Brain Matters

News from the Florey Institute of Neuroscience & Mental Health

STEM CELL TRIALS

PARKINSON'S AND STROKE PATIENTS SET TO BENEFIT

PAGE 4

THE FLOREY

SPRING 2017

Director's Report

Welcome to the Spring edition of *Brain Matters* for 2017.

Welcome to our Spring newsletter – thank goodness there are leaves on the trees and some warmth in the sunshine.

Since writing to you last time, I am pleased to report several of our talented researchers have attracted some highly competitive fellowships.

Dr Song Yao received an Australian Research Council Future Fellowship for his discovery that a part of our brain previously thought to lie dormant after development can, in fact, continue to develop new brain cells throughout our lives. This knowledge will allow Song to continue his search for breakthrough treatments for hypertension – a major cause of stroke. His Future Fellowship will give Song the security to pursue this high-risk, high-reward science.

Four of our most promising mid-career scientists were awarded National Health and Medical Research Council 'Boosting Dementia Research' Fellowships. Drs Thibault Renoir, Brad Turner, Daniel Scott and Blaine Roberts will apply their unique insights, skills and knowledge to this seemingly most intractable of diseases. They were chosen because of their extremely strong track records, and potential for innovative new thinking.

Finally, I would like to recognise Dr Yen Ying Lim who you can see on page 3 where she has written to you, our supporters, on her exciting Healthy Brain Project.

Yen has been named the "Young Researcher of the Year" by the Bethlehem Griffiths Research Foundation, great supporters of the Florey over the years. We thank the Foundation again for its wonderful philanthropic leadership.

Along with the visible success stories highlighted here, I would also like to recognise all of our extremely hardworking and driven researchers. There is so often a large dose of luck in receiving these fellowships and awards, and I want to assure you, our supporters, that we at the Florey endeavour to support all of our researchers through the lean times, as well as the good.

Your help can be, dare I say, invaluable in this regard.

Your generosity directly impacts on our quest to combat brain disease. Thank you.

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

A new beginning

At the opening of the new Melbourne Dementia Research Centre: Centre Director Professor Ashley Bush, Federal Health Minister Greg Hunt, Florey Director Professor Geoffrey Donnan and University of Melbourne's Dean of Medicine, Dentistry and Health Sciences, Professor Shitij Kapur.

Professor Ashley Bush and Dr Scott Ayton recently spoke to nearly 700 people who gathered in Ivanhoe to hear about the Florey's research into Alzheimer's disease.

Organised by Member for Jagajaga, Jenny Macklin MP, the response was remarkable. The mood in the hall was upbeat, despite the serious topic. Ashley and Scott told the audience how 45 years of combined work are coming together into a ground breaking clinical study known as the 3D Trial (Deferiprone to Delay Dementia).

If you are over 65 and noticed that your memory is declining, or you are newly diagnosed with dementia, you can register your interest in being involved in the study at 3D@florey.edu.au. Eligible participants will be contacted when the study opens for enrolment later this year.

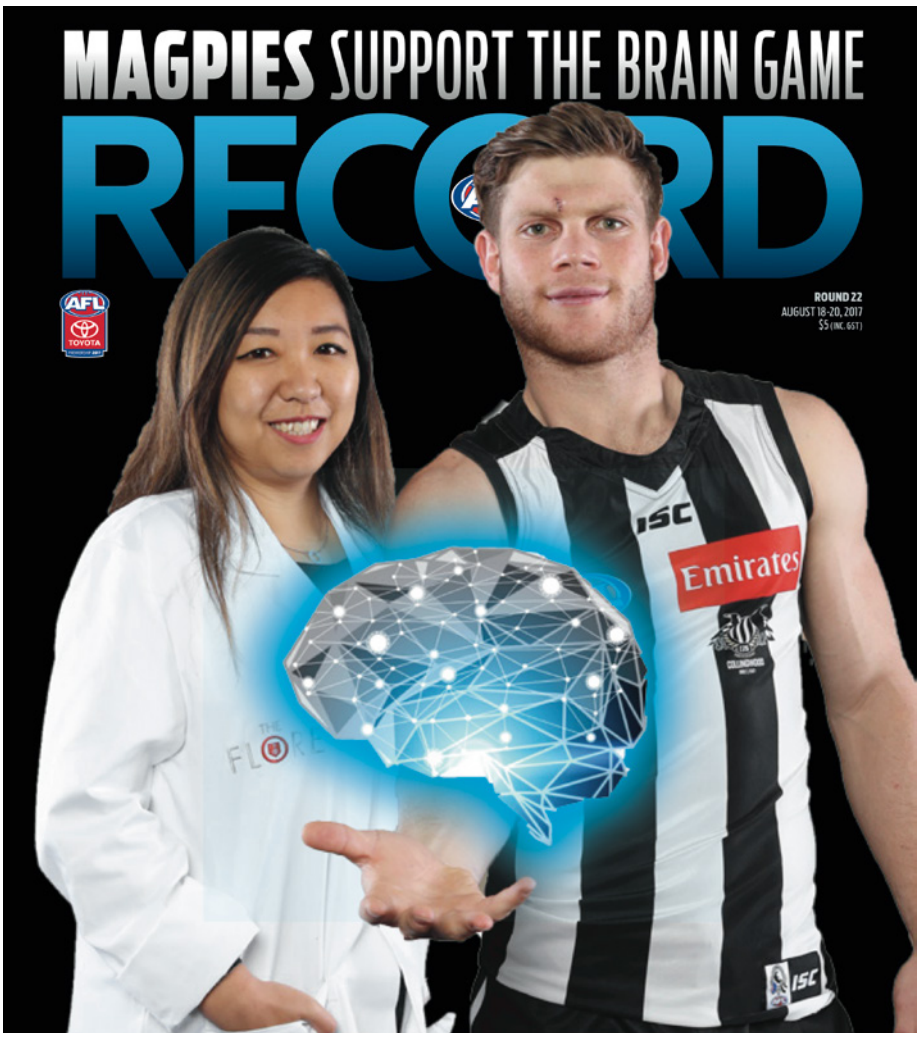
As well, Ashley has recently launched the new Melbourne Dementia Research Centre, an initative between the Florey and the University of Melbourne. The initiative will bring together nearly 200 researchers across Melbourne, fast-tracking diagnosis and treatment of Alzheimer's disease.

The Centre, the first of its kind in Australia, has funding of more than $22 million from the National Health and Medical Research Council (NHMRC), and $4 million in support from other funders. It will be home to researchers working on improved diagnostics, treatments, and ultimately a cure for dementia.

The Centre was officially launched by Health Minister Greg Hunt (above). Mr Hunt heard how Magnetic Resonance Imaging (MRI) and Positron Emission Photography (PET) facilities will play a crucial role in the 3D Trial.

"The aim is to use imaging as a common diagnostic tool for older Australians. One day, I hope it will be as common as a mammogram, a prostate test or a colonoscopy," Ashley says.

We hope we will develop an affordable and efficient way of diagnosing people at risk of dementia, which in turn will allow for early intervention and prevention of the disease's progression."



Dr Yen Ying Lim stars on the cover of the Footy Record with Collingwood vice-captian, Taylor Adams.

An experience to remember

The Florey is seeking 5000 Australians for a major study of dementia and Collingwood Football Club has been helping us spread the word. Here, Florey researcher, Dr Yen Ying Lim, talks about her moment at the 'G'.

As one of the lead investigators of the Florey's Healthy Brain Project, I had the pleasure of attending the Brain Game this year – a partnership between Collingwood Football Club and the Florey Institute to promote awareness of brain and mental health. Held at the huge MCG, I watched as Collingwood played Geelong on a lovely sunny afternoon. I tried not to look at the number of people reading the Footy Record which featured a cover of me alongside Collingwood vice-captain, Taylor Adams.

The game represented the culmination of an amazing week. Leading up to the Brain Game, I chatted on radio shows, prime-time television, and was interviewed by leading national newspaper journalists! Usually, I spend my days running analyses, setting up experiments and pondering the mysteries of Alzheimer's disease. Suddenly, I was given a crash course in media, recording videos with Eddie McGuire, Ross Oakley and Taylor Adams, and attending photoshoots! It was a whirlwind fortnight that culminated in the footy match, but more importantly, the interest and response from the Australian public was most overwhelming. We managed to enrol 3200 of the 5000 participants needed for the Healthy Brain Project – a phenomenal effort in such a short period of time!

We are recruiting 5000 middle-aged Australians (40-65 years old) and plan to follow them over five years to determine what combination of genetic and lifestyle factors may increase risk, or protect, against the development of dementia in late-life. We need such large numbers because this will help us develop more accurate predictions, and increase our ability to detect subtle, but important, effects that can sometimes be hidden in small studies.

> **"Dementia is very personal to me. My grandmother was diagnosed with Alzheimer's disease nearly 10 years ago... I think she'd be proud of my chosen career path"**

Dementia is very personal to me. My grandmother was diagnosed with Alzheimer's disease nearly 10 years ago, and I bore witness to the heartbreaking aftermath. I was always one of her favourites, and as her memory deteriorated, I was one of the last people she could remember before she entered a coma. I like to think she'd be proud of my chosen career path, and that she'd be grateful for all the support that I've received from the Florey, the Collingwood Football Club, and the Australian public for my efforts in fighting dementia.

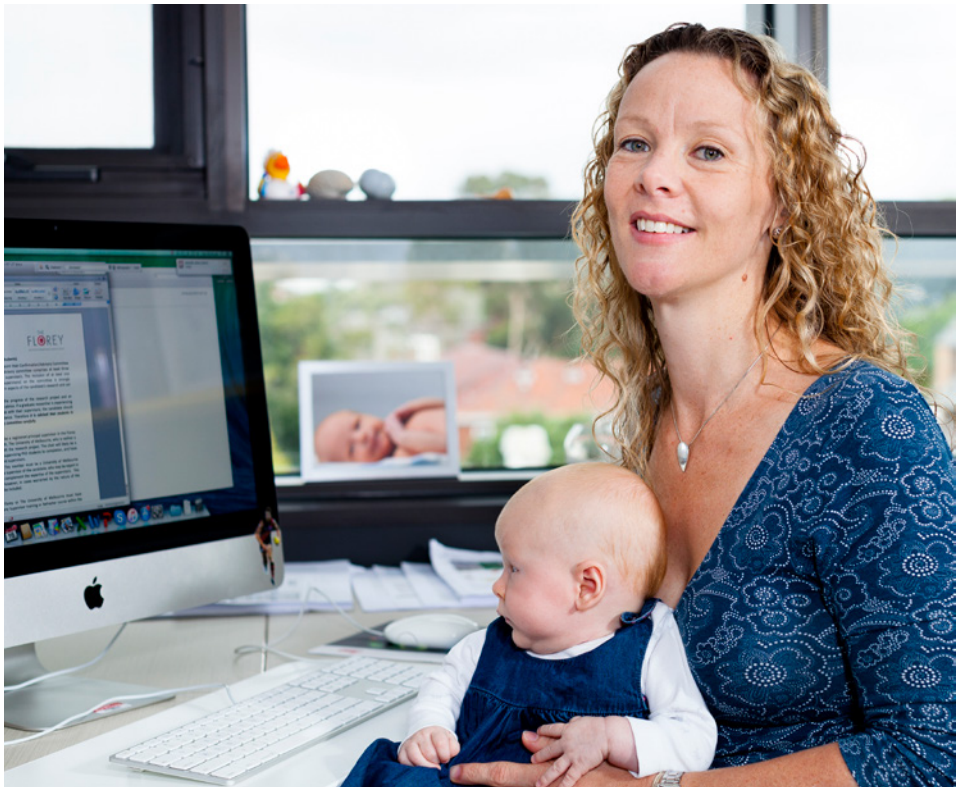
While I had the privilege of being the face of it all, the true magic occurred behind the scenes. I would like to thank everyone who worked incredibly hard to make the Brain Game the success that it was, especially the wonderful media team at the Florey, the brilliant people at Kayo Consulting, and my incredibly dedicated Healthy Brain Project team.

I am so humbled by the support that Eddie McGuire, Taylor Adams and the management of Collingwood Football Club have provided to the Florey and the Healthy Brain Project. Thank you for your time and your commitment to promoting brain health. Your support is invaluable to us.

And finally, to all of who you signed up to the Healthy Brain Project, donated to it, and helped spread the word about it, I thank you with all my heart. You are the unsung heroes of medical research. Thank you for your dedication to combating debilitating brain diseases like Alzheimer's disease.

To find out more about the Healthy Brain Project, or to sign up to it, please visit us at: healthybrainproject.org.au

Building bridges for patients and her colleagues



Professor Clare Parish and her daughter, Ellen.

Professor Clare Parish, head of our stem cells and neural transplantation laboratory, is currently in a scientific purple patch. Along with close friend and equally talented colleague, Dr Lachlan Thompson, she has just published three high-profile publications attracting lots of attention.

The reason? Latest research from the stem cell team could lead to a human clinical trial for Parkinson's disease in as little as two years. Grafts originating from stem cells could be implanted, restoring levels of dopamine to the brain of a person living with Parkinson's disease.

Since graduating from Monash in 2002, Clare has been on a stellar career track. She first obtained a CJ Martin Postdoctoral Fellowship from the National Health and Medical Research Council (NHMRC) after completing her PhD with Professor Mal Horne at Monash Medical Centre.

A series of major international awards allowed Clare to set a solid foundation in establishing and describing preclinical Parkinson's disease models, which allow researchers to study the disease in the lab setting with accelerated timeframes. Parkinson's in humans can take decades to develop, whereas laboratory models allow new discoveries to proceed at a much faster rate.

In 2008 Clare received both an NHMRC project grant to fund the lab, and a Career Development Fellowship. She teamed up with Dr Lachlan Thompson to fast track Parkinson's disease research into patient treatments. The 'dynamic duo' meet for a morning coffee every day to think up cool experiments. "These coffees are by far the most stimulating part of my day. We catch up to ask each other 'what if we did this?'."

The brainstorming pays off. Clare was awarded a Senior Medical Research Fellowship from the Viertel Charitable Foundation in 2011. "The Viertel Foundation are just such lovely people," enthuses Clare. "There is a real family feel around the Viertel. You look at the list of recipients and most have gone on to be phenomenal senior scientists."

Clare is starting a new collaboration to bring stem cells to the Parkinson's clinic.

A series of major international awards allowed Clare to set a solid foundation in establishing and describing preclinical Parkinson's disease models, which allow researchers to study the disease in the lab setting with accelerated timeframes.

"The Viertel Fellowship gave me the security to take on some high-risk, high-reward science. For a long time, critics of the field had been saying that stem cells won't work for treating disease. One by one we've addressed each of their objections, and will be taking our therapies into the clinic in a couple of years."

Clare has very much blazed her own trail with stem cells and Parkinson's disease, using the gold-standard of induced pluripotent stem cell (iPSC) derived brain cells. These are produced by taking skin cells taken from a patient, 'turning back the clock' to make them into stem cells and then 'fast forwarding' again to produce mature brain cells. Depending on the various molecular cocktails you puff onto the stem cells, you can make the appropriate type of brain cells for the transplant you plan to perform. This might be to treat Parkinson's by replacing cells in the substantia nigra, or cortical cells to treat stroke or traumatic brain injury.

Clare has very much blazed her own trail with stem cells and Parkinson's disease. While in in the UK a clinical trial is currently underway (TRANSEURO), focused on the use of human fetal tissue for transplantation into Parkinson's disease patients, Clare is striving to see the gold-standard of induced pluripotent stem cells (iPSC) reach clinical trials here in Australia soon. She also hopes to use the technology in the field of stroke – a newer research focus of her team.

Clare and Lachlan are now starting a collaboration with Professor Roger Barker from Cambridge University, to apply his knowledge of successfully transplanting tissue grafts to their iPSC-derived brain cells.

Professor Barker has been running a major European trial, and Clare hopes to leverage his expertise to run a human trial with a bank of laboratory-derived dopamine cells in two years. The trial will run at the Royal Melbourne Hospital, in collaboration with Parkinson's neurologists who have the clinical expertise and connections to run human Parkinson's disease trials.

The future looks bright for this aspiring future leader, and for the patients she's striving to help.

Dr Lucy Palmer

Dr Lucy Palmer, a researcher in sensation, learning and memory at the Florey, was one of this year's prestigious Viertel Fellowship recipients, and Clare has pegged Lucy as a total winner.

"Lucy has this amazing attitude and willingness to work with whoever knocks on her door, rather than say 'I'm too busy' or 'I don't really think that's going to work'. She's got it."

Lucy is one of the vanguard of mid-level female researchers at the Florey. While Clare is the most senior female leader at the Parkville campus, she greatly appreciates the solidarity and comradery of the new wave of female lab leaders she has around her, and credits the Florey's gender equality team for the slow but steady progress toward gender parity at all levels.

Professor Mal Horne

Professor Mal Horne, a Parkinson's disease neurologist and Clare Parish's PhD mentor, has just raised another $20 million in capital for his spin-off company Global Kinetics Corporation.

The company was born off the back of research Mal was doing to measure Parkinson's symptoms and their response to treatment. A $20,000 grant from the Vowell Foundation kickstarted that work, which now has the potential to become the world's leading Parkinson's measurement tool.

Professor Roger Barker

Professor Roger Barker has been awarded the 2018 Allan and Maria Myers International Visiting Fellowship and plans to visit the Florey early next year.

While here, he will work closely with Clare and Lachlan to advise them on best practice procedures for clinical trials, as well hearing the latest on advances in the Parkville precinct.

Could sugar improve memory after a brain injury?

Florey researchers investigating ways to reduce brain cell death in Alzheimer's disease have stumbled on to a possible treatment for traumatic brain injuries.

Dr Stuart Portbury and Associate Professor Paul Adlard have used trehalose, a sugar molecule commonly added as a food sweetener, and as a 'carrier' in medicines, to improve brain function following a traumatic injury.

Traumatic brain injury (TBI) is a major health problem around the world, and is one of the leading causes of death and disability in high-income countries. Around 700,000 Australians are living with a TBI and serious long-term disabilities. There are many causes of TBI, but most are due to car accidents, physical assaults in younger people and falls in older people.

Increasingly, media attention is also focusing on the mild but cumulative brain injuries sustained during contact sports like American football and Australian rules football, and TBIs sustained by military veterans are affecting their ability to live full, rich lives after leaving military service. Over 200,000 U.S. service members deployed to Central Asia and the Middle East have been officially diagnosed with TBI since 2003.

Clearly, TBI is a serious issue and we desperately need treatments to accompany standard rehabilitation therapies to repair these injured brains.

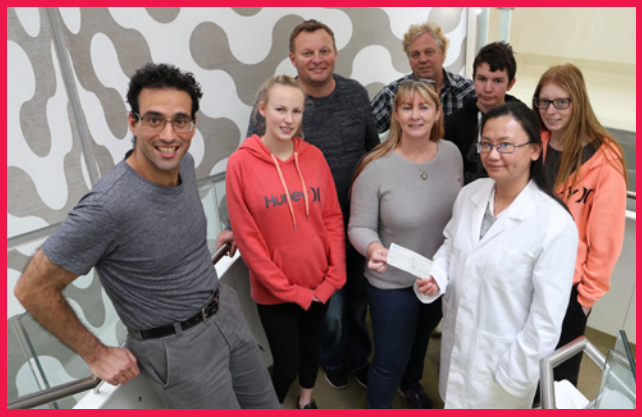
Publishing their research in the journal PLOS One, the two Florey researchers showed (in preclinical models) that treatment with trehalose, but not maltose, a related sugar molecule, is able to improve performance on a number of memory and behavioural tasks following a TBI.

These tests included spatial-memory tasks, as well as tests of short-term memory and willingness to explore new environments. In each test, trehalose restored an ability to remember important or familiar locations. Importantly, trehalose was only administered after the injury in order to mimic the clinical setting, and these cognitive enhancing effects were observed a month after the injury.

Following TBI, the brain undergoes many dramatic molecular changes that ultimately result in brain cell death. Curious to know how trehalose was exerting its amazing effects, the researchers performed detailed molecular profiling of the brains following TBI.

They quite unexpectedly discovered that trehalose treatment increased levels of synaptophysin, a surrogate marker for the number of synapses in the brain (the connections between neurones). Additionally, they also saw that trehalose induced the birth of more new brain cells in response to the injury, which can integrate into and enhance the brain's circuitry. In order to explain this, the team measured levels of key growth-promoting molecules for newly-born brain cells, including the protein, brain-derived neurotrophic factor (BDNF). Sure enough, levels of the protein were increased in the same brain areas, indicating that trehalose is probably helping to protect and regenerate parts of the brain.

The team will now test different doses of trehalose – more may indeed be better – and to work out exactly how trehalose exerts its actions. The fact that the benefits observed in this TBI model may also have profound implications for other brain disorders, and diseases of ageing, is also at the forefront of their minds and will form part of their future work moving forward. Be sure to check back for updates.

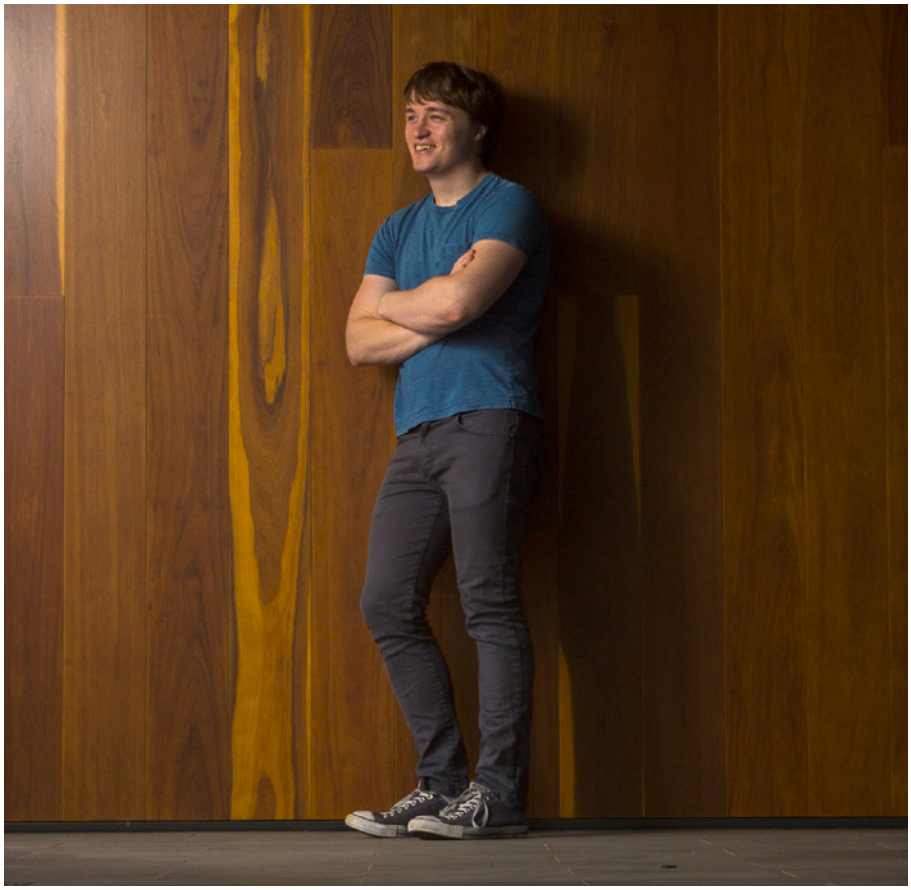


Front row L– R: Dr Amit Lotan, Jessica Sheehan, Kellie Adams, Dr Ya Hui Hung.
Back row L– R: Rex Sheehan, Andrew Adams, Aaron Adams, Taylor Adams.

The Florey's researchers are constantly amazed by the generosity of the community in supporting our work in so many different ways. We would like to thank Andrew and Kellie Adams and members of the NPC Disease Foundation who recently donated $50,000 to Professor Ashley Bush and Dr Ya Hui Hung to further their work into Niemann Pick-Type C disease. Sadly, Andrew and Kellie's two children, Aaron and Taylor are affected by this devastating and fatal condition. Also visiting to see the laboratories were Jessica Sheehan and her father, Rex. Dr Amit Lotan was also there to say thank you.

Donations such as this are the result of the constant community outreach work, despite the families' own battles. It's humbling and a poignant reminder of the importance of our research.

Is flexible thinking valuable?... Maybe. But then again...



Florey PhD student, Ariel Zeleznikow-Johnston works with well-behaved mice.

Most parents will be used to arguing with their kids over too much 'screen time'.

These fights, however, don't happen in the Florey's epigenetics and neural plasticity laboratory. Instead, everybody gets equal access to the touchscreen tablets, and everybody gets a reward of a strawberry milkshake for avid use.

The twist in the lab is that the study subjects vying for quality screen time are two groups of carefully bred mice, who PhD student Ariel Zeleznikow-Johnston has diligently trained to use the touchscreens.

The iPad-happy mice are starting to produce some fascinating findings which Ariel and his PhD supervisors Professor Anthony Hannan, Dr Emma Burrows and Dr Thibault Renoir, hope will show a direct link to strategies to combat Huntington's disease, Alzheimer's disease and other brain ailments or forms of dementia.

It would appear that living in an enriched environment, with cognitive stimulation and physical exercise, can have a bearing on the ability to be 'cognitively flexible', when it comes to being able to change thinking or deal with shifting problems. The findings published in the journal, Neuropharmacology, address a problem often associated with the ageing brain – the ability to be flexible and to reverse direction, to adjust one's mindset to suit a new situation.

The mice are split into two groups, where one group lives in boring, unstimulating housing, and doesn't get much physical exercise, while the second group lives in a much more engaging and novelty-filled environment with room to explore, cognitive stimulation and physical exercise. Ariel's paper showed that this second group of mice performed better than the bored mice when it came to problem solving and performance on touchscreen challenges.

The exciting part of the work, according to Anthony, is that the rodent challenge directly translates to human psychological testing methodology.

"Humans, if they are being assessed for cognition these days, will generally be using a tablet device like an iPad or a similar technology – it's a common way to do psychological tests," he says.

Ariel's work focusses on cognitive stimulation, physical activity and stress, as potential enhancers or inhibitors of cognitive flexibility.

Behind such tests are theories examining changes in the mice brains at a molecular and cellular level and how that may correlate with humans. Ariel says he is not only looking for factors that could be proven to delay or affect the onset of brain conditions, such as various forms of dementia, but also for where an enriched environment, cognitive stimulation and physical exercise does not make a difference.

The work could eventually lead to new drugs or therapeutics ('enviromimetics') that can mimic or enhance in humans the stimulation that appears to help Ariel's mice achieve greater cognitive flexibility.

So how do you train a mouse to use a touchscreen, let alone complete increasingly sophisticated challenges for milkshake rewards?

"You have to do it slowly and gradually," Anthony says. "They first have to get used to the idea that touching their nose on the screen gets them anything, and then they get used to the idea that there is an associated reward and gradually behaviour shapes in a way where they realise they actually have to look at the screen and touch the right stimulus on the screen to get the reward, so it goes through a series of easy tests that move on to harder tests."

Ariel says the most basic test sees a mouse press A or B with its nose, receiving a reward for A, but not for B. Ariel then moves into what's known as 'reversal learning tasks'. The same mouse presses A and nothing happens, because the test has been switched so that B now offers the milkshake. Ariel's study found that the mice enjoy cognitive stimulation and physical exercise in their enriched environment and are better at figuring out and retaining such changes in reward actions and delivery, compared to the bored and sedentary mice from the less stimulating environment.

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News & Events

Save a minute, save a week of life

Professor Leonid Churilov, Head of statistics and decision analysis at the Florey.

New Florey research has revealed an exciting finding for those treating stroke patients in an emergency department. It will prompt emergency teams to run even faster when they receive a stroke patient – straight to theatre.

Every minute sooner a stroke survivor has a blood clot removed by surgeons, saves them almost five extra days of healthy life. The surgery, known as endovascular clot retrieval therapy, literally sucks a clot from the brain via a stent in the groin.

The startling finding has been published by the Florey's head of statistics and decision analysis, Professor Leonid Churilov. Leonid performed computer modelling based on statistics from stroke patients in Helsinki, Australia, and the Netherlands.

The work, published in Neurology in conjunction with stroke neurologists, Dr Atte Meretoja and Florey director, Professor Geoffrey Donnan, builds on the group's previous work looking at the use of a clot busting drug known as tPA. This is the standard drug given to stroke patients, but it can currently only be given up to 4.5 hours after the stroke, and only in people with a confirmed clot or blockage.

Endovascular clot retrieval is a relatively recent intervention, and is used when a patient has a blocked large artery in their brain. A so-called retrieving stent is inserted in their groin and fed up into their brain, where a tiny wire cage is deployed around the clot and then dragged back out of the brain, thereby restoring vital blood flow.

Most significantly, younger patients, under 55 years old, who suffered moderate to severe strokes gained more than a week of healthy life for each minute saved.

In 2017 there will be almost 56,000 new and recurrent strokes - one every nine minutes - and of those, 30 per cent will happen to someone of working age.

This research highlights the importance of transporting patients with large artery blockage in their brain to a dedicated stroke centre as fast as possible – every minute makes a big difference.

Thank You

The Florey thanks our recent donors who kindly donated $100 or more between May 2017 and September 2017*

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For more information contact the editor,
Amanda Place: amanda.place@florey.edu.au or +61 411 204 526

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