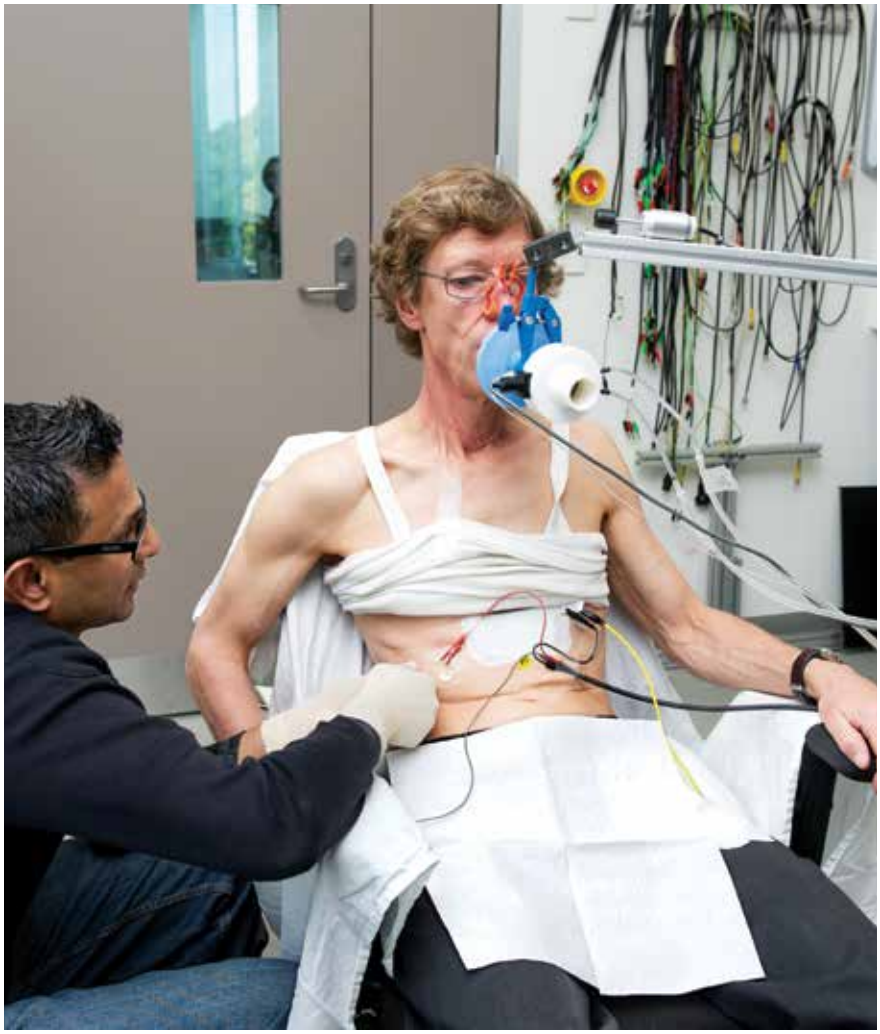
Low back pain is the most common reason for early retirement and cost to the Australian economy exceeds $8 billion per year. Unfortunately, the best available evidence suggests that most treatments for low back pain are not effective at producing meaningful reductions in pain or disability. Dr James McAuley is leading a randomised controlled trial focused on a new treatment which is likely to have a major impact, both in Australia and internationally.

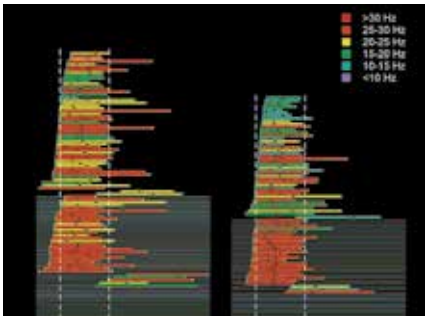
Pain biology education, combined with a sensorimotor retraining program, aims to normalise sensation. The intervention is designed to improve sensory, motor and spatial awareness of the lumbar spine in a graded manner. The initial stage aims to improve familiarity and ownership over the back using graded tactile and spatial discrimination training, implicit and explicit motor imagery training and motor imagery performance. Proprioceptive biofeedback training is also involved, emphasising localised activation. Participants will learn specific independent movement control of their backs. Finally, progressive functional retraining in a feedback rich environment is undertaken. This involves performance of full range spinal movements and specific tasks nominated by the patient as problematic with visual, tactile, proprioceptive and verbal feedback.

This research will establish new targets for intervention and spearhead the development of new treatment approaches to manage this costly and distressing health condition.

Dr James McAuley's research is focussed on the development of new treatments for low back pain

Dr Chaminda Lewis is learning to make intramuscular recordings of activity in the diaphragm with the subject being Prof Simon Gandevia





Colour-coded images of the behaviour of two human breathing muscles

Self-experiments: measuring breathlessness in SCI patients

> The laboratory at NeuRA is the only one in the world to use this technique.

Self-experiments have long been a part of science and medicine.

Self-experimenters have proven invaluable to the medical research community, and to the patients they are seeking to help.

Prof Simon Gandevia is well known for putting himself 'under the microscope' and is perfecting a measurement technique he and his team developed to measure breathlessness in people with spinal cord injury (SCI). Researchers are investigating dyspnoea, the sense of breathlessness, which is common after cervical SCI as a result of partial paralysis or muscle disuse. People living with cervical SCI report dyspnoea as an important symptom. One of the causes is the increased effort, or neural drive, to breathe, due often to their partially paralysed breathing muscles. This can be tested by measurement of the neural drive to the diaphragm, the primary inspiratory muscle, and assessed by measurement of the discharge of single motor units in the diaphragm.

These measurements can be made safely with an electrode inserted through the chest wall below the pleural reflection with the help of ultrasound imaging.

The laboratory at NeuRA is the only one in the world to use this technique – the most accurate method of assessing neural drive to breathe. Researchers will measure the discharge rates of diaphragm single motor units during quiet breathing before and after respiratory muscle exercise training in participants with chronic cervical SCI.

This project will provide the first direct measures of neural drive to the diaphragm in people with SCI and advances understanding of mechanisms underlying any changes in dyspnoea after respiratory muscle training.

Understanding neurogenesis

"Any man could, if he were so inclined, be the sculptor of his own brain."

The above quote was written by Ramón y Cajal more than 100 years ago, but only recently has it been proven true.

In 1998, it was discovered that the hippocampus can generate new neurons throughout a lifespan, not just during neurodevelopment. Furthermore, for better or for worse, experience-dependent changes in neurogenesis are associated with fine-tuning hippocampal function, mainly memory.

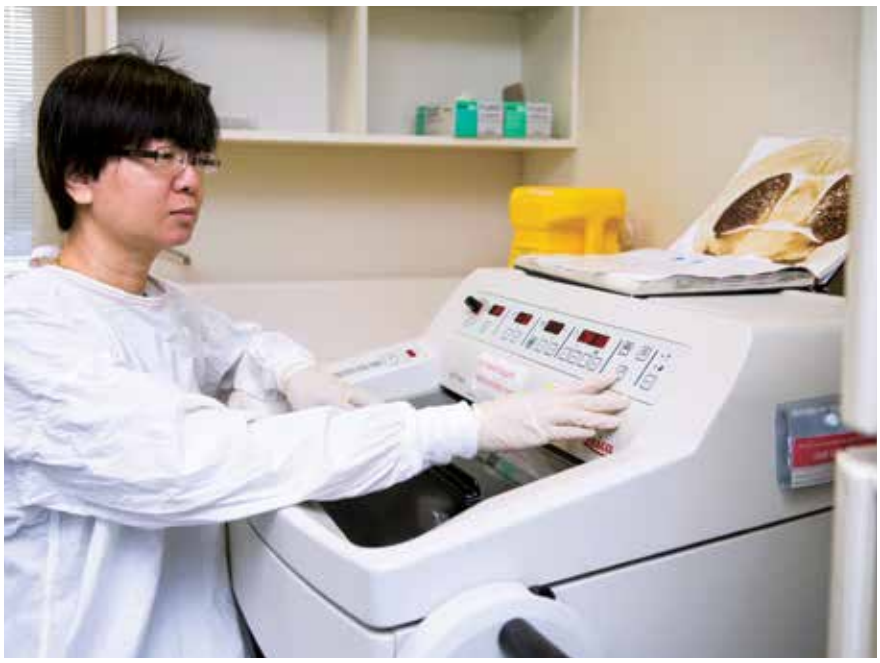
Stress negatively impacts on neurogenesis, but environmental enrichment does the opposite. Scientists in the Paxinos group are investigating what novel experiences may facilitate neurogenesis.

Laboratory mice were treated to highly enriched environments, including spacious housing, varied textures and bedding, exposures to toys and physical exercises, and challenges to balance and memory, such as climbing structures, seesaws, and tunnel mazes. Not least, mice are given pleasant aromas.

> "The hippocampus can generate new neurons throughout a lifespan"

The cells involved in neurogenesis were labeled and the numbers and types of cells were compared to those of mice that didn't have enrichment. An encouraging trend was found for enrichment to increase the number of hippocampal neurons.

The next step is to understand the neural circuitry underlying this change. This project will help in understanding not just how to sculpt brain regions, but how to reform those affected by age-related neurodegeneration.



Dr YuHong Fu prepares tissue for histological analysis

Predicting brain activity

A computer-based model of the visual system has been developed to predict the outcome of future experiments.

Dr Mark Schira has developed software, called stimBOLD, that predicts and computes how the visual cortex processes information. It simulates the same measurement activity without performing an actual MRI.

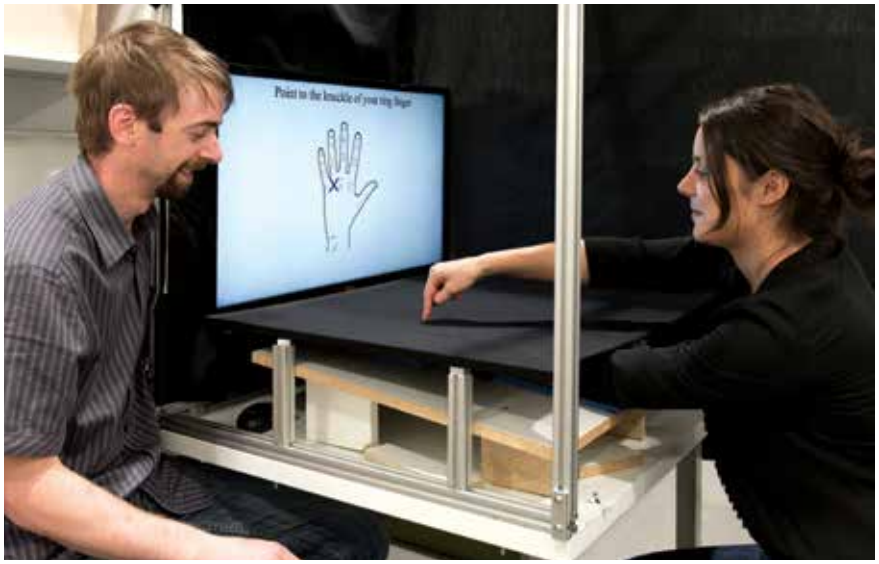
Similar to a weather forecast that predicts future weather patterns using an algorithm, Dr Schira and colleagues have created algorithms that predict how the brain processes visual stimuli, how this processing changes the blood flow, and how these changes will be measured with fMRI.

stimBOLD takes any short 6-7 minute video and approximates what the brain is doing, and will do, when processing visual stimuli. The visual cortex is rather reliable in its behaviour hence why the team created the software around how this area of the brain works.

The algorithms have been created by integrating our existing knowledge about how all these processes work. Implementing such computer software provides proof that this area of the brain is understood well enough to make accurate predictions.

From this, the team will discover exactly where our understanding of the visual cortex might still be lacking. This knowledge will assist in the design of optimal experiments and investigation.

Dr Lee Walsh explains his experiment to a volunteer as she practices the task she will need to perform during the experiment



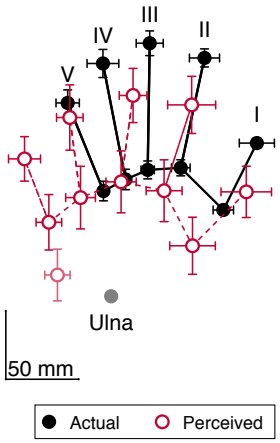
A paradigm shift in proprioception

Proprioception is the sense of our body's own actions. It is how we know where our body is in space.

Disruption to proprioception can occur in many clinical conditions, including dystonia, stroke and Parkinson's disease. When people have problems with proprioception, they cannot make normal movements. Over the last decade, numerous new findings have led to a paradigm shift in how we understand proprioception. This shift is so profound that a 'New' proprioception is being defined.

Classical proprioception is considered to come mostly from signals generated by receptors in the muscle, skin and joints. The 'New' proprioception extends this view as we now know that signals generated in the brain are also important for sensing the body and its movement. This new knowledge is not yet being used in a clinical setting and the testing of people with proprioceptive problems is the same as it has been for 30 years. At the forefront of 'New' proprioception is Dr Lee Walsh, whose work has played a major role in directing these changes in the field.

Dr Walsh works with Prof Simon Gandevia to use the new knowledge to develop tests that can be used in both the laboratory and the doctor's surgery.



The healthy subject's hand was placed on the table and she was asked to point to particular parts of her hand. The black lines are where her hand was; the red lines are where she thought it was. Note that the red (perceived) hand is too short, too wide and in the wrong place.

> In problems with proprioception, people cannot make normal movements.

Developing analysis algorithms

With the study of the human brain, it is interesting to know which parts of the brain are used for particular tasks.

Brain activation patterns can be studied with the aid of functional neuroimaging techniques.

Dr Ben Cassidy's research involves developing analysis algorithms for two methods of functional brain imaging: Functional MRI (fMRI) and Magnetoencephalography (MEG). By improving the algorithms used to examine the data, more accurate and useful results are obtained.

In such a multidisciplinary field it is impossible for any one researcher to be expert in the full scope of neuroimaging experiments; from applied psychology to theoretical physics and statistics there are many factors involved in successful research.

Dr Cassidy's work aims to inform neuroscience researchers about their choice of data analysis techniques, so that they can be confident that their end results will be valid. Functional neuroimaging research has escalated in the past two decades, however the data analysis methods in popular use are often not appropriate to match the increasing complexity of experiments being devised.

Much of his research aims to provide other researchers with the opportunity to conduct new types of cognitive experiments, where previously there would have been no appropriate tools to analyse those results.

This is especially apparent in the analysis of resting-state brain activity, pharmacological effects on the brain, and other such behaviour which cannot be elicited with a simple on-off stimulus pattern during an experiment.

Dr Muireann Irish's research into semantic dementia has revealed striking impairments in theory of mind

The neural signature of theory of mind

In everyday life, we are faced with social situations in which we must consider the perspectives of other people.

> Theory of mind was investigated using a simple task involving cartoon scenes.

Theory of mind (ToM) refers to the uniquely human capacity to infer the beliefs, feelings, and intentions of others.

This innate aptitude to consider perspectives distinct from our own is fundamental to successful social interactions. For example, we can instinctively understand and appreciate how a colleague might feel when their latest paper is rejected. Alterations in theory of mind have been revealed across a number of clinical conditions, including autism, schizophrenia, and bipolar disorder.

In a recent study, Dr Muireann Irish revealed striking impairments in theory of mind in semantic dementia, a subtype of frontotemporal dementia, and has clarified the neural substrates of these deficits.

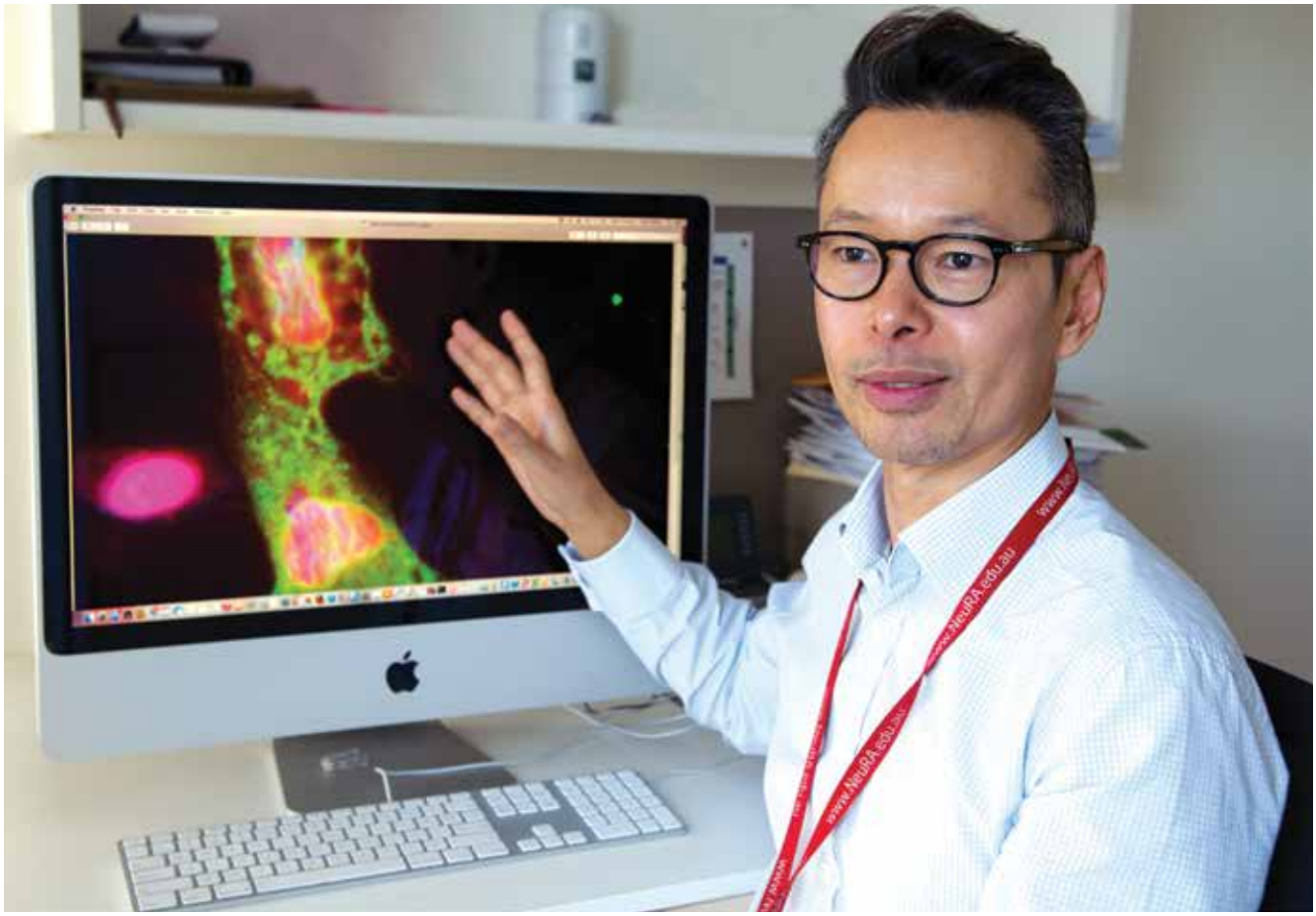
Traditionally, semantic dementia has been conceptualised as a language disorder, with patients exhibiting a global loss of world knowledge. It remained unclear, however, whether theory of mind was also affected in this syndrome. Dr Irish investigated theory of mind using a simple task involving cartoon scenes.

Participants were asked to describe the humorous aspect of the scene, however, in some trials the humour could only be conveyed by referring to the mental state of the cartoon characters. Patients with semantic dementia showed striking difficulties on this ToM task. Using structural neuroimaging analyses, Dr Irish revealed that damage to structures in the right temporal lobe of the brain underpinned ToM deficits in semantic dementia.

This study is the first to clarify the neuroanatomical signature of ToM impairments in semantic dementia and reveals important insights into key components of the 'social brain'.

Structures in the right hemisphere of the brain appear crucial to support complex acts of social inference, allowing us to understand and empathise with others.

Assoc Prof John Kwok shows a fluorescent microscopic image highlighting the SIGMAR1 protein, green, in cultured neuroblastoma cells and the pink stain highlights the nucleus of these cells



Alzheimer's disease – new treatments on the horizon

Researchers have identified a molecular pathway controlled by the SIGMAR1 gene, which may be important in the movement of molecules within a cell.

When not functioning properly, the gene can alter key biochemical pathways involved in Alzheimer's disease and other neurodegenerative disorders. Assoc Prof John Kwok and his team identified mutant forms of the gene in several families with a heritable form of dementia. By understanding how these mutations affect the way the gene performs its normal function, we can start to design strategies to restore the normal function of the gene.

They have identified a panel of drugs that act on the SIGMAR1 gene product currently being used in clinical practice to treat other disorders besides Alzheimer's disease including schizophrenia and anxiety. The researchers will test each one of these compounds to determine which of them result in significant improvement of the treated animal models. As these compounds are already approved for use in humans, they can rapidly move to the next stage of clinical trials without costly pre-clinical testing.

In another neurodegenerative disease, frontotemporal dementia, Assoc Prof Kwok's team has already published a study that identifies the hormone progesterone, which also targets the SIGMAR1 pathway, as a possible treatment for the disease. They have shown that levels of the hormone are significantly lower in patients with frontotemporal dementia compared to healthy people of similar age. They also demonstrate that the hormone had a protective effect by reducing the severity of symptoms in mice that are genetically predisposed to develop this form of dementia. The next step will be to determine whether the hormone can be used as a treatment for frontotemporal dementia patients.

> “These compounds are approved for use and can rapidly move to the next stage of clinical trials.”

tDCS reduces symptoms in schizophrenia

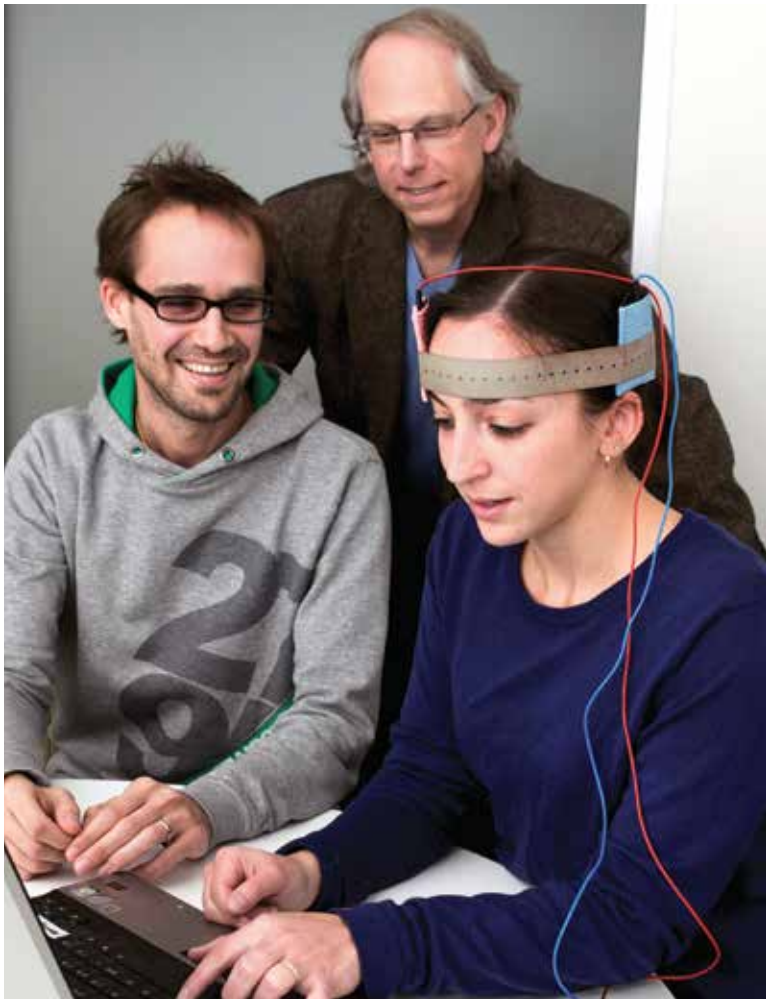
People who suffer from schizophrenia often experience symptoms such as hearing voices and problems with thinking and planning.

Antipsychotic treatments help some people with schizophrenia manage these symptoms but these medications often do not completely reduce them. Therefore, new treatments for people with schizophrenia are urgently needed.

A form of brain stimulation, called transcranial Direct Current Stimulation (tDCS) has been shown to improve thinking in healthy people and reduce some of the symptoms that people with schizophrenia may experience. This form of brain stimulation uses a very mild electrical stimulation that is applied by electrodes placed on the scalp and is considered to be safe.

Dr Tom Weickert is leading a study that is using this technology to increase activity in brain regions important for thinking, planning and problem solving and decrease activity in brain regions that cause symptoms such as hearing voices when there are no voices present. Participants in the study will receive 20 minutes of brain stimulation five days a week for two months while they are playing a computerised game.

The aim of using tDCS in this way is to help those in the community living with schizophrenia to lead more balanced lives by decreasing problematic symptoms associated with the disease.



Dr Thomas Weickert, Jochen Kindler and Danielle Weinberg simulating tDCS

Ben Rowlands

Brain metabolism

It is an often-quoted myth that "we only use 10% of our brain".

In reality, the whole brain is always active and is a highly dynamic organ, with small but rapid fluctuations of tightly controlled activity occurring every second in all brain regions. In neurodegenerative, metabolic and inflammatory diseases of the brain however, metabolic disorder is part of disease pathology. Prof Caroline Rae and PhD student Ben Rowlands believe outcomes of people suffering from neurological disorders may be improved by a process that occurs in the brain known as 'acetylation'.

Acetylation is the attachment of an acetyl group to a protein; this process can significantly modify the protein's function. Acetylation occurs very rapidly on thousands of proteins in the brain, increasing and decreasing the activity of many of the proteins that play important roles in controlling how the brain regulates energy.

Removal of the acetyl group can be achieved by another group of proteins known as Sirtuins which act to restore normal protein function. By selectively targeting these Sirtuins with drugs that are already known to increase life span and reduce ageing, this research will focus on uncovering how acetylation may be key to unlocking how the brain is able to rapidly respond to changes in the environment. This will provide a better understanding of how brain energy levels can be improved during ageing and neurodegenerative diseases.

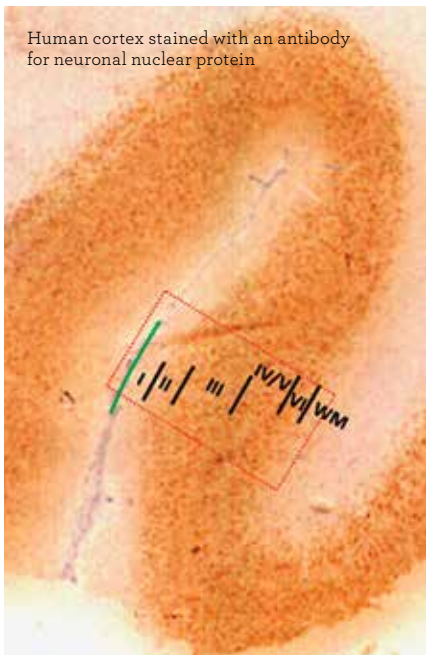
Dr Vibeke Catts has found increased levels of cell death markers in the grey matter of some people with schizophrenia

Biological pathways

for the body to develop and stay healthy, genes, cells and organs must work in unison

Biological factors in schizophrenia

Dr Vibeke Catts is exploring the biological factors that cause cell death in schizophrenia.



Human cortex stained with an antibody for neuronal nuclear protein

Schizophrenia is a debilitating mental illness that typically strikes young people just as they are transitioning into adulthood. The absence of signs of degenerative changes in brain tissue from individuals with schizophrenia has previously led scientists to believe that abnormal foetal brain development dooms vulnerable children to develop schizophrenia later in life.

Dr Vibeke Catts and colleagues recently unveiled evidence that challenges this notion. They found increased levels of cell death markers in the grey matter of some individuals with schizophrenia. This suggests there is an ongoing disease process involving cell death pathways in those with schizophrenia. The levels of cell death markers were associated with decreased numbers of a particular subtype of inhibitory neuron, called somatostatin interneurons.

These regulate the excitability of the common, large pyramidal neurons. But they, themselves, only represent a tiny proportion of the total neuron number in the cortex, which perhaps explains why a decrease in their number may have been overlooked previously.

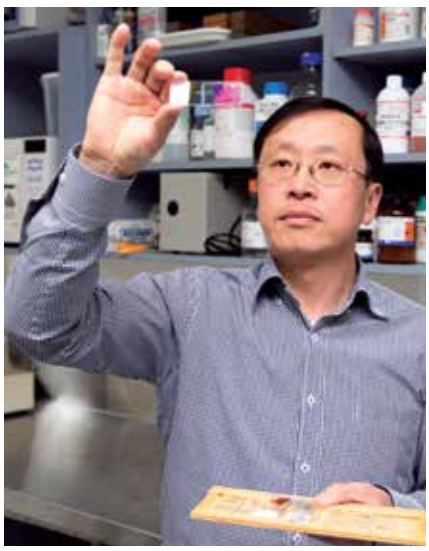
The team now hopes to prove conclusively that somatostatin interneurons express the cell death markers and determine why this type of neuron may be particularly vulnerable to death in individuals with schizophrenia. This knowledge may open possibilities for intervention to provide growth and survival support for these neurons and prevent ongoing cell death.

By activating neural protective mechanisms, researchers may be able to restore cognitive and social function in people living with schizophrenia.

> Researchers may be able to restore cognitive and social function in people living with schizophrenia.

Risk-factor genes in Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder characterised clinically by dementia, and pathologically by abnormal deposition of neurotoxic amyloid-beta peptide in the brain.



Dr Scott Kim studies the role of a particular gene, ABCA7, in the Alzheimer's disease process

In Alzheimer's disease (AD), neurons in certain brain regions degenerate and cannot function properly causing loss of memory and cognitive functions with significant and increasing impairment of everyday activities. The exact cause of AD in the vast majority of cases is still unknown.

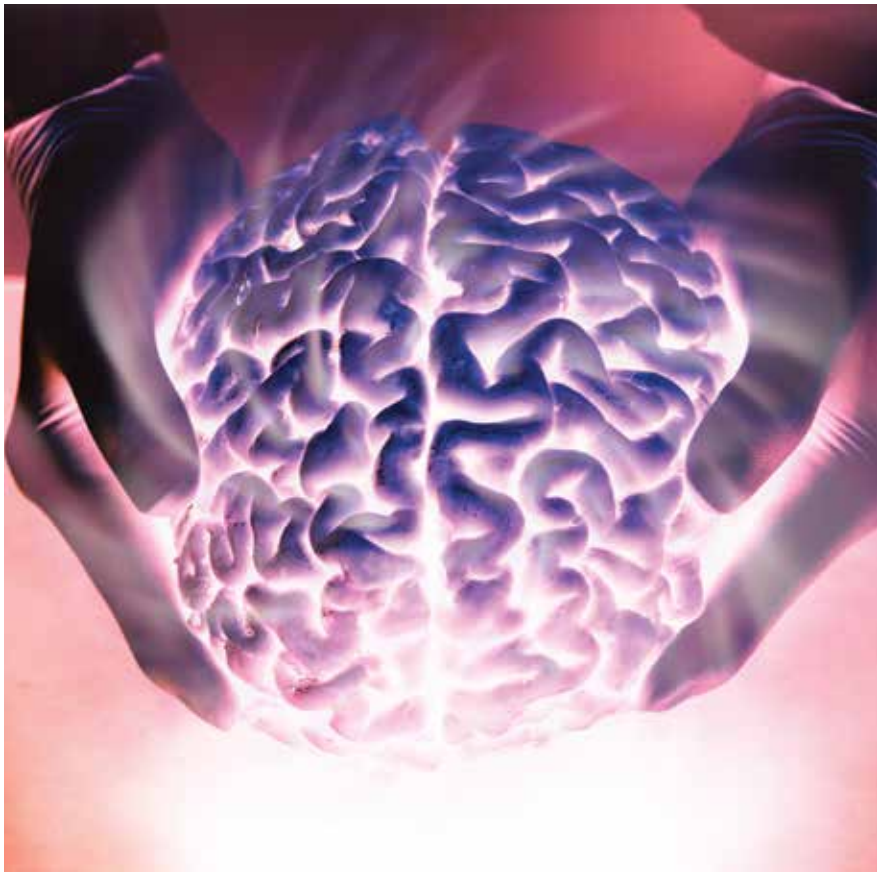
Genome-wide association studies (GWAS) provide an examination of many common genetic variants in different individuals to see if any variant is associated with a disease or trait.

These studies normally compare the DNA of two groups of participants: people with the disease (cases) and similar people without (controls). A recent GWAS comprising 25,900 AD cases and 41,584 controls, revealed that the ABCA7 gene was associated with an increased risk for the disease. ABCA7 is one of several new genes recently identified by large GWAS studies; only apolipoprotein E has a stronger association with Alzheimer's.

The discovery of ABCA7, and other risk-factor genes, has provided significant new insights into understanding how Alzheimer's develops.

To test the hypothesis that ABCA7 is linked to Alzheimer's, Dr Scott Kim generated AD mice that lacked the ABCA7 gene. He found that ABCA7 deletion caused significant increases in the deposition of amyloid-beta peptide in the brain.

The aim of his current research is to determine the exact role of ABCA7 in the disease process. Understanding the underlying molecular mechanisms will reveal new pathways for controlling amyloid-beta pathology and potentially provide new avenues for the therapeutic treatment of Alzheimer's disease.



NeuRA scientists endeavour to understand if the blood brain barrier is compromised in psychosis

Blood brain barrier and psychosis

Researchers are asking a question about schizophrenia that has not been answered before – Is the blood brain barrier compromised in psychosis?

> “Evidence of an increase in inflammatory signals in the blood of people with first episode and chronic schizophrenia is substantial.”

Schizophrenia and bipolar disorder are diseases that affect an estimated 680,000 people in Australia and cost the economy $4.7 billion a year, yet their pathogenic mechanisms are little understood. One idea that has gained momentum recently is that abnormal peripheral immune activation triggers or exacerbates psychosis.

Prof Cyndi Shannon Weickert and colleagues suggest that one way immune activation in the blood could impact the brain is by altering the blood brain barrier (BBB), a multi-cellular structure responsive to signals from the immune cells. The BBB is highly selective to circulating substances. There are multiple mechanisms by which immune activation can disrupt the BBB and lead to harmful neurological outcomes in ageing and neurodegenerative disease. The extent to which this is occurring in psychotic illnesses, that also impact the brain, is unknown.

Evidence of an increase in inflammatory signals in the blood of people with first episode and chronic schizophrenia is substantial. For the first time, the team has also identified elevations in inflammatory signals, or cytokines, inside the brain in a subset of ~30-40% of people with chronic schizophrenia and bipolar disorder.

These findings have led the team to hypothesise that people with psychosis and increased inflammation have an altered BBB. They are now testing the status of the BBB in post-mortem tissue from patients with psychosis and testing for BBB breakdown to determine how increased circulating cytokines in the blood of individuals relate to symptoms of the disease.

Researchers will employ a cellular model of the BBB to test the effect of serum from controls and patients grouped by inflammatory status, and determine the best way to interrupt or repair cytokine induced changes in the BBB.

Importantly, they can test the extent to which their novel therapeutic approach, giving an antibody to block the elevated cytokines (see CATS trial opposite page), can improve the functioning of the BBB and protect the brain from the damaging inflammatory signals that are found in some people with schizophrenia.

CATS clinical trial

A new study using an anti-inflammatory antibody to treat language and memory symptoms of schizophrenia is underway.

There are different causes of schizophrenia, and infection and inflammation may be one of the possible causes. Some people with schizophrenia have hidden signs of immune system activity that do not usually trigger obvious signs and treatment. These hidden signs suggest long-term biological distress.

A new clinical trial led by Dr Thomas Weickert will be the first to test for these hidden signs of infection in people with schizophrenia. It uses a new medication to reduce the harmful by-products of an over activated immune system.

The Canakinumab Add-on Treatment for Schizophrenia (CATS) Study will use a medication called canakinumab, to reduce symptoms and improve thinking in people with schizophrenia. This medicine is approved for use in familial cold autoinflammatory syndrome to reduce the harmful by-products of immune system overactivity.

Canakinumab is a class of medication that decreases the levels of the protein interleukin-1beta (IL-1ß). The IL-1ßprotein is produced in response to inflammation in the body and canakinumab can decrease IL-1ßprotein and inflammation by absorbing, or binding, the interleukin protein.

It is expected that this medication, when used in addition to standard antipsychotics, will result in reduced symptoms and improved thinking abilities in people with schizophrenia who have elevated inflammation markers in their blood.

Prof Cyndi Shannon Weickert is The Macquarie Group Foundation Chair of Schizophrenia Research, a joint initiative of NeuRA, SRI, UNSW and the Macquarie Group Foundation. It is supported by NSW Health.

Prof Cyndi Shannon Weickert and Dr Thomas Weickert are taking a new therapeutic approach to protecting the brain from damaging inflammation in schizophrenia

Clinical heterogeneity

Is it other genes, the environment or life events?

Some patients present with features typical to the behavioural variant of frontotemporal dementia (bvFTD) but do not show any changes on brain imaging and, in many cases, their symptoms remain stable for many years. This results in diagnostic uncertainty. These patients often visit numerous doctors and specialists without ever getting an explanation of their symptoms, which sometimes include prominent psychotic features.

In a recent study aimed at improving diagnosis in bvFTD, Prof John Hodges and colleagues analysed patients with an unclear diagnosis and reviewed their clinical changes over time. Importantly, the team tested for the presence of the C9orf72 genetic abnormality. The presence of this genetic abnormality appeared in approximately half of the patients with an unclear diagnosis.

Within that half, some patients were found to have slow disease progression whilst others deteriorated rapidly, but certainly all had bvFTD.

This study demonstrates the importance of detailed longitudinal follow-up, and highlights the marked clinical differences in patients carrying this genetic abnormality.

Awareness is now being raised amongst clinicians that the C9orf72 genetic expansion needs to be considered when diagnosing, particularly in individuals with normal brain imaging.

Why some patients with an abnormal expansion in the C9orf72 gene progress rapidly whereas others do not remains unclear. Future studies need to establish the contributions of other genes, the environment and life events. These results have implications for patients whose diagnosis can now be confirmed.

Whole exome sequencing to understand bipolar disorder

Current research is focused on the identification of genes implicated in bipolar disorder.

Genetic studies by Dr Claudio Toma show that bipolar disorder, which affects around 1% of the population, is highly heritable. But the causative genes are still largely unknown, despite large-scale international efforts.

The number of genes involved in bipolar disorder is estimated to be high, and each is expected to have a different level of importance in their genetic contribution to the disease.

Families with multiple members affected are more likely to bear mutated genes of strong consequence to the disease.

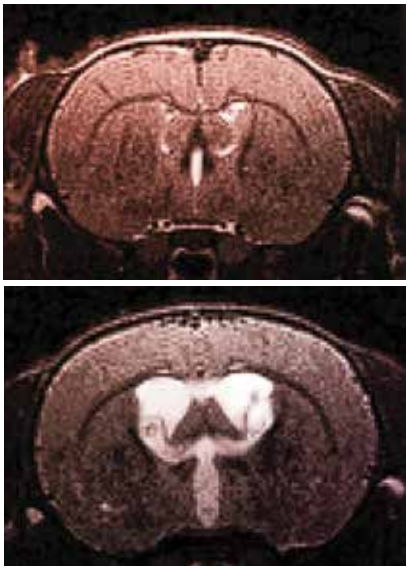
Dr Toma and his colleagues are studying the DNA of 15 families with bipolar disorder, each with at least four affected members. They are sequencing all the genes of selected family members using a technology called 'whole exome sequencing' which allows screening for potentially deleterious mutations shared by affected individuals in the same family.

The aim is to identify genes directly involved in the disease, which will lead to a better understanding of how and why people develop bipolar disorder.

The results of this study will improve early diagnostic procedures and targets for future therapeutic developments.

> "Families with multiple affected members are more likely to bear mutated genes."

Dr Claudio Toma's genetic studies show that bipolar disorder is highly heritable



High resolution anatomical images of a normal (top) and hydrocephalic (below) rat brain acquired using Magnetic Resonance Imaging

Understanding hydrocephalus

Hydrocephalus is a devastating structural neurological disorder marked by enlarged brain ventricles due to accumulation of cerebrospinal fluid.

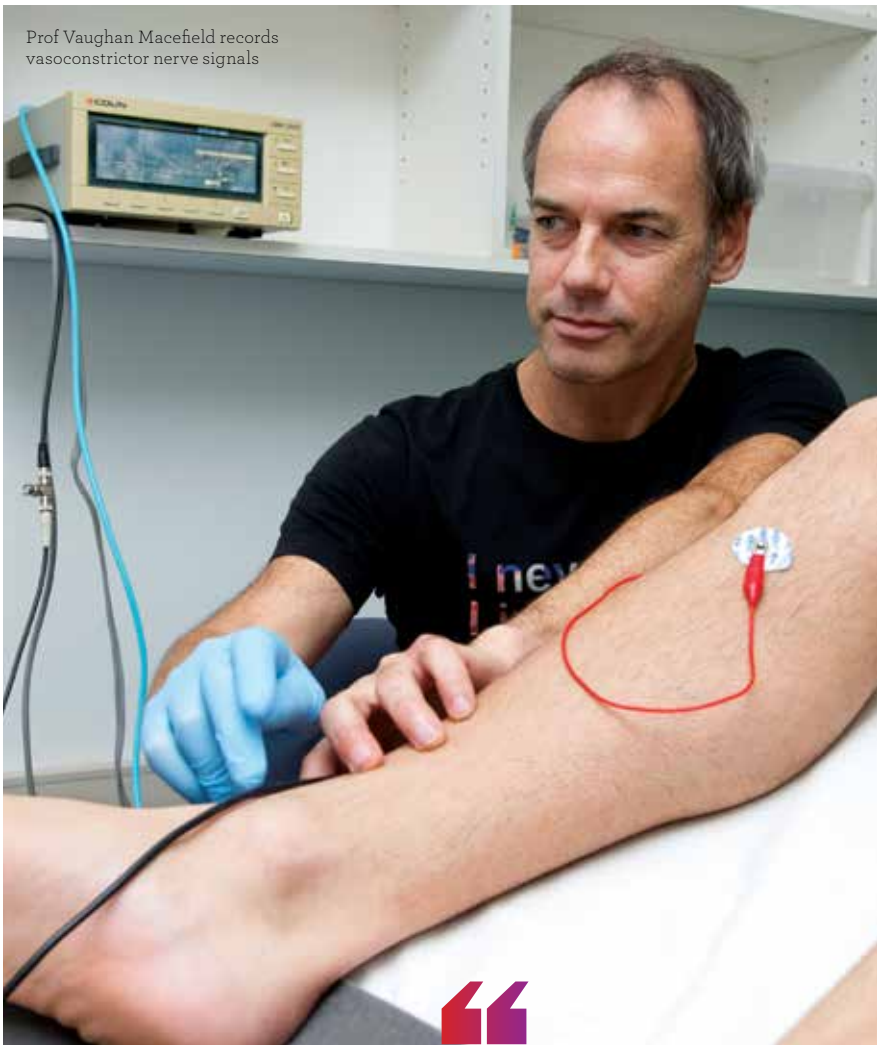
The current treatment and diagnosis of hydrocephalus is inadequate due to a lack of understanding about the mechanisms behind its development. By using novel MR technology, Dr Shaokoon Cheng and Lauriane Juge are tracking how important physiological factors in the brain change during hydrocephalus. The goal is to identify new imaging biomarkers that can help with the diagnosis and prognosis. Change in brain tissue stiffness has been widely known to play an important role during the development of hydrocephalus.

Over the past few decades, scientists have studied this by measuring brain tissue stiffness in-vivo, which requires a craniotomy. This procedure is invasive and brain tissue stiffness measured using this method is limited to the superficial layer and is likely to include stiffness of the dura and other brain tissue structures.

In a world first, by using MR Elastography, the team has characterised how brain tissue stiffness changes during the development of hydrocephalus non-invasively and in the deeper brain regions. This unique finding paves the way to develop MR indices that can be used as treatment prognosis and therefore improve the clinical management for patients.

Blood pressure and the brain

Blood pressure needs to be kept constant – too low and we faint, too high and we may suffer a stroke.



Prof Vaughan Macefield records vasoconstrictor nerve signals

Diseases such as obstructive sleep apnoea (OSA), in which collapse of the upper airways during sleep causes repetitive episodes of low blood oxygen, lead to high blood pressure due to an increase in neural drive to the blood vessels.

Prof Vaughan Macefield and his research team have developed the means of recording the vasoconstrictor nerve signals at the same time as imaging the brain.

It is the only team in the world using this technique to identify areas of the brain responsible for generating vasoconstrictor drive.

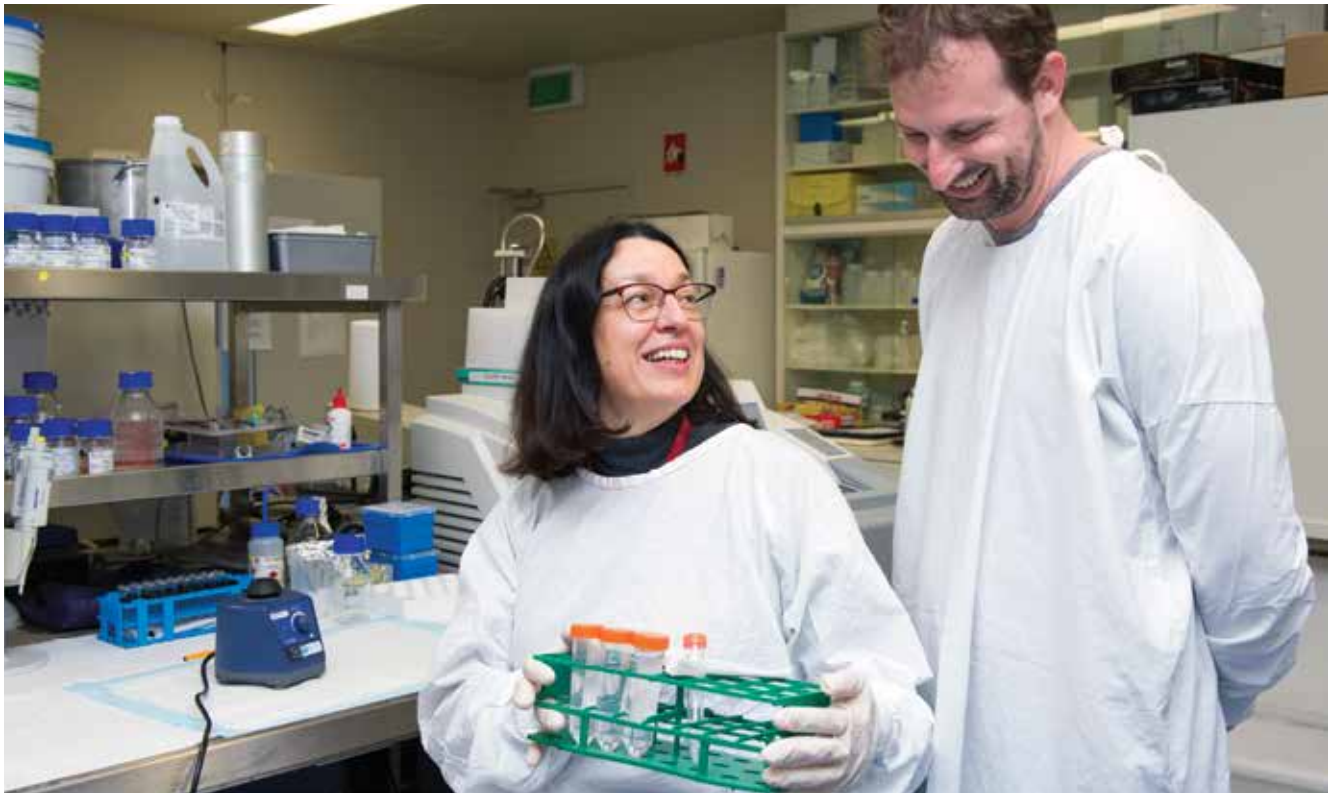
They have just completed a study that followed 20 volunteers with OSA over a year, showing that the structural and functional changes they saw in the brain are essentially reversed by treatment with continuous positive airway pressure (CPAP).

The researchers now plan to investigate other forms of high blood pressure, such as renovascular hypertension – brought about by narrowing of the arteries to the kidneys. By recording nerve signals and brain activity before and after treatment, through balloon distension or stenting of the artery, they will develop a better understanding of any specific damage in areas of the brain controlling blood pressure.

This knowledge may lead to the development of new treatments that will improve the blood pressure of those living with cardiovascular disease.

“It is the only team in the world using this technique to identify areas of the brain responsible.”

Prof Glenda Halliday and Dr Nic Dzamko aim to identify potential transporters that allow alpha-synuclein to be taken up into brain cells



Unraveling the Parkinson's puzzle

Parkinson's disease is defined by the accumulation of a protein called alpha-synuclein in the brain.

How or why this protein accumulates in Parkinson's disease brain cells or what it does is largely unknown, but there is much interest in stopping its accumulation to see if it halts the progression of Parkinson's disease.

Painstaking studies that have taken place both here in Australian and internationally, have established that the alpha-synuclein protein accumulates and spreads through the Parkinson's disease brain in a predictable pattern. This predictable spreading of alpha-synuclein occurs over the 20-30 year Parkinson's disease course gradually affecting more and more brain regions.

Increasing evidence suggests that this spreading of alpha-synuclein occurs in a prion-like manner. That is, alpha-synuclein is taken up by one brain cell and somehow induces the accumulation of endogenous alpha-synuclein in that cell, which is then released and taken up by the next brain cell and so on.

Research by Prof Glenda Halliday and Dr Nicolas Dzamko aims to identify potential transporters, that allow the alpha-synuclein to be taken up into brain cells in the first place.

By examining brain tissue from Parkinson's disease cases, they have identified proteins potentially involved in the uptake and accumulation of alpha-synuclein. These proteins are increased in the Parkinson's disease brain and strongly associate with accumulation of the alpha-synuclein protein. They are currently making brain cells that no longer contain these candidate alpha-synuclein transporters and will determine if they can prevent the uptake of alpha-synuclein and reduce its ability to spread through the Parkinson's disease brain.

“Increasing evidence suggests that this spreading of alpha-synuclein occurs in a prion-like manner.”

It is thought that alpha-synuclein accumulation is bad for brain cells, contributing to their dysfunction and the symptoms of Parkinson's disease. If so, then identifying the proteins responsible for the spread and/or accumulation of alpha-synuclein could now provide new means to treat Parkinson's disease.

The genetics and neuroscience of resilience against trauma

Researchers are paving the way towards a biological resilience signature.

> To address this gap, they are investigating the flipside of mental illness – resilience.

Mental illnesses such as depression and anxiety are among the leading contributors to the burden of disease. These disorders are often triggered by exposure to some sort of traumatic life event. However, not all people exposed to trauma develop a mental illness; some are able to adapt and cope with the stress or may even be resilient. The significant underlying neurobiological and genetic features of resilience still remain largely unknown.

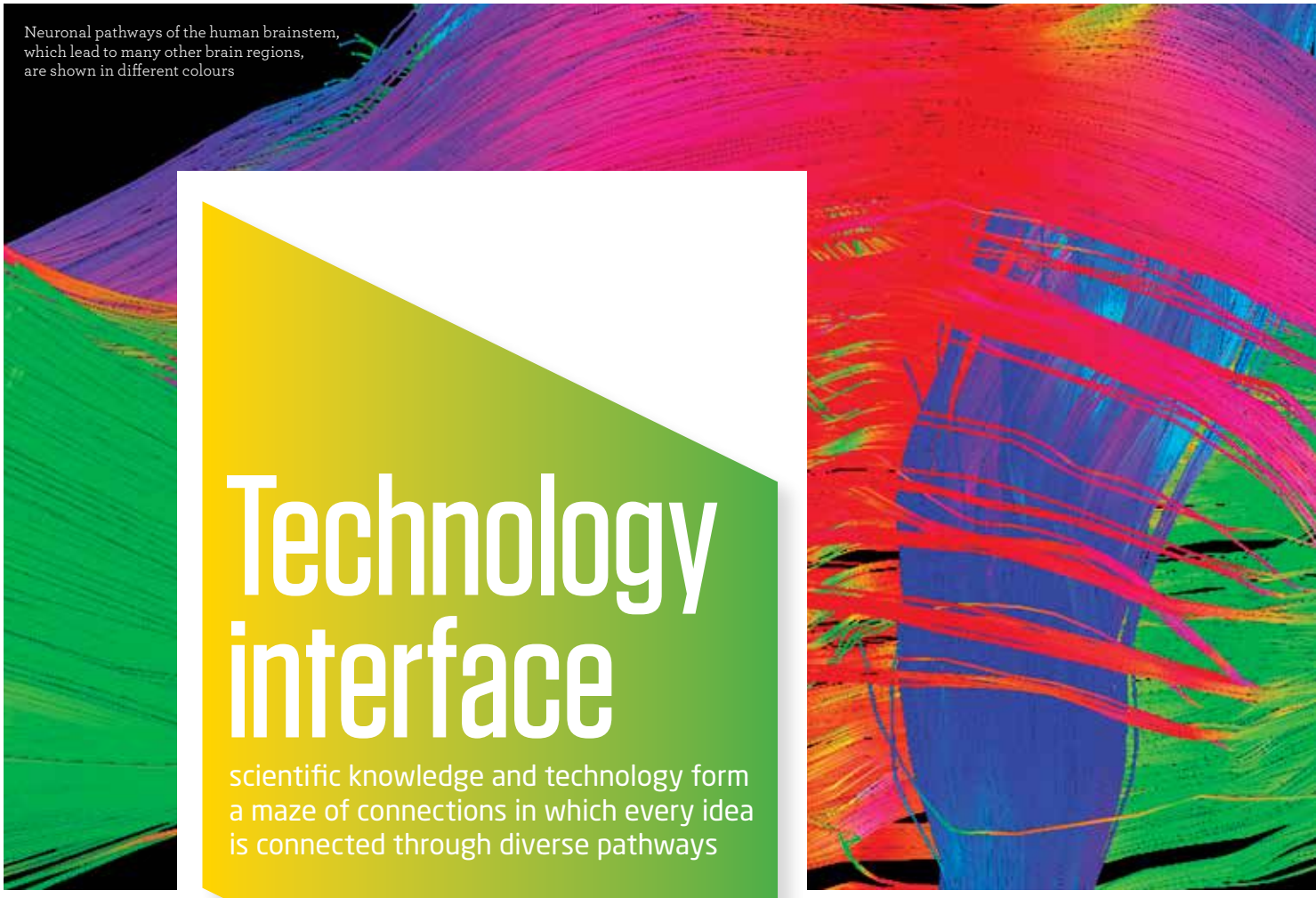
Dr Justine Gatt is investigating the neuroscience of people who are resilient against trauma and serious adversity, and the role our genes and environment have in this process. The contribution of genetics to mental illnesses can vary from 40% for disorders such as major depression and anxiety up to 90% for disorders such as bipolar disorder. The role of environment is also important, with clear evidence highlighting the detrimental impact that stress and trauma can have on the developing brain. Identifying genes that contribute to these illnesses is difficult. Not everybody who experiences trauma develops a mental illness.

To address this gap in knowledge, Dr Gatt and team are investigating the flip side of mental illness – resilience – with the hope that this new approach will grow our understanding of why some people get sick and others do not when exposed to the same traumas.

The research team has now started to measure the factors that contribute to an individual's resilience and has recently developed a questionnaire to measure qualities that define wellbeing and resilience over time called COMPAS-W. Results from this psychological measure can be combined with genetics and brain imaging to start to paint a picture of a biological resilience signature. With this information, the team plans to evaluate possible intervention strategies, such as cognitive brain training strategies, that could be used to promote increased resilience.

The next step is to understand the specific neural pathways that predict levels of resilience to trauma over time.

Dr Justine Gatt is investigating the neuro-genetics of resilience including an examination of ways to promote optimal wellbeing



Neuronal pathways of the human brainstem, which lead to many other brain regions, are shown in different colours

Technology interface

scientific knowledge and technology form a maze of connections in which every idea is connected through diverse pathways

3D brainstem atlas

Histology is the examination of the cellular make up of the brain, and has been the gold-standard for identifying the groups of cells and pathways that have specific characteristics and functions.

Prof George Paxinos

Prof George Paxinos is now producing an electronic atlas of the human brainstem, combining MRI and histological images. In 1995, Prof Paxinos and Xu-Feng Huang produced 'Atlas of the Human Brainstem' where almost 500 structures were outlined at microscopic level. The original stained slices of human brainstem will now be documented electronically in high resolution and reconstructed in 3D, so they can be compared to MRI images.

A series of different magnetic settings can create different contrasts in brain images much like different stains can show up different cells on slices of tissue. The same histologically-defined nuclei and pathways boundaries defined in the Brainstem Atlas, will be identified one by one on the MRI scans.

Until recently, the human brainstem was largely inaccessible to MRI because the structures were too small and the MRI resolution too low. Technical advances have dramatically improved MRI, however, there are still limited frameworks for interpreting the images. Good frameworks for identifying brain structures in MR images are important for accommodating advances in neurosurgery and neurology.
Prof Paxinos' project, funded by the NHMRC, will gather MRI scans from healthy volunteers using a regular 3 Tesla scanner but also using a far more powerful 7 Tesla research-only scanner for even better comparison images.

Extremely high resolution MR microscopy data from postmortem brainstems will also be acquired from collaborators at Duke University, USA.

The project will ultimately create an MRI electronic atlas of the brainstem compatible with tablet computers – a powerful and convenient reference for researchers and clinicians alike.

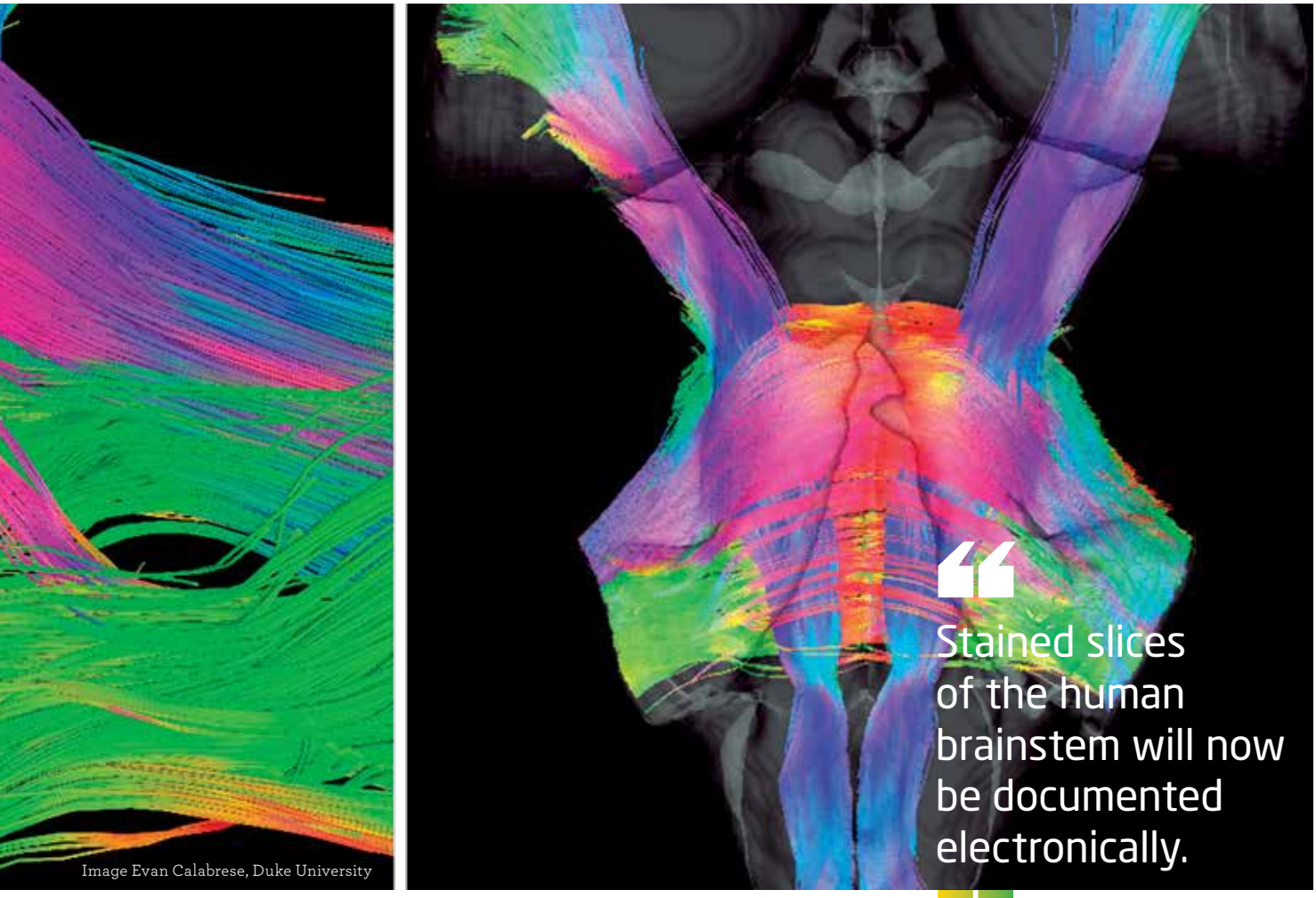


Image Evan Calabrese, Duke University

> Stained slices of the human brainstem will now be documented electronically.

Technology and science – a recipe for independent living

From the age of 65 years and older, falls happen more frequently and affect quality of life.

PhD student Trinidad Valenzuela explains how to use the *Standing Tall* app to participants Robert and Joy Wilson

Accidental falls are a major contributor to the burden of disease in older Australians and a major public health problem. Exacerbating the situation is that many elderly people are reporting an actual fear of falling.

The most effective way to prevent falls is to undertake specific exercises including challenging balance training for at least two hours per week for a minimum of six months. But many older people are unaware that this exercise is a proven effective strategy for preventing falls. The pioneering work of Dr Kim Delbaere and her team includes using new technologies to design individual exercise programs. Mobile apps that assist in the assessment of fall risk have already been released. This technology has opened up many possibilities such as the convenience of 'doing the right training' in your own home via an internet connection.

A new app currently being tested, called *Standing Tall*, is a unique program which offers individually-tailored, progressive and high-intensity balance exercises. It includes an in-built coach and activity planner to encourage users to exercise more frequently. The planner uses goal setting, reminder options, and it also allows for self-monitoring of a user's progress.

Currently the team is conducting a randomised controlled trial to test its effectiveness. If successful, it will promote healthy ageing and enhanced quality of life by reducing falls, at a low cost for the health care sector.

Predicting improved treatment for OSA

Currently it is not possible to predict which Obstructive Sleep Apnoea (OSA) patients will benefit from the use of a mandibular advancement splint, but researchers are aiming to predict outcomes based on new imaging methods.

OSA is a common sleep disorder, most prevalent in middle aged and older males and the obese, in which the upper airway repeatedly collapses during sleep, obstructing airflow. OSA is associated with daytime sleepiness, increased risk of accidents, heart disease and stroke.

Current first line treatment, CPAP, is effective, but poorly tolerated by patients, and thus not well adhered to – only 50% of patients comply. Mandibular advancement splints are an alternative treatment, but are only effective for about half of patients. Predicting who will benefit from them is an important unsolved clinical challenge.

This project, led by Prof Lynne Bilston, aims to test whether two novel imaging biomarkers can predict treatment response to mandibular advancement splints. Prof Bilston's team will also seek to develop simplified versions for clinical use and define how biomechanical and neural factors influence treatment outcome.

> Can two new imaging biomarkers predict treatment response?

In a cohort of 146 OSA patients who are candidates for mandibular advancement splint treatment, tagged MRI methods will be used.

The project has the potential to provide a reliable method of predicting treatment outcomes from mandibular advancement splint therapy. The advantages of this treatment compared to CPAP include simplicity and portability, no requirement for a power supply or battery pack, and better patient acceptance.

Prof Lynne Bilston demonstrates how a mandibular advancement splint repositions the jaw in a more forward position, to widen the upper airway during sleep

Dr Liz de Rome studies test participant Dr Greg Peoples inside a heat chamber at the University of Wollongong

Protecting motorcycle riders

Improving the safety of motorcycle and scooter riders.

Dr Julie Brown's research is in injury prevention on Australian roads. She currently leads a program investigating the quality of motorcycle protective clothing which aims to facilitate the implementation, availability and use of safety technologies to reduce risk of injury to riders. Road traffic injuries are predicted to become the third leading contributor to the global burden of disease after heart disease and major depression by 2020.

Dr Brown and her team, including Dr Liz de Rome, are investigating the risk factors for crashing, how new technologies might help make motorcyclists safer on our roads, the impact of heat and fatigue on riders, and the performance of motorcycle protective clothing currently available on the Australian market.

Recent findings reveal a large variation in the quality of protective clothing being worn by Australian riders, highlighting a need for improvement in the area of impact protection. Data also shows that some motorcycle clothing, if worn on long rides in hot Australian summer conditions, can lead to potentially dangerous increases in body temperature. Work will continue in these areas to reduce motorcycle rider injury.

Shining a light on brain activity in toddlers with autism

Using fNIRS opens doors and provides new opportunities for studying brain activity that was not previously possible.

> Measuring the reflected light gives a way to map the brain activity.

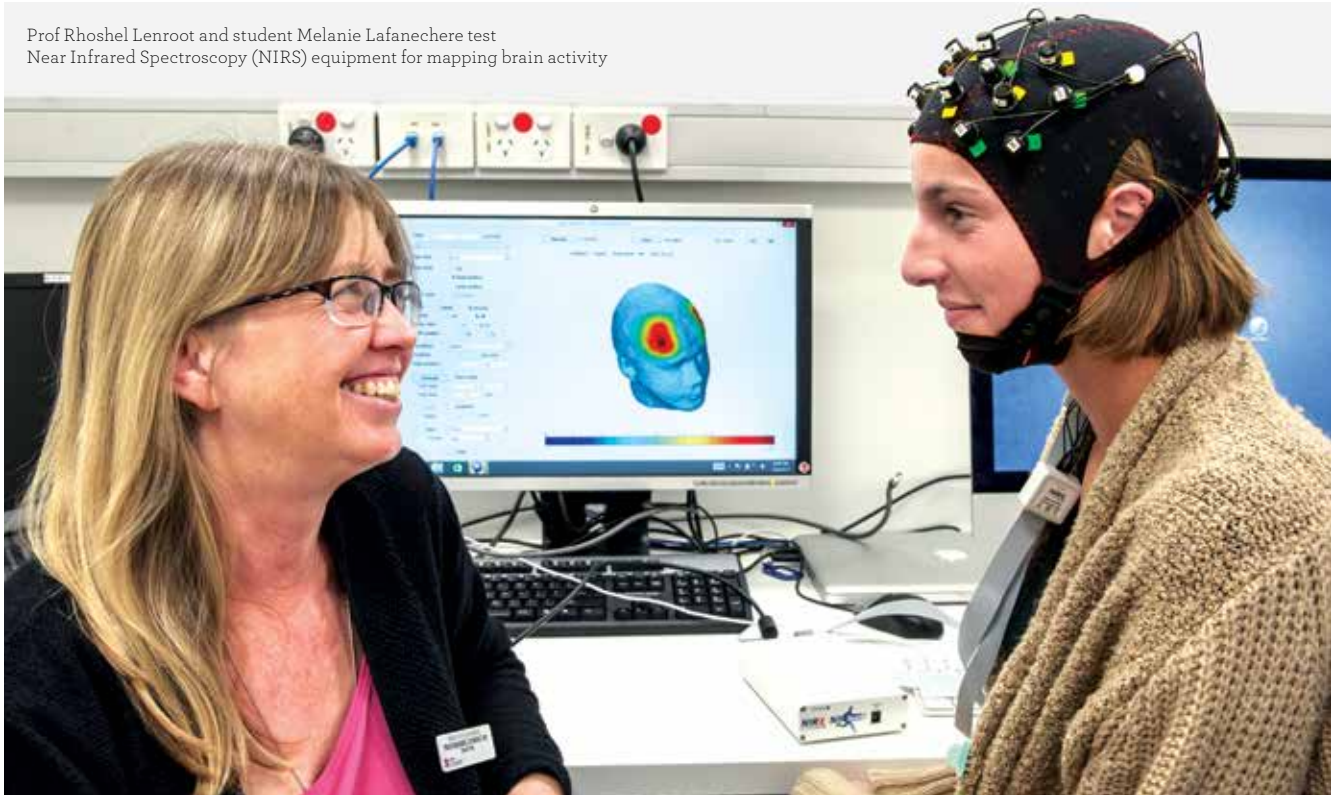
Autism spectrum disorder, or ASD, is a complex developmental disability; signs typically appear during early childhood and affect the ability to communicate and interact with others. There is no known single cause of autism, but increased awareness and early diagnosis and intervention lead to significantly improved outcomes.

Techniques such as functional magnetic resonance imaging, or fMRI, have revolutionised neuroscience by allowing investigators to map differences in brain activity associated with neuropsychiatric disorders such as autism. However, fMRI requires participants to lie still inside an MRI scanner. This limits the kinds of activities people can undertake during an MRI, and some participants also find it difficult to tolerate.

Prof Rhoshel Lenroot and her research team have introduced a recently developed technique called Functional Near-Infrared Spectroscopy, or fNIRS. This measures brain activity using light giving researchers a new way of studying brain activity in real-world settings.

Very low frequency, or near-infrared, light is projected from special optodes, like miniature flashlights, that are set in a cap similar to that used in an EEG. The light goes through the skin, muscle, and skull and into the outermost layers of the brain. While much of this light is absorbed, some is reflected back outside the head where it can be detected and measured by special sensors. The amount of reflected light varies with the level of activity of different brain areas; measuring this variation in the reflected light provides a way to map brain activity.

The first project Prof Lenroot's group is undertaking is to study any significant effects on brain activity of an intensive early intervention program for toddlers with autism.



Prof Rhoshel Lenroot and student Melanie Lafanechere test Near Infrared Spectroscopy (NIRS) equipment for mapping brain activity

Restoring balance function using a take-home rehabilitation device

Dizziness and imbalance after vestibular organ injury affect about 800,000 Australians and, due to health care and work lost, is estimated to cost the Australian economy $28 billion per year.

Assoc Prof Migliaccio is wearing the device head-unit that contains the head orientation sensors and the micro-mirror controlled laser system

> A major complaint after injury is the inability to maintain stable vision.

A major complaint after injury is the inability to maintain stable vision during everyday activities where the head moves, e.g. walking or standing in a moving bus.

Stable vision relies on the vestibulo-ocular reflex (VOR) to control the eyes, which in turn relies on the head movement signal coming from the vestibular organ. Common causes of damage to the vestibular organ and nerve include ototoxic drugs, Meniere's disease, infection, autoimmune diseases, head trauma, tumours and the surgery to remove them, and ageing.

Assoc Prof Americo Migliaccio from NeuRA, and Assoc Prof Michael Schubert from Johns Hopkins University in the USA, have developed a vestibular rehabilitation technique that challenges the VOR to improve by gradually increasing the difficulty level of a VOR training task from low to high.

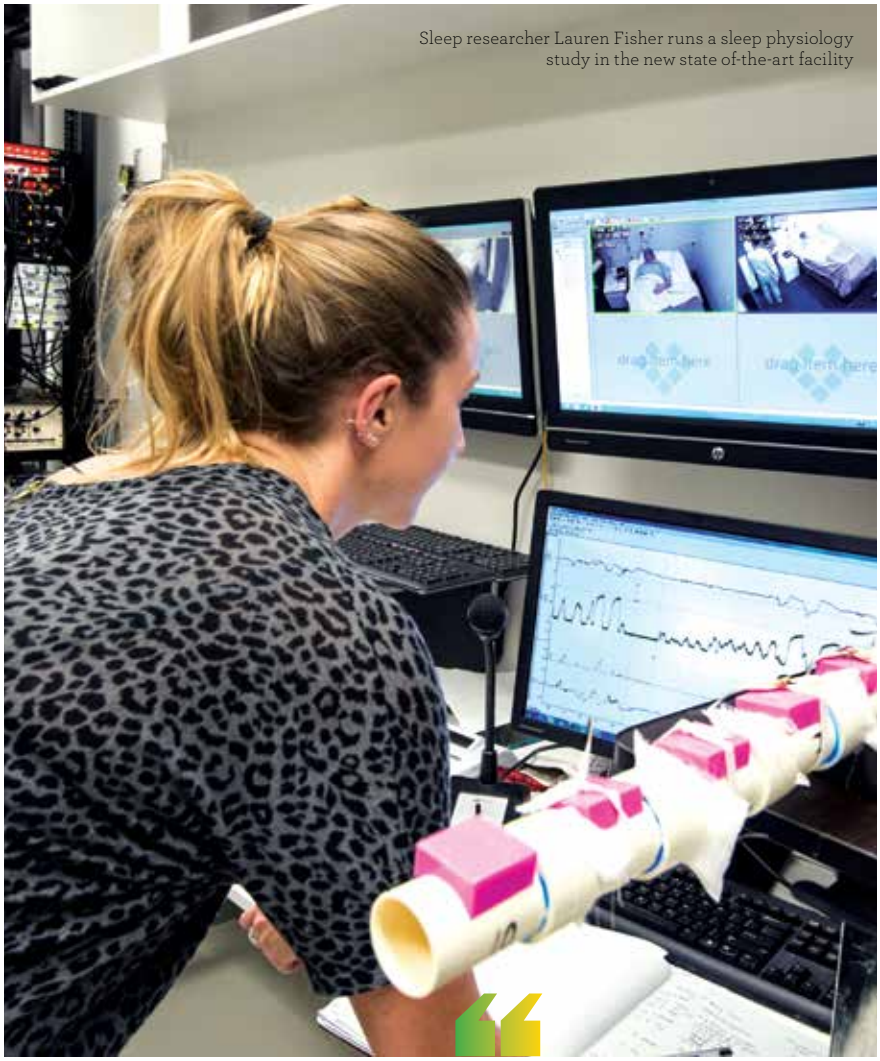
To make this new type of training possible, Assoc Prof Migliaccio and his team at the Balance and Vision Laboratory at NeuRA developed a portable device that measures a patient's head movement and projects a laser dot on the wall in front of the patient that they must visually-track while moving their head.

The digital device consists of a wearable headband with head-sensing and laser projection units, touchscreen display, on-board memory to record training, wireless connectivity to a PC or smartphone, and audio feedback during training to help patients perform the task.

Exploded view of the microprocessor controlled rehabilitation device developed at NeuRA

World-class sleep disorder facility

Sleep-disordered breathing encompasses a range of sleep disorders characterised by snoring, choking and gasping during sleep or excessive daytime sleepiness.



Sleep researcher Lauren Fisher runs a sleep physiology study in the new state of-the-art facility

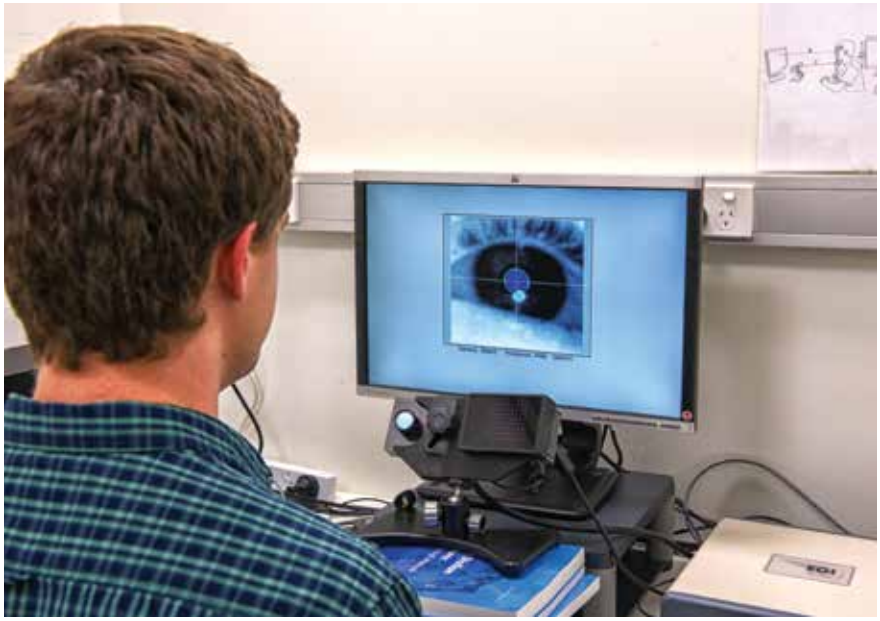
> The state-of-the-art upper airway phenotyping facility is the largest of its type in the world.

More than 1.5 million Australian adults suffer from sleep disorders which have serious health consequences. Current treatments such as continuous positive airway pressure are very effective but unfortunately often poorly tolerated. Assoc Prof Danny Eckert and his sleep research team have developed new techniques to determine the key causes, or phenotypes, of sleep-disordered breathing. The state-of-the-art upper airway phenotyping facility at NeuRA is the largest of its type in the world. It allows the team to measure key causes of sleep-disordered breathing in individual patients and develop new targeted therapies.

Each acoustically sealed bedroom is accompanied with an ensuite bathroom, remotely accessible programmable lighting system and infra-red cameras. In an adjacent central control room, up to 64 channels of electrophysiological data can be collected simultaneously including electroencephalography, electromyography, electrooculography, pressure signals, airflow, carbon dioxide and oxygen levels. A prototype modified CPAP machine is also used to determine precisely why a person gets a serious sleep disorder called Obstructive Sleep Apnoea, or OSA.

The sleep researchers work closely with Prof Lynne Bilston whose team has developed biomechanical imaging tools to measure how the airway muscles move during breathing. They then combine these approaches in several research projects to develop and test new individualised therapies to treat sleep-disordered breathing.

Close-up of participant's eye showing corneal reflection (light blue) and pupil area (dark blue) – these are used to track attention while viewing pictures of emotional faces



Empathy link to eye contact

Conduct problems such as aggressive and oppositional behaviour in early childhood are the single biggest risk factors for mental disorders in adulthood.

Children with conduct disorders who display callous and unemotional traits, characterised by limited emotionality and lack of empathy, do not respond well to treatment.

Research has shown that such children have impaired eye contact and fear recognition that may result from less activity in the amygdala. Emotional recognition improves when attention is intentionally directed towards the eyes of other people's faces.

This suggests improving attention to emotional cues may play a helpful role in treatment. It is currently not known whether such redirection of visual attention results in more normal brain activation, particularly of regions involved in responses to emotion such as the amygdala.

Using a combination of fMRI, autonomics and eye tracking technology, the goal of the EMPATHY study led by Prof Rhoshel Lenroot is to determine whether manipulation of eye contact in children with conduct problems associated with callous and unemotional traits results in more normal brain and physiological responses to signs of distress in others.

Researchers are examining whether the amygdala in children with callous and unemotional traits is able to respond at more normal levels when the right cues are being seen. The results will help design new treatments for children with conduct problems.

> Children with conduct disorders have impaired eye contact and fear recognition.

Concept to creation

Devices used for experiments are purpose-built to suit researchers' needs.

In the scientific world, researchers are continuously developing new methods of testing their theories. To create bespoke equipment requires skilled engineers who not only have the technical and practical ability to design and manufacture precision machinery, but also to liaise with scientists on the specifics of equipment that can provide precise data.

Under Facilities Manager, Mark O'Hara, the institute employs three engineers with over 50 years experience to provide this unique service so that researchers can achieve cutting edge results. Their skills and qualifications are mechanical, design and electronic trades-based. Examples of projects include designing and building a complex leg device to investigate contractual properties of human muscles, and an abrasion tester for assessing the effectiveness of motorcyclists' protective clothing.

The process used to create research equipment includes initial consultation, creation of a brief and development of drawings for the computerised numerical control mill. Components are manufactured from a range of materials including aluminium, perspex, timber, steel and plastics. Electronic circuit boards are assembled in-house. Both engineering disciplines work closely to ensure the end result reflects the integrity of the original design which will be refined and tested prior to laboratory use.

Understanding the science of human anatomy and the brain can be challenging for the engineers but the ability to 'think outside the box' and absorb new skills enables the methodology, framework and on-going development process to reach the required outcome.

Merging technology

Researchers are combining popular video-game technology with sophisticated wireless recording systems to monitor the progress of stroke patients during therapy.

> Patients have shown increased activity in muscles that were thought to be paralysed.

The Nintendo Wii provides an engaging form of rehabilitation that can be individualised to the needs and progress of each patient based on the Wii-Sports games of golf, bowling, baseball, tennis and boxing. Because it is fun, patients do more than is required, and they continue therapeutic activities long after the 14-day program ends.

The wireless telemetry system records limb movement, muscle activity and heart rate. Dr Penelope McNulty's group has shown that the Wii-Sports games promote improved movement control so that patients can selectively choose movements that are appropriate to the task at hand, regardless of whether that is larger and faster movements or smaller and slower movements. They have also shown increased muscle activity after 14 days even in muscles that were thought to be paralysed. This means that patients with very low levels of movement ability after stroke can benefit from Wii-based Movement Therapy.

Dr McNulty has demonstrated that a 14-day program of Wii-based Movement Therapy is as effective as the current best practice for upper-limb rehabilitation after stroke, Constraint-induced Movement Therapy with two important differences. First, there was a strong patient preference for Wii-based Movement Therapy that encouraged high compliance and continued self-directed, high-intensity rehabilitation activities for 12 months or more after therapy. Second, Wii-based Movement Therapy improves cardiovascular fitness in stroke patients but constraint therapy does not. This is important because stroke patients have approximately half the fitness of age-matched healthy people, and decreased cardiovascular fitness is a significant risk factor for recurrent stroke.

The use of technology has not only provided rehabilitation that patients want to do, it has allowed an understanding of how and why this therapy works so that individualised therapy can be designed for every patient.

Dr Penelope McNulty analyses a stroke patient's data collected during therapy

Dr Claire Shepherd, Manager of the Sydney Brain Bank – improvements in diagnosis, a clearer understanding of the cause, and the development of effective treatments for neurodegenerative disorders can be achieved through the study of human brain tissue

Global gateway

integrating and promoting global research and health opportunities through collaboration

Brain banking

New developments in molecular neuropathology throughout the global research community have increased demands for brain tissue.

Stained brain tissue slides

The Sydney Brain Bank, located at NeuRA, was established as a centralised resource for the collection, characterisation, storage and distribution of human brain tissue. Researchers in Australia and overseas investigating areas such as basic disease mechanisms, earlier and more accurate diagnosis, genetic contributions to diseases, better treatments and, ultimately, cure and prevention, can request this tissue for their studies.

The past decade has shown that the study of human brain tissue is essential to increasing the understanding of how the nervous system functions. Neurochemical and anatomical studies focusing on the biological nature of the severe mental illnesses are now emerging and bringing new hope for understanding the underlying brain mechanisms responsible for psychosis and other symptoms associated with these debilitating brain disorders.

In order to perform research into the neurological or psychiatric disorders, it is also important to collect healthy control tissue.

A high worldwide prevalence of neurodegenerative diseases including Parkinson's and Alzheimer's disease, and psychiatric conditions including schizophrenia, has placed these illnesses at the front edge of neuroscience research.

This trend has resulted in an increased demand for well-characterised human brain tissue samples.

Cultural diversity impacts HIV research

The dynamics of the HIV epidemic in Australia are changing.

Dr Lucette Cysique and researcher Jessica Patti demonstrate the multicultural cognitive test battery

In Australia, people from culturally and linguistically diverse (CALD) backgrounds now account for a significant proportion of heterosexually based HIV infection. Dr Lucette Cysique's international HIV investigations have recently focused on HIV in Australian CALD communities.

To understand the effects of HIV on brain functions, Dr Cysique uses neuropsychological testing to assess the level of cognitive function in HIV-infected people. HIV can cause a direct neurotoxic effect on the brain and can develop into a spectrum of neurocognitive difficulties – mild, moderate or severe – called HIV-associated neurocognitive disorder (HAND).

But the methods used in this testing have been developed in 'Western' countries so their use in culturally diverse groups can pose problems. Without adaptation, the tests cannot accurately assess the level of cognitive difficulties. Incorrect estimation in various neurological or psychiatric disorders can result in patients receiving inappropriate treatment due to under, or over diagnosis.

Dr Cysique and her PhD student at Melbourne University, Carl Moller, have developed a low-cultural bias cognitive screening and standard neuropsychological test for HIV-infected CALD Australians. The framework for improving the cross-cultural validity of neuropsychological tests will be potentially applicable, internationally, to other diseases as well as HIV.

The provision of culturally responsive and equitable services will ensure quality health care for all.

Dr Hoang conducts a 2-minute walking test with a stop watch on a volunteer to measure mobility tolerability and gait – impaired mobility is rated as the most debilitating problem by people with MS

Fall risk in multiple sclerosis

Multiple sclerosis (MS) is a disabling disease of the central nervous system that disrupts the flow of information within the brain, and between the brain and body.

Studies show that at least 50% of people with MS experience frequent falls. And of those who fall, 50% sustain injuries that require medical care. As a result, the fear of falling can cause people with MS to restrict their daily activities, with significant impacts on quality of life and health.

In a recent study, Prof Stephen Lord, Dr Phu Hoang and their US colleagues at Oregon Health and Science University assessed the number and types of medications used by 248 adults with MS both here in Australia and in the United States. At the high end of the scale, participants reported taking up to 19 medications and up to 11 supplements daily.

A major finding was that the use of multiple medications significantly increased fall risk. With respect to specific medications, antidepressants nearly doubled the risk of falling, whereas dietary supplements were not associated with any change in falls risk.

> “Stained brain tissue slides.”

Encouragingly, neurologically active medications including MS disease modifying therapies (DMTs) were associated with fewer falls.

Prof Lord and his American colleagues suggest that health care professionals should be vigilant in discussing the need for each medication with people with MS, to ensure the right balance is reached when managing the complex range of symptoms experienced as well as reducing the risk of falls.

CRPS focus

Pathological pain doesn’t serve as a protective function.

Complex regional pain syndrome, or CRPS, is a condition that is particularly problematic because it is triggered by a seemingly minor trauma, yet it is seriously debilitating for sufferers.

An international group of collaborators from The Netherlands, UK, Belgium and Italy, led by Prof Lorimer Moseley, is undertaking a series of major projects making advances into understanding risk factors and potential mechanisms of pathological pain – pain that does not serve to protect the body yet remains active. It is often associated with disturbances such as movement problems, blood flow disruption and sensory sensitivity.

In a recent large-scale trial into CRPS, over 1,500 wrist fracture patients were assessed within a week of their fracture and followed for four months, at which time 3% of patients were diagnosed with CRPS. A subsequent global study sampled cytokine levels soon after fracture in those at high and low risk of CRPS. They also found that pathological pain is associated with dysfunction in the same neurological processes that underpin spatial processing. They are now testing two new hypotheses that seek to explain the transition from acute to chronic pain, laying the groundwork for new treatments to prevent this transition and alleviating chronic pain for millions of sufferers, worldwide.

Prof Lorimer Moseley

Amanda Ayliffe receives the first DIAN clinical trial medication. She is seen here with husband David, NeuRA's Dr Bill Brooks and Mirelle D'Mello, and Judith Taylor, Oncology Day Centre, POW Private Hospital

Alzheimer's clinical study underway

The Dominantly Inherited Alzheimer Network (DIAN) is an international research partnership of leading scientists determined to understand Alzheimer's disease (AD) through the study of a rare form that is caused by a gene mutation.

Funded through a multi-year research grant from the National Institute on Aging in the USA, DIAN currently involves fourteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. Prof Peter Schofield is the Site Principal Investigator at NeuRA.

DIAN has now commenced a clinical trial arm called DIAN-TU (DIAN Trials Unit) and NeuRA is one of 27 participating international sites. The first trial, DIAN-TU-001, aims to prevent the development of symptoms in at-risk family members by giving one of two monoclonal antibodies, solanezumab and gantenerumab.

In this study, participants are randomised to receive one of these drugs, which targets amyloid beta in the brain, or to receive a placebo. Participants receive monthly doses of trial medication for two years and the effect will be measured by PET scans and spinal fluid analysis. The Site Principal Investigator for this clinical trial is Dr Bill Brooks.

Amanda Ayliffe, 46, is NeuRA's first participant in the clinical trial. She had predictive testing at 34 and discovered that she had inherited the family's disease-causing genetic mutation.

Most people with AD have no apparent cause for their condition, but some families like Amanda's have an inherited form of AD in which a genetic mutation can be identified as the cause. Amanda's father died of AD at 58, having been diagnosed in his 40s, and her uncle at 52. Recently she has begun to notice symptoms such as early-stage cognitive impairment and memory loss.

> "The first trial aims to prevent the development of symptoms in at-risk family members."

Although there are differences between dominantly inherited AD and the more common age-associated sporadic disease, the results of this study will have clear implications for future studies and treatments across the Alzheimer's disease spectrum.

New horizons

identifying a new and diverse range of clinical and translational research

Plasticity and the spinal cord

Researchers are using brain and nerve stimulation techniques to enhance pathways in the spinal cord that transmit signals from the brain to the muscles.

Sensory neuron grown in culture

Repetitive pairing of stimuli to the brain and peripheral nerves at specific timing intervals can alter signals in the spinal pathways that control voluntary muscle activity.

This technique has therapeutic potential for enhancing activity at synapses that transmit commands from the brain to the muscles. PhD student Siobhan Fitzpatrick and postdoctoral researcher, Dr Jessica D'Amico, are investigating the technique which may be relevant for those with decreased muscle control, such as in incomplete spinal cord injury.

In many areas of the brain, changes in synaptic connections between nerve cells occur in response to specific activity of the cells. This 'plasticity' depends on a type of receptor found on nerve cells known as the NMDA receptor. The team will determine whether plasticity in the spinal cord also depends on NMDA receptors, by having volunteers ingest a compound that blocks these receptors temporarily. If changes after paired stimulus protocols are prevented when the receptors are blocked, it can be inferred that the receptor plays a crucial role in these changes in the human spinal cord.

Greater understanding of the mechanisms of the plasticity occurring after paired stimulus protocols may lead to new therapeutic targets for improving neural connections in the spinal cord.

Siobhan Fitzpatrick investigates decreased muscle control such as in incomplete spinal cord injury

Disruption to hippocampal neurogenesis

The hippocampus is an area of the brain located in the temporal lobe involved with memory formation and learning.

Once controversial, but now acknowledged as fact, the hippocampus is one of the few areas where new neurons are generated into adulthood. This process is called neurogenesis. These newly formed neurons may help with learning and memory across life, but neurogenesis can be impacted by many factors including exercise, stress, hormone levels and medication.

Disruption to hippocampal neurogenesis is thought to occur in schizophrenia, depression and Alzheimer's disease. Katie Allen and colleagues have found further evidence that neurogenesis is reduced in people with schizophrenia, suggesting it may contribute to memory problems commonly found in this illness. Some factors that control the number of new neurons produced have been identified as schizophrenia risk factors. How certain factors may contribute to reduced neurogenesis in schizophrenia is also being studied.

Katie Allen sorts microscope slides that have been stained to detect new-born cells in brain tissue

Increase in testosterone at adolescence may contribute to the onset of schizophrenia in certain vulnerable people, as this is the most common age when the illness emerges. Testosterone exposure during this time period can influence the number of newborn neurons in the hippocampus.

This research increases understanding of the pathways that may lead to decreased cognitive ability in people with schizophrenia and may inform treatments to restore these abilities.

Optimising care for dementia patients after a fall

Taking advantage of improved data linkage systems within the Australian healthcare system is allowing researchers to map and better understand the patient journey.

The most common cause of hospitalisation in people with dementia is injury, predominantly as a result of a fall. Once in hospital, people with dementia have longer lengths of stay, experience a higher rate of complications such as urinary tract infections, pressure areas and delirium, and have poorer outcomes than cognitively healthy people of the same age. Hospitalisations for fall-related injuries in older people generally have increased over the last decade, however it is unknown what impact the increase in the prevalence of dementia in the community is having on this trend.

Dr Lara Harvey is an injury epidemiologist whose research utilises recent advances in data linkage capacity in Australia to develop a clear understanding of the causes, consequences and the human and economic cost of injury in people with dementia. The increased capacity means more information is available across a larger number of data sources.

Linking data from a number of large administrative health datasets provides, for the first time, the ability to track a person's pathways through the health care system and also to map the subsequent health outcomes. Using data in this way creates a clearer picture of a person's journey after a fall.

Although it is still early days, so far the news is good for people with dementia. Dr Harvey's research highlights that rates of hospitalisation for people with dementia have decreased over the past ten years. Fall-related hip fracture rates have decreased by around 5% per year for people with dementia, yet there is no corresponding decrease for older people *without* dementia. The reasons for this unexpected finding are not clear and require further exploration.

Findings from Dr Harvey's research will inform strategies, guide clinical practice and, ultimately, optimise the care provided to people with dementia who have sustained an injury through a fall.

Dr Lara Harvey's research includes trends in fall-related hospitalisations in the older population and the use of linked data to describe the population burden of fall-related injury

> Hospitalisations for people with dementia have decreased over the past ten years.

A participant, setup by Dr Carberry to take part in the reflex study, has had a catheter inserted via the nose to allow the measurement of the pressure at the back of the throat

Understanding how upper airway muscles work

The genioglossus is a fan-shaped muscle within the tongue and, during breathing, it is reflexively activated to move the tongue forward to help keep the airway open.

Changes in the electrical activity to this muscle during sleep combined with anatomical factors (e.g. a small or narrow upper airway or enlarged tongue) contribute to airway closure during sleep resulting in obstructive sleep apnoea (OSA).

Dr Jayne Carberry from NeuRA's sleep laboratory has been using neurophysiological techniques to understand precisely how the upper airway muscles work.

By blocking receptors in the upper airway that are sensitive to changes in airway pressure and flow, and increasing the demand on the upper airway muscles by applying suction, or negative pressures, she has determined that the reflex response of the tongue muscle was not altered. This finding challenges previous notions that the surface receptors in the upper airway are responsible for this important protective reflex response.

Switching off the negative pressure stimulus also induced a similar genioglossus reflex response, suggesting that the reflex also occurs to a change in airway pressure; contradicting the current belief that it is specifically a 'negative' pressure reflex.

The findings provide important information on how the airway muscles are controlled. This has significant implications for the development of therapies that target the upper airway muscles in treating sleep disorders.

Language deficits in dementia

Memory failure is the most common cognitive change in Alzheimer's disease.

A proportion of Alzheimer's disease patients present with insidious language deterioration as the predominant symptom. This clinical syndrome, formally known as logopenic progressive aphasia, is characterised by word-finding problems and profound difficulties with sentence repetition. This pattern of language deterioration can easily be confused with deficits seen in other dementias, notably frontotemporal lobar degeneration, which raises serious diagnostic challenges.

Combining clinical and neuropsychological investigations with advanced neuroimaging analyses and biomarkers, Dr Cristian Leyton is developing novel clinical tools to better characterise the complexity of language alterations in dementia and improve dementia diagnosis. He has demonstrated that dementia patients, who make phonological errors in their speech – that is those who use incorrect speech sounds – tend to have Alzheimer's pathology in their brain.

To improve the understanding of the complexity of language manifestations in dementia, Dr Leyton is currently investigating changes in cognition and brain structure over time in affected patients. He has also designed an app that provides self-administered language tasks, so that individuals with progressive language deficits can re-learn words using audio-visual strategies. The aim of his research is to improve understanding of progressive aphasias due to Alzheimer's disease and provide the rationale needed for better therapeutic interventions.

Effects of abnormal breathing

A person takes over 15,000 breaths in 24 hours a nd every time you breathe your brain sends signals to multiple respiratory muscles via your spinal cord to expand your chest and abdomen.

Dr Anna Hudson studies the neural control of respiratory muscles in health and disease

In healthy people, this process is automatic but, for some, breathing requires voluntary input from a different region of the brain called the motor cortex that controls all voluntary movements we make.

Dr Anna Hudson studies the neural control of respiratory muscles in health and disease. She is investigating if there is atypical brain activation during breathing in respiratory diseases such as chronic obstructive disease and asthma.

Electroencephalography – recording of brain activity over the scalp – is being used to detect when there is abnormal activation of the motor cortex during breathing.

Using this technique, Dr Hudson has shown that the motor cortex is required to maintain normal ventilation in patients with central hypoventilation syndrome, a genetic disorder that affects breathing control. Usually, the motor cortex is not activated in normal ventilation.

> Is there atypical brain activation during breathing in respiratory diseases?

Dr Hudson is also investigating how atypical activation of this brain region in respiratory disease is related to breathlessness, an intense and frightening sensation and sleep disturbance, with the goal of improving the disease outcome.

Psychiatric problems in Parkinson's disease

In addition to difficulties with movement, patients with Parkinson's disease often experience neuropsychiatric symptoms, such as depression or impulsive behaviours.

These symptoms can be very distressing for individuals with Parkinson's disease and their family members, with current treatment options limited.

Previously, it was thought these symptoms were solely caused by chemical imbalances in the brain. PhD student Claire O'Callaghan has identified that physical shrinkage, or atrophy, of key brain regions is also associated with a higher prevalence of neuropsychiatric symptoms.

Understanding the role of these structural brain changes is critical in order to help predict which patients might go on to develop these symptoms. More importantly, researchers can now use this information to better understand the relationship between structural brain changes and chemical imbalances. This substantial work has helped promote an increased awareness that multiple factors contribute to neuropsychiatric symptoms.

Understanding the multiple factors that are implicated will be key to the future development of more targeted therapies for these disabling symptoms.

This year, Claire completed her PhD and is now continuing her work on neuropsychiatric symptoms at the University of Cambridge as part of a post-doctoral fellowship.

Comparing epigenetic profiles to understand longevity

PhD student, Jessica Lazarus, is investigating the potential role that epigenetic modification plays in longevity

Centenarians are a unique group that provide further evidence that dementia is not an inevitable part of ageing.

People who achieve extreme longevity typically postpone age-related disease until the last few months of life.

This is a key research focus of PhD student, Jessica Lazarus, who is investigating the potential role that epigenetic modification plays in longevity. She is also interested in what people can do in their daily lives to stay healthy into older age.

Using whole genome sequencing, she is comparing the epigenetic profiles of centenarians who are cognitively healthy, to the epigenetic profiles of a younger group, those aged between 70 and 90 years, who have impaired cognition.

Heritable changes in gene expression that do not involve changes to the underlying DNA sequence are referred to as 'epigenetic'. These modifications involve biochemical changes across genes which can switch the affected genes on or off.

Epigenetic modifications are essential for normal human physiology, however abnormal epigenetic changes may be part of a disease process. These modifications can be triggered by environmental factors, such as diet, smoking habits, and the use of pharmaceutical drugs. Interestingly, epigenetic modifications are potentially reversible which has significant therapeutic implications.

> Epigenetic modifications are potentially reversible which has therapeutic implications.

DNA methylation is a major epigenetic mechanism. Jessica is measuring DNA methylation, as a marker for epigenetic modification, in purified DNA from her population groups.

This work aims to provide evidence about the epigenetic modulation of the healthy ageing process. It may allow better characterisation of age-related disease and may also expose novel therapeutic targets for age-related neurodegenerative disease.

Communication access

opening the doors to NeuRA's research through stories that connect, inspire and inform

Digital media

Increasingly, digital media is becoming a powerful tool for sharing scientific messages, research, and expert opinion within real time and collaborative environments.

Researchers, scientists and clinicians are turning to online platforms to publicise and discuss their research, solicit participation from the public, and communicate with peers. Patients, carers and healthcare workers are using digital media as a search mechanism for support and information.

NeuRA's digital strategy incorporates platforms such as WordPress, LinkedIn, Facebook, Twitter, YouTube, Soundcloud and Wikipedia, along with Google's advanced suite of digital tools. Through social media, research groups have acquired participants for projects and clinical trials, including a trial for the treatment of schizophrenia, a child restraint study, and a trial testing mandibular splint therapy for Obstructive Sleep Apnoea. Facebook has been particularly useful in sourcing volunteer participants.

The NeuRA YouTube channels provide an excellent communication conduit to dementia care support groups. They also a provide informative overviews on topics ranging from frontotemporal dementia to announcements of new technologies and visits from celebrities such as, most recently, comedian and mental health advocate, Ruby Wax.

Podcasts use the Soundcloud and iTunes platforms to share content with similar diversity, and have been named 'new and newsworthy' by iTunes. Although a newly embraced platform, podcasts have garnered myriad listens and it continues to grow.

The use of digital media to promote fundraising activities such as the NeuRA BIG Run, Bridge for Brain Research Challenge, Memory Cycle and the Great Wall of China Discovery Trek has been invaluable.

NeuRA's online brand visibility has grown significantly with monthly digital interactions numbering in the tens of thousands.

Science in the media

Media is a powerful communication tool. It's influence helps promote current research and achievements, provides exposure to the mass audience and garners support for important studies, clinical trials, events and fundraising.

How can science enrich the community's engagement with research? Scientists know that news coverage for their research is educational and visibility in the media important. It provides information for those who seek the latest findings on many diseases or conditions. Actively promoting NeuRA's research is paramount.

Dr Muireann Irish and Dr Rebekah Ahmed were invited to review the Oscar winning film 'Still Alice' for the online news portal, *The Conversation*. Dr Ahmed followed the review with an opinion piece for the Sydney Morning Herald about NeuRA's dementia research. Prof George Paxinos generated discussion in the Fairfax press – both the Age and the Sydney Morning Herald – with an opinion piece to mark Valentine's Day. Prof Paxinos' wry look at why brains should appear on the cards of lovers instead of hearts sparked a debate and Letters to the Editor about where emotion lives.

Prof Peter Schofield is often called upon to comment on research issues. Recently Channel Seven filmed him commenting on a Finnish study about a formula

that can slow down mental ageing and possibly prevent dementia.

During Mental Health Week, both Prof Rhoshel Lenroot and Prof Cyndi Shannon Weickert were invited into the ABC to contribute their views on the national initiative. Prof Shannon Weickert joined Lynne Malcolm on 'All in the Mind' to discuss how NeuRA's schizophrenia research is moving into new era of understanding. Prof Shannon Weickert also featured on Richard Fidler's 'Conversations'.

Prof Lynne Bilston's study elicited many enquiries after an appearance on Channel Nine News discussing a new clinical trial – testing mandibular splint therapy for obstructive sleep apnoea.

Media matters

Following is a snapshot of where researchers have gained recent exposure in the media.

PROF TONY BROE: ABC Classic FM with Margaret Throsby on the epidemic of healthy ageing and rates of dementia in Aboriginal Australians.

DR JAMES BURRELL: SBS news on an American study that showed chocolate beneficial for brain health.

ASSOC PROF OLIVIER PIGUET: 4BC weekend breakfast on the probability of an accurate blood test to diagnose dementia being discovered.

DR REBEKAH AHMED: English-speaking radio station in Korea on dementia rates, not just in Australia, but globally.

DR LIZ DE ROME: Illawarra Mercury on motorcycle protective clothing and the study aimed at reducing risk for riders by testing heat and abrasion resistance.

PROF RHOSHEL LENROOT: ABC 702 discussing child and adolescent mental health.

DR KIM DELBAERE: Medical Express on depression, antidepressants, poor balance and cognitive function associated with increased risk of falls in the elderly.

ASSOC PROF TIM KARL: Channel Seven explaining his work into cannabidiol, a component of cannabis which may prevent Alzheimer's disease.

DR PHU HOANG: SBS news on research into the benefits of dance mats for people with Multiple Sclerosis.

NeuRA is established as an independent, not-for-profit company, Neuroscience Research Australia. All Directors of the NeuRA Board and the NeuRA Foundation Board are honorary members.

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Chair, NeuRA Foundation
Director, 2014 – present
Member, Nomination Committee

Prof Peter Schofield, FAAHMS PhD DSc
Appointed by the Board
Director, 2007 – present
Member, Building Committee
Member, Investment Committee
Member, Nomination Committee

The NeuRA Foundation is responsible for all fundraising and sponsorship activities.

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Ian Kennedy OAM
Director, 2009 – present
Stephen Blackman, MBA, AFin, AAusIMM
Director, 2014 – present
Member, Finance Risk Audit & Compliance Committee

NOT SHOWN:
Ian Harris, BSc MComm (Mkting) GAICD
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Dr Paul Nicolarakis, MBBS BSc(Hons)
Director, 2014 – present

Through giving

Effective philanthropy

> I decided to leave a gift in my will towards neurological research.

Pip Hill is a member of the *Commitment to Cure Society* bequest program and made the generous decision to leave a bequest after losing her brother to dementia and her mother to a stroke.

"My brother was a brilliant mathematician and poet. When the day came that I had to help him write his own name, I was completely devastated. It was at this point I decided to leave a gift in my will towards neurological research. I hope that, through research, we can prevent other families from losing their loved ones to neurological disorders and disease."

> I have since signed up as a regular monthly giver as I feel it is worth supporting research.

Keith Dudley was a research volunteer who became a member of the *See It Through To A Cure* regular giving program, making a monthly gift to support research.

"After attending a lecture for National Seniors some years ago, I was very impressed with the research conducted at NeuRA into the prevention of falls in the elderly. I subsequently signed up as a volunteer in their program and was impressed by NeuRA's work and the dedication of their staff. I have since signed up as a regular monthly giver as I feel it is worth supporting research in the knowledge that my money will be well used and will assist greatly in their research."

> We cannot hope to cure this terrible disease ourselves.

Back row: Evan Brownsmith, Nicole Parkinson, Kelee Hawker and Blair Richards
Front row: Megan Mann and Caitlin Mann

Accounting Firm PKF Lawler Tamworth and Walcha, NSW ran the City2Surf 2014 in support of motor neurone disease (MND) research.

"We cannot directly improve the lives of MND sufferers, nor can we make it easier on their families. We cannot hope to cure this terrible disease ourselves, but we know that our contribution to NeuRA will help the very people who just might. Perhaps more importantly, through demonstrating a willingness to 'give it a go', we are setting a great example to the community of Tamworth. We want to show that it's important to get out there and have a crack, not because we should, but because we still can."

Evan Brownsmith
PKF Lawler Runner

> This research has the potential to save lives and improve quality of life.

Although an innovative approach to an unresolved health problem, Dr Kim's Delbaere's 'Standing Tall' project needed financial backing in its trial stages to provide sufficient evidence for NHMRC funding.

"Gandel Philanthropy was thrilled to support this successful fundraising challenge that has seeded ground-breaking research into falls prevention. Falls are the leading cause of injury-related hospitalisation of older people. This research has the potential to save lives and improve the quality of life of thousands of Australians."

Vedran Drakulic,
CEO of Gandel Philanthropy

Dr Kim Delbaere with the Standing Tall app

Contact details

Neuroscience Research Australia
ABN 94 050 110 346

Margarete Ainsworth Building
Barker Street Randwick
Sydney NSW 2031 Australia

Telephone +61 2 9399 1000
Facsimile +61 2 9399 1005
Email info@neura.com.au
Postal Address PO Box 1165
Randwick NSW 2031 Australia

neura.edu.au
Follow us on Facebook and Twitter

NeuRA
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Editor Anne Graham
Writers Anne Graham, Siobhan Moylan
Photography Anne Graham
Design and Production Designer Rice

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