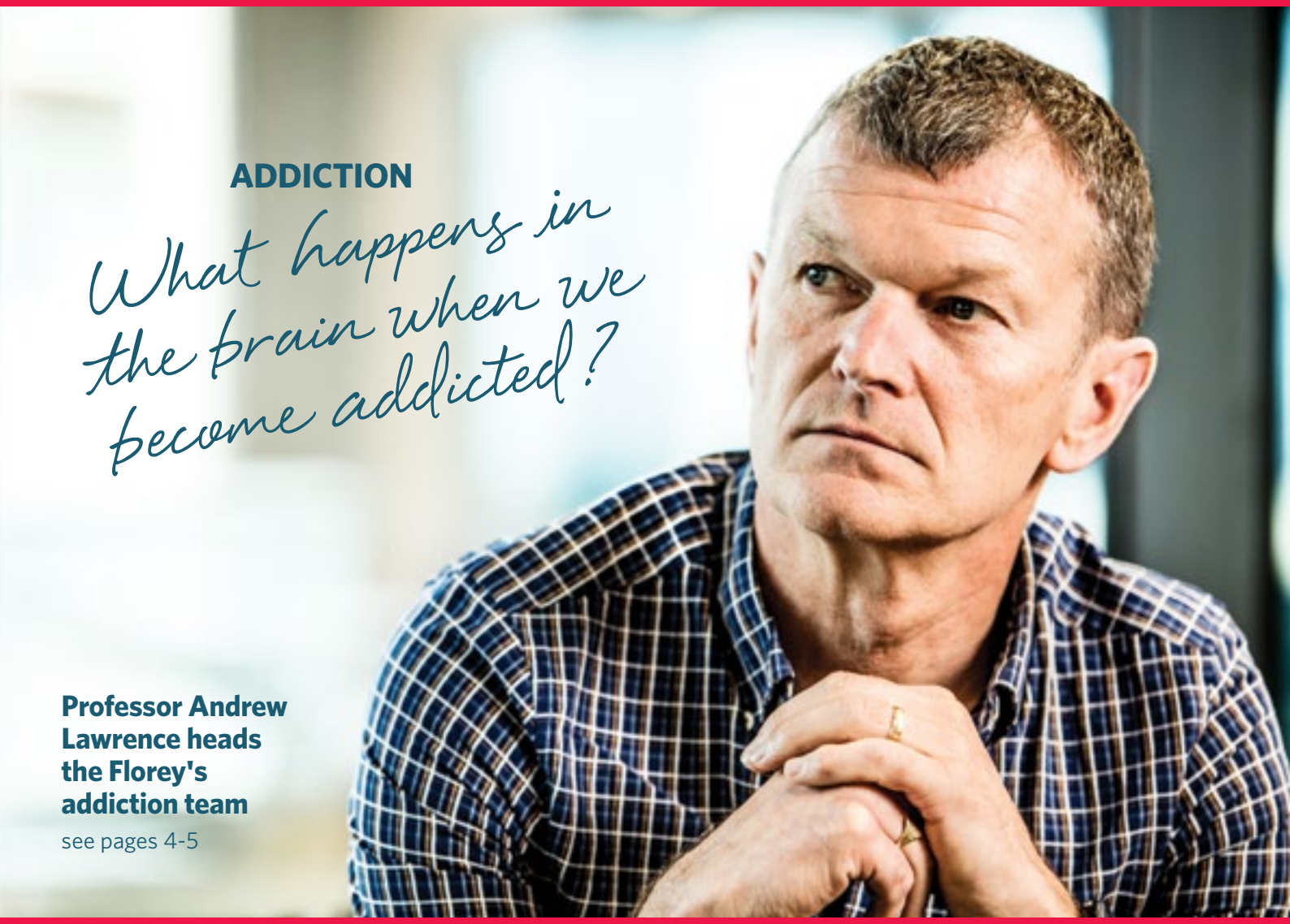
Brain Matters

NEWS FROM THE FLOREY INSTITUTE OF NEUROSCIENCE & MENTAL HEALTH



ADDICTION

What happens in the brain when we become addicted?

Professor Andrew Lawrence heads the Florey's addiction team

see pages 4-5

THE FLOREY

SUMMER 2015

DIRECTOR'S REPORT

As the festive season approaches, the Florey's scientists are heads down, fingers to the keyboard, applying for precious grant funding to help secure their employment for another few years.

Of course, the Florey does all it can to support our researchers but at the end of the day, the National Health and Medical Research Council supplies scientists' wages. Christmas can be a tough time, wondering if one's grant application will be successful, hoping to continue a promising advance in brain disease or a treatment for mental illness.

With this in mind, I am very excited to tell you about a wonderful new initiative called the *Florey Brains Trust*.

A unique fundraising group is being created, led by some truly great Australians.

These well-known ambassadors are soon to help us spread the word about the Florey and our efforts to build a secure endowment for the Florey's future. We look forward to making an announcement soon.

If you are interested in joining the Brains Trust, please visit www.floreybrainstrust.com.au or call 1800 063 693.

We are asking members to:

- Encourage family, colleagues and friends to join the *Florey Brains Trust* and to give generously
- Keep in touch with the great work happening here and to spread the word
- Come along to our events and build the network of people who care about brain health.

The *Florey Brains Trust* is headed by Ross Oakley AM, the ex-St Kilda great and former CEO of the AFL. He is doing a wonderful job as our Foundation Council Chairman.

I urge you to join. We have some truly fascinating events planned exclusively for members involving social and informative opportunities to listen, share and enjoy.

When you join the *Florey Brains Trust*, you will be a member of something special.

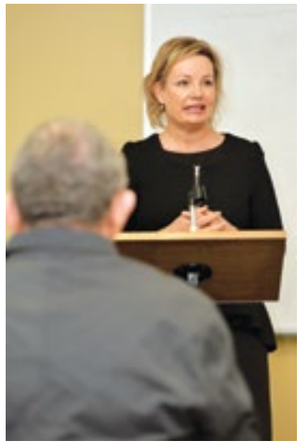
Yours truly at this joyous time of the year,

Professor Geoffrey Donnan, AO
Director, the Florey Institute of Neuroscience & Mental Health

Time-critical stroke care for Albury

People living in the Albury Wodonga region who suffer a suspected stroke will now receive expert neurological opinion from Melbourne – without leaving their hospital bed.

The new stroke telemedicine program was launched by Federal Health Minister, Hon Sussan Ley MP and Florey Chair, Mr Harold Mitchell AC.



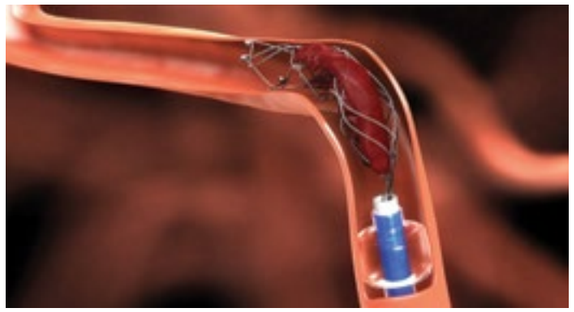
Federal Health Minister, Hon Sussan Ley launches the Florey's stroke telemedicine program.

"This service is vital when you consider that over 400 people in the Albury Wodonga region suffer a stroke each year and approximately 250,000 Australians are living with the consequences of stroke," Ms Ley says.

"It is the leading cause of long-term adult disability with about 50 per cent of survivors dependent on others to help them with everyday living. For this reason alone, we need to do all we can to help those with a suspected stroke to receive fast, expert assessment – wherever their location."

The Florey has developed the stroke telemedicine program, linking city-based neurologists to emergency department doctors in 16 rural and regional Victorian hospitals.

Patients are now assessed to determine if they are suitable for new endovascular surgery where a brain clot is removed using a stent. These recent advances are improving survival rates and are reducing disability but rapid diagnosis and treatment (within six hours of the stroke onset) is essential for the best outcomes.



Patients assessed as suitable for a new procedure are flown from rural hospitals to Melbourne where a stent is inserted into the brain to remove the clot causing a stroke, as illustrated in this image. With such great results, the Florey team is keen to go nationwide with stroke telemedicine.

> **"We need to do all we can to help those with a suspected stroke to receive fast, expert assessment – wherever their location."**
>
> The Hon Sussan Ley

Dr Mathias Dutschmann is developing the Florey's understanding of the fundamental brain mechanisms associated.

Take a deep breath...

Dr Mathias Dutschmann is fascinated by the body's innate desire to breathe. Of course, we all take breathing for granted until something interrupts the automatic mechanism and suddenly, we are acutely aware of our need to get oxygen into our lungs.

Breathing is central to life, making it one of the oldest and most fascinating areas of neuroscience. Amazingly, we still don't really understand it. Apart from being an intriguing puzzle, we need to know how breathing works so we can address a range of medical problems.

Matt and his team from the Systems Neurophysiology division know their work will help us find new ways to diagnose neurodegenerative diseases like Parkinson's and Alzheimer's, and will provide insights into autism, Rett syndrome and speech disorders in premature babies.

"Breathing is the first thing you do when you're born, and the last thing you do before you die. It is life's most central process – I'm compelled to study it," Matt says.

Breathing depends on a master command system in the brain, driving 24/7 skeletal muscle contractions. It is actually the same process used to keep your feet moving so you don't fall over, but the breathing pattern never stops; it just alters when we talk, cough, sneeze, sniff or hold our breath.

This perpetual motor pattern is generated in the brainstem, the ancient or 'reptilian' brain. The crucial structure for breathing is known as the pons, (Latin for "bridge'). As Matt says when lecturing: "The captain stands on the bridge." No captain? The ship sinks.

Matt's group is determined to unravel the pons' neural circuitry. He estimates there are about one million neurons involved, but that only about 20 per cent of these actually generate the required pattern. His group uses a number of advanced genetic optical tools to create their circuit diagrams but he favours old-fashioned techniques.

The team wants to discover how we generate complex breathing patterns when speaking and swallowing. His group has developed sophisticated ways to produce complex motor patterns, like those seen in vocalisation and sniffing in response to airborne irritants. When Matt presents irritants, like peppermint or menthol, to his preparations he can elicit a "sniff-like" response in cells.

These fundamental issues of life pose many exciting questions when it comes to translating lab-based research to help patients. Significantly, the group can see cell death occurring much earlier in the brainstem than in the higher brain regions responsible for memory loss and personality changes in Alzheimer's and Parkinson's animal models. The mice begin to have trouble sniffing, and end up breath-holding instead. By the time the animals show overt signs of dementia, they may have lost 50 per cent of their pons cells.

This reflects the patient experience, where people with the earliest stages of neurodegenerative diseases like dementias and motor neuron disease often have trouble swallowing, controlling their voice, or breathing properly while asleep. These symptoms can be subtle and hard to detect, but could be picked up for example during a simple "sniff test" given during a GP consultation. If a patient fails the "sniff test", they could be recommended for an amyloid scan, to detect the formation and build-up of toxic amyloid in the brain.

Matt's work could help the most precious patients of all, premature babies. Due to delayed brain stem maturation, preterm infants are at higher risk for swallowing difficulties, breathing disorders and speech disorders like stuttering. Developing diagnostic tools to predict the likelihood of these disorders could pave the way for earlier, more effective interventions.

Understanding ADDICTION

The Florey is home to around 50 researchers and students who are trying to understand how the brain becomes addicted so they might intervene.

Professor Andrew Lawrence and the Florey's addiction team: Dr Jee Hyun Kim, Dr Robyn Brown, Prof Andrew Lawrence, Dr Christina Perry, Dr Heather Madsen and Dr Jhodie Duncan.

Addiction can tear families apart. Whether people are addicted to drugs like alcohol, nicotine, cocaine, ice (methamphetamine), or to destructive behaviours such as gambling or overeating, the consequences can be devastating. People vulnerable to addiction may lose their jobs, incur huge financial debts, or suffer from a number of associated health disorders.

Addictive substances activate the brain's reward pathway that evolved to make us keep doing things that are good for passing genes on; eating food, drinking water and having sex.

There is also an emerging debate around "behavioural" addictions, such as overeating, online pornography, or gambling. Are these true addictions, in the same way that people are compelled to seek drugs? Increasingly it seems the answer may be yes.

In the past, addiction was seen as a failure of will power, but recent discoveries at the Florey shed light on the underlying biochemical and environmental reasons. Why are 10-20 per cent of people susceptible to addiction when they start using drugs, while others stop using when the negative consequences outweigh the high? As Professor Andrew Lawrence, head of the Florey's addiction research team, says, "These numbers are akin to playing Russian roulette. The best option is not to play. In reality though, people like using alcohol and drugs, and for many this will not lead to a problem."

> **"Addiction is a chronic relapsing brain disorder, not some kind of moral weakness."**

"Addiction is a chronic relapsing brain disorder, not some kind of moral weakness."

Andrew's addiction group is particularly interested in the relapse process. An addict may abstain for a period of time, but when presented with a drug-taking cue or a stressful experience, they can quickly relapse into drug use. Why does this happen? How can we prevent it? Florey researchers have identified underlying brain regions and pathways involved, and are probing new treatment targets that may help to prevent relapse.

Alcohol

The Florey's investigation of binge drinking examines its serious consequences including brain inflammation, brain cell death and effects on learning and memory.

According to Dr Christina Perry: "We know that long-term alcoholism causes severe and irreversible brain damage, but the effects of binge drinking punctuated by periods of abstinence – behaviour typically seen in teenagers and young adults – are far less well understood."

> **"This work will have immediate public health benefits, providing more accurate information on the effects of binge drinking."**

This work will have immediate public health benefits, providing more accurate information on the effects of binge drinking. Much like road safety campaigns, benefits are seen when people are shown the effects of their behaviour, rather than just being told to not do something.

Christina has been awarded a Society for Mental Health research grant to enable this work, as a result of the ABC's "Mental As" campaign.

Methamphetamine

"Ice" is the crystallised form of methamphetamine. Users experience rapid feelings of pleasure due to its ability to powerfully activate the brain's reward pathway, which evolved to respond to natural rewards like food and sex.

Prolonged ice use leads to chemical changes in the brain's reward pathway that reduces the user's ability to experience pleasure from other activities such as socialising, and may eventually lead to disorders like depression.

Chronic users also begin to associate the paraphernalia or environment around their drug use with the pleasurable effects of the drug. This means that even after going to rehabilitation, addicts can very quickly relapse when exposed to those cues.

Dr Jee Hyun Kim and Dr Heather Madsen are studying these effects in a model of adolescent methamphetamine abuse. The reward pathway in the adolescent brain has not finished developing and may in fact be overactive, making the power of drug associated cues harder for adolescents to resist. This may prolong drug cravings for recovering addicts, and the researchers' ultimate aim is to develop a therapeutic intervention to overcome these cravings and help keep kids off drugs.

Food addiction

Obesity has major implications for public health policy. Our research indicates the need for tightly regulated advertising of foods high in fat and sugar.

So-called palatable foods, high in fat and sugar, have become widely available. In rats 'exposed' to a high sugar and fat diet, around one-third will stay a normal weight (by simply reducing their intake of food), one-third will become overweight, and one-third will become obese. These proportions parallel those found in western societies today. As with drug addiction, not everyone exposed to high fat high sugar food will overeat and become obese, leading Dr Robyn Brown to ask – is some obesity due to food addiction, rather than simply eating too much?

Robyn has measured the connections between brain cells in animals on high fat and sugar diets and has found significant changes in neuroplasticity – the brain's mechanism to facilitate new learning. This altered plasticity resembles that seen in cocaine-addicted animals. This suggests that for some people high fat and high sugar foods could be addictive.

She is now testing an altered form of a naturally occurring compound that restores correct levels of the brain's reward pathway activation. The compound restores appropriate synaptic plasticity, behavioural flexibility and a reduction in addictive behaviours.

Inhalant use

Florey research aims to address the very serious fact that more and younger adolescents are abusing inhalants. Teenagers who abuse inhalants risk brain damage, altered growth, metabolic disorders and a potential for an increased risk of adult-onset disorders such as diabetes.

Between 2007 and 2010, inhalant use skyrocketed by 23 per cent. Of concern, two-thirds of all inhalant users are adolescents, and of those, half are just 12 – 13 years old. This is thought to be driven by the fact that commonly abused products such as paint thinners, super glue, aerosols and petrol are all easily obtained by teenagers. In addition, inhalants result in a rapid high which wears off quickly so it's much easier to keep substance use hidden from family and teachers. Subtle initial brain deficits in users gradually become amplified, resulting in global brain damage.

> **"Two-thirds of all inhalant users are adolescents, and of those, half are just 12 – 13 years old."**

Dr Jhodie Duncan is currently interested in metabolic consequences of inhalant abuse on height, weight, and dietary preferences. Her lab integrates epidemiological data with an animal model of inhalant abuse, the only group in Australia conducting this type of research.

Jhodie has found that rats sniffing the harmful compounds found in glue for example prefer diets high in fat and sugar during extended abstinence but actually have lower weight gain if exposure occurs during adolescence. She believes this is due to a failure in the body's sugar regulation and abnormal fat deposition, which could lead to lifelong consequences such as type 2 diabetes.

Jhodie's current work is aimed at translating these findings into human populations, beginning with Indigenous communities from the Northern Territory.

Stopping the slide from stroke to dementia

Can we prevent a person who has suffered a stroke from slipping into dementia?

In a national first, fourteen researchers from diverse backgrounds – led by the Florey – will come together to:

- prevent cognitive decline in stroke patients and
- develop treatments to stop further vascular damage.

The funding is part of the Australian Research Council's and the National Health and Medical Research Council's Boosting Dementia Research Initiative.

The team will be led by the Florey's A/Prof Amy Brodtmann and will involve researchers from Melbourne, Germany, Canada and the US.

"The evidence is compelling. We know that vascular burden is the strongest risk factor for dementia," says Amy, a neurologist and the chief investigator.

"The time has come to ask not whether, but how do vascular burden and injury cause dementia and neurodegeneration?"

"This grant will allow us to fast-track our efforts to prevent and treat the global epidemic of dementia."

The team will use mass population studies, stem cell science, brain imaging - identifying tau and amyloid build-up in the brain - and large clinical trials to develop therapies for specific groups. Those living with diabetes or atrial fibrillation (who are at greater risk of stroke) will be targeted.

Each different type of stroke is associated with development of Alzheimer's disease. In fact, 10 per cent develop dementia soon after their first stroke and more than a third have dementia after recurrent strokes.

Dementia is now the second leading cause of death in Australia and no cure exists. Over 340,000 people are living with dementia, including one in four over the age of 85.

By 2050, it is estimated that nearly one million Australians will have dementia and 7500 will be diagnosed each week.

Chief investigator and neurologist, A/Prof Amy Brodtmann.

"The financial cost and human toll is huge so we are driven to prevent dementia first by identifying specific groups at risk, and then actively intervening to stop it before it begins."

Among the range of activities to be undertaken during the five year study, the team will measure brains to assess levels of atrophy, will work with diabetics to examine the link between undiagnosed heart disease and brain shrinkage, and, using animal models examine whether pathological proteins are deposited after stroke.

We are seeking people 50 or over living with Type 2 diabetes (who do not have a history of stroke or dementia) to help us with this study. If you would like to participate, please email ewerden@florey.edu.au to register.

The A4 trial – slowing the progression of Alzheimer's

Can we delay the onset of Alzheimer's disease? The average age of onset for Alzheimer's is 80 years of age. If we could push that out by just five years it would make a huge difference to many people's lives.

The Florey is the only Australian site of a new worldwide trial of a drug designed to prevent the buildup of the toxic amyloid protein that is associated with Alzheimer's disease.

In the last few years, the Florey has been instrumental in developing the technology to determine whether an individual is on the pathway to Alzheimer's. This early detection means we can start to give drugs in the early stages of the disease, with the aim of preventing or delaying its progress.

If you are between 65-85 years of age and have a healthy, normal memory but perhaps are worried about getting dementia, or have a family history of Alzheimer's, you could be eligible for the trial. As part of the trial you will receive a health assessment, memory testing and will have a brain scan to see if there is a build-up of the amyloid protein.

A short introductory video to the trial can be viewed here. To register your interest call 1800 443 253, or head to florey.edu.au.

Keep your mind active – learn something new!

Have you been to one of our public lectures this year?

Professor Anthony Hannan.

The Florey has offered 20 free public lectures this year from our Parkville headquarters. The auditorium has been abuzz with members of the public and community groups coming to hear how we can keep our memories active, prevent a stroke, live with Alzheimer's, avoid depression, and cope with Parkinson's... to name just a few of the topics discussed.

Engaging with the Florey's amazing researchers is a great way to keep your mind stimulated and to learn something new. While we are researching very serious illnesses and disorders, we also celebrate the wonders and capacity of the human brain.

"It was a great privilege to hear from eminent scientists about their extraordinary work, their international connections and progressive research."

"These were wonderful lectures that have been able to describe the complex in simple terms. The content was very relevant and I now have a deeper understanding of brain diseases and the work the Florey is doing."

Our public talks in 2016 will include another series on Parkinson's disease with the legendary Prof Mal Horne, sport and concussion with Prof Paul McCrory, retaining an active memory (a sell-out in 2015) with Prof Bob Wood and a forum on Alzheimer's with a range of experts.

If you are not able to come to the Florey, many of our lectures are recorded and placed on our YouTube channel so you can watch from home.

If you are interested in attending events in 2016 or organising a group to attend, please email us at info@florey.edu.au. Details of the 2016 lecture series, including new topics and favourites from this year, will be posted on our website soon.

"I am very interested in developments in curing brain diseases and making life better for people with quadriplegia. Thank you."

florey.edu.au/news-events/events-seminars

Honour for Dr Lucy Palmer – a young leader on the rise

Dr Lucy Palmer has been named an Allen Institute for Brain Science Next Generation Leader, recognising her enormous contribution to international neuroscience. She will undertake the Seattle institute's role for a three-year term while based at the Florey in Melbourne.

Lucy has been selected as one of this year's six outstanding and innovative contributors from emerging scientific leaders around the world. She will be offered opportunities to network, to advise others and will receive informal training at one of the world's most innovative brain research institutions.

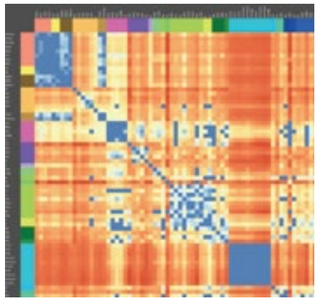
Lucy runs her own neural network laboratory at the Florey in the epilepsy division. She obtained a Masters in Science from the University of Minnesota and was awarded with a PhD from the Australian National University in 2008. She completed postdoctoral studies at the University of Bern, Switzerland and Humboldt University, Berlin before returning to join the Florey in 2013.

Dr Lucy Palmer.

Her laboratory investigates the dendritic activity and underlying neural networks contributing to sensory perception and behaviour in the mammalian brain.

Florey Director, Professor Geoffrey Donnan, has welcomed the recognition for Lucy. "We are incredibly proud to count Lucy as a member of our research team. Her work is profound and important as we seek to understand exactly how different brain regions connect and communicate," Prof Donnan says.

"Lucy's work will help us understand brain injury, attention deficit hyperactivity disorder, schizophrenia and depression."



From the Allen Brain Atlas: The patterning of gene usage across the structures of the adult human brain is highly stereotyped and reproducible. This heatmap represents the common structure of this patterning across individuals. Hotter red shades represent brain regions that are very different in their transcriptional regulation, while cooler blue shades represent regions of high similarity.

Source: casestudies.brain-map.org/ggb

Next Generation Leaders are selected each year through a competitive application process from a pool of international applicants.

The non-profit Allen Institute (www.alleninstitute.org) was launched in 2003 with a seed contribution from founder and philanthropist Paul G. Allen. Today, a mix of government, foundation and private funds enable it to share knowledge generously with neuroscientists around the world. Given the Institute's achievements, Mr. Allen committed an additional $300 million in 2012 for the first four years of a ten-year plan to further propel and expand the Institute's scientific programs, bringing his total commitment to date to $500 million. The Allen Institute's data and tools are publicly available online at www.brain-map.org.

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Improving lives through brain research

Stop press: A bionic twist in gut inflammation

Thanks to a large US grant, the Florey will lead a major new project to:

- define neural pathways that reduce inflammation of the gut
- develop bionic technology to electrically stimulate and record signals from the vagus nerve
- fast-track the pathway to human clinical trials of neuro-stimulation for the treatment of inflammatory bowel disease.

According to principal investigator, Professor Robin McAllen, inflammatory bowel disease is debilitating to patients and expensive to communities and health services.

"Current therapies are inadequate in terms of effectiveness, side-effects and cost. In the US, irritable bowel disease, ulcerative colitis and Crohn's disease are very common. Annually, they cost $6.3 billion in direct care, the productivity loss due to absenteeism is $3.6 billion and the personal suffering is huge," Robin says.

Fellow principal investigator, Professor John Furness adds that these diseases are relapsing and remitting, beginning in young adulthood and continuing throughout life. "And what's more, the prevalence of irritable bowel disease is increasing," John says.

Professor Rob Shepherd, Director of the Bionics Institute and another principal investigator, says the strength of multi-disciplinary research in Melbourne is renowned, citing the development of the cochlear implant and a bionic eye. "Therapeutic nerve stimulation for the treatment of inflammatory conditions is a novel approach that requires the specialist team of scientists, engineers, computer scientists and clinicians," he says.

The vagus nerve travels from the base of the brain to the chest and abdomen, carrying a wide assortment of signals to and from the brain. It supplies the heart, lungs, digestive tract, pancreas and other organs. It has only recently been discovered that it controls inflammation.

The increased incidence of inflammatory bowel disease in war veterans may be stress-related. Post-traumatic stress causes immune deficiencies which, in turn, can trigger lung, gut and other inflammatory illnesses.

A surgical team, led by Professor Bob Jones at the Austin, is renowned for establishing both the first liver and the first intestine transplant surgery in Australia. The team will create detailed functional and anatomical maps of the vagus nerve pathways.

The Florey is leading the four-year, $US6.07 million project with partners, the Bionics Institute, the University of Melbourne and Austin Health. The Defense Advanced Research Projects Agency will fund the work.

THANK YOU

The Florey thanks our recent donors who kindly donated $500 or more between June and September 2015.

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