New Zealand Brain Research Institute

Newsletter
November 2020

Research Director's Report

Well, 2020 has certainly been an interesting year. Despite the lockdown and worldwide pandemic, we have been very productive with publishing new research findings, and in just the last few months we've had two of our PhD and three Masters students finish their projects. Three new PhD and one new Masters students have recently started and we wish them all the best for their studies. We also have two new post-doctoral research fellows.

Dr Sam Harrison is working to quantify the prevalence and progression of apathy in Parkinson's, while Dr Sarah Perry is investigating how the cough reflex changes as a function of cognitive decline and the impact that has on overall health. We're pleased to have them all on board with us at the New Zealand Brain Research Institute.

This newsletter includes an update on our Huntington's disease clinical drug trial from Clinical Director, Professor Tim Anderson, as well as some of the results from our Parkinson's Covid-19 lockdown study. Taking what we learned from the Covid-19 lockdown we're planning to move a number of our research assessments online, reducing the testing burden for participants.

As always, we are thankful for your support of NZBRI, and we hope you enjoy reading our latest research and updates.

Dr Michael MacAskill
Research Director

International Huntington's disease drug trial

By Professor Tim Anderson and Dr Laura Paermentier

Huntington's disease (HD) is a progressive genetic neurodegenerative disease. It is caused by an abnormally long (expanded) huntingtin gene on chromosome 4. It is an "autosomal dominant" disease, which means that an affected person has a 50% chance of passing it on to their child.

We all carry two huntingtin genes on chromosome 4, one inherited from each of our parents. Like any gene, these are made of a repetition of little blocks of DNA which are translated into a protein: in this case, the huntingtin protein. This protein is very large and it is often described as an airport hub, allowing many other proteins to interact and to connect. It is therefore essential to the overall function of cells.

While most people carry two huntingtin genes of normal size, HD patients carry one "normal" gene and one expanded gene. The huntingtin protein produced by the expanded gene has an abnormal shape and is toxic to the cells, especially brain cells. While all areas of the brain are ultimately affected, the damage starts in the basal ganglia, a deep region of the brain that is responsible for body movements. It gradually progresses to other areas including the cerebral cortex, and affects both cognition and behaviour. Anxiety, mood and temperament changes are common. In due course most people with HD become disabled with unwanted jerky or twisting body movements (chorea) and dementia.

Symptoms start on average around 40 years of age. However, the size of the gene partly influences the age of onset and therefore some patients can develop signs and symptoms in their teens or twenties while others may develop symptoms much later, even in their seventies or eighties.

Laura Paermentier, Clinical Research Coordinator, (right) working with a Huntington's patient

It is not unusual for new cases to emerge without any known family history.

We have been participating in Huntington's research since 2012 through an incredibly valuable worldwide observational study, the ENROLL HD study, which is ongoing. We have more than 100 people involved as part of the study here at the NZBRI.

Over the last few years, clinical trials of gene therapies have moved out of the labs into the clinics and in July 2019, we started volunteers with HD into a phase 3 double-blind clinical trial of anti-sense oligonucleotides (ASOs) sponsored by Roche (BN40423). ASOs are small artificial pieces of DNA that interrupt the making of proteins. An earlier Roche phase 2 trial in 2018 in HD patients had found that ASOs were safe, well tolerated and capable of reducing the amount of harmful huntingtin protein in the brain. The only way to measure the huntingtin protein is by collecting some cerebrospinal fluid (CSF), the liquid that surrounds and bathes the spinal cord and brain. This is done via a lumbar puncture (inserting a needle at the base of the spine).

The only way to deliver ASOs to the brain is via intrathecal injection with a lumbar puncture. ASOs mix with the CSF and eventually they make their way up to the brain where they act.

Around 880 participants are currently enrolled worldwide in this international clinical trial, with nine of these participants enrolled with us here at NZBRI. The trial is targeted at patients who are in the early phase of the disease and showing symptoms of Huntington's disease. Each one attends a study visit every two months and undergoes a whole raft of assessments including neurological examinations, questionnaires about daily activities, cognitive testing, blood and urine sample collections. A smart phone and wearable device (smart watch) are used to measure daily activities, and several brain MRIs are done during this two-year study.

Fifty per cent of patients are on placebo (dummy drug) injection every two months, 25% receive the "real" ASO treatment every two months, and the remaining 25% receive an alternating treatment of placebo/"real" ASO every two months. These groups are needed to enable interpretation of the results. Neither we nor the patients know what treatment they are getting and this is therefore called a *double blind placebo controlled trial.* Also, helping with this trial are Beth Elias from NZBRI, Dr Susie Newton and Dr Jeremy Foate (both anaesthetists) and Canterbury Health Laboratory staff Ros and Cath.

This is the first of a number of exciting clinical trials being planned aiming to lower the damaging mutant huntingtin protein by dampening or silencing the huntingtin gene. There is an enormous amount of hope worldwide around those trials and we are privileged to work with a group of brave patients who have volunteered for this treatment trial. They are taking a big leap to make a tangible contribution to what we expect to be ultimately an effective therapy for HD in the future. Who knows what other neurodegenerative disorders could be trialled in this way using different agents?

Collecting the cerebrospinal fluid during a lumbar puncture

Results from our Covid-19 Parkinson's research

By Kyla-Louise Horne

The COVID-19 lockdown disrupted every aspect of our lives, including the NZBRI's longitudinal Parkinson's project. During this time, we were unable to conduct face-to-face research as, like all New Zealanders, we were at home. Overseas there had been reports that Parkinson's patients experienced increases in their non-motor symptoms due to COVID-19 lockdowns, however, direct comparisons with pre-lockdown levels of non-motor symptoms had not been investigated. At NZBRI we were in the unique position of already having up to 13 years' worth of longitudinal data from our study participants. Using this, we were able to conduct a study to determine if there were changes in mood during lockdown when compared with the participants mood before lockdown

What participants enjoyed most during the COVID-19 lockdown

To examine if lockdown affected non-motor symptoms in Parkinson's disease, and to remain in contact with our participants during this unprecedented time, 171 Parkinson's patients and 49 control participants without Parkinson's from the longitudinal study were contacted between the 17th of April and the 22nd of June 2020. Online surveys and telephone interviews were used to assess self-reports of current anxiety, depression, neuropsychiatric symptoms and participants' ability to perform everyday tasks. Advanced statistical modelling was used to compare these findings with data collected prior to the COVID-19 lockdown.

We found the only change relative to the pre-lockdown period was greater everyday functional impairment in those Parkinson's participants with dementia. There was no other evidence of changes associated with lockdown in participants. The NZBRI assessors, Leslie Livingston, Sophie Grenfell, Beth Elias, Marie Goulden, Maddie Pascoe and Bob Young, noticed that both control and Parkinson's participants without dementia had similar daily life experiences during lockdown. Participants reported that the negative aspects of lockdown-induced physical isolation were the decreased ability to carry out shopping and leisure activities, and reduced social contact, especially not being able to see friends and family. The Parkinson's participants also felt isolated and controls reported missing their freedom. The positive aspects of lockdown included spending time at home, having more time for reading, and extra free time. During lockdown, both groups reported feeling highly supported by the New Zealand Government and that they were satisfied with the amount of COVID-19 related information they were receiving from official sources. Both groups, understandably, reported that they were feeling somewhat stressed, on average, about the current situation.

In summary, there was no evidence that New Zealand's lockdown affected anxiety, depression, neuropsychiatric symptoms or participants' ability to perform everyday tasks, when compared to levels prior to the COVID-19 lockdown. We think that the resilience of New Zealanders during lockdown may reflect the Government's policies and response, together with the low national incidence of COVID-19 infections during this period.

We would like to thank the research participants, their partners and the control group for participating in this Covid-19 study. We're constantly in awe of these amazing people and their willingness to help research Parkinson's disease.

Research participant, Richard Wethey, enjoying spending time in his garden

Recent research publications

Dr Campbell Le Heron

Dr Campbell Le Heron recently published in the Journal of Neuroscience, a preeminent journal in the neuroscience community. Campbell investigated mechanisms of decision-making and the role the chemical messenger dopamine plays in that process.

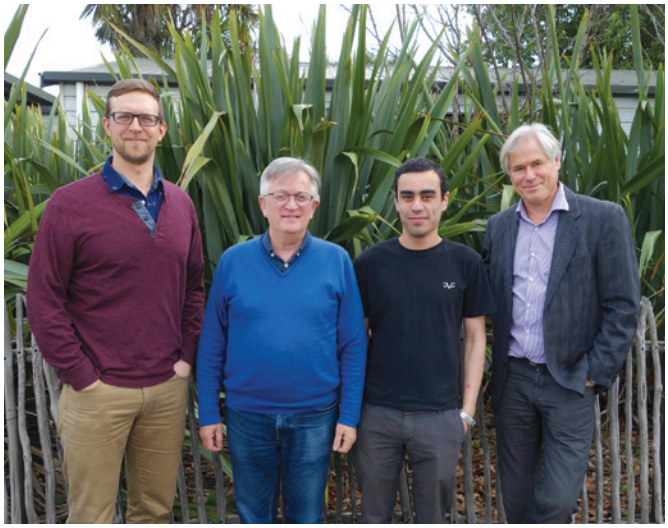
Results demonstrated a specific role for dopamine in deciding when to move on from the current activity to another one, in order to pursue greater rewards. This research brings important insights about normal human behaviour that the team are planning to leverage to better understand motivational deficits that occur in the context of brain diseases. This is particularly relevant because Parkinson's disease results in lower production of dopamine in the brain.

Professor Tim Anderson, Dr Toni Pitcher and Dr Tracy Melzer, who contributed to the international ENIGMA study.

Brain imaging and genetic data from our Longitudinal Parkinson's Study contributed to the March 2020 Science paper from the international ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analyses) study group. In this study of over 50,000 people (including those with a variety of different disorders as well as healthy controls), some 300 genetic sites were identified that influence the brain's surface area and thickness of the cortex (the outer layer of the brain). Some regions of the genetic structure identified in the paper may also be relevant to the risk of Parkinson's, and this paper will stimulate a great deal of further research in this area.

For a full list of our recent research publications visit nzbri.org/Labs/Publications/ or call us on 03-5956-800.

Health Research Council Grant



Dr Tracy Melzer, Professor John Dalrymple-Alford, Dr Reza Shoorangiz and Professor Tim Anderson

In a time of funding uncertainty, we are very pleased that Professors John Dalrymple-Alford and Tim Anderson have received a Health Research Council Grant to lead a new study, investigating predictors of cognitive health for people with Parkinson's disease. Alongside Dr Reza Shoorangiz and Dr Tracy Melzer, their aim is to determine a more accurate prognosis for patients.

"Knowing who is at risk of rapid decline is important for that person and their whanau and the management of their condition. This funding will be a major boost to this kind of research. We plan to use a unique combination of biomarkers to help predict cognitive impairment in people with Parkinson's disease," Professor Dalrymple-Alford says.

Researcher Profile
Dr Sam Harrison

Welcome to Dr Sam Harrison, who has just arrived from the UK. He'll be working with Dr Campbell Le Heron on a Canterbury Medical Research Foundation-funded project, looking at the brain mechanisms that underlie loss of motivation in people with Parkinson's disease. The aim is to quantify the prevalence and progression of apathy in Parkinson's, taking advantage of the longitudinal study we have at NZBRI, and to use brain imaging data to determine the earliest neural changes that predict the development of apathy.

Student Profile
Dr Megan Stark

"It's clear that there are still more questions to ask, however removing amyloid from the equation is a big step towards solving the mystery of cognitive decline in Parkinson's disease."

We're so proud of Dr Megan Stark, who was awarded her PhD through the University of Otago and was placed on the Health Sciences Divisional List of Exceptional Doctoral theses. This means her thesis is amongst the top 10% examined and is exceptional for its research content, originality, quality of expression, and accuracy of presentation. Megan's PhD investigated potential biomarkers (clinical and laboratory clues) of cognitive impairment and conversion to dementia in Parkinson's disease. Her primary finding was that amyloid (a type of protein) plaque deposition in the brain in this group of Parkinson's patients was comparable to levels seen in healthy ageing.

It is likely that these plaques (prominent in Alzheimer's disease) do not drive the cognitive impairments seen in Parkinson's, in the absence of other changes occurring in the brain. This is unlike Alzheimer's disease which is associated with such protein build-up. Megan's research is one part of a team effort, to gain a clearer picture of what may or may not be causing this important non-motor aspect of Parkinson's disease.

Fundraising News

The New Zealand Brain Research Institute relies solely on research grants, fundraising and donations. We usually have three main fundraising events throughout the year. For more information about our work or how to support us please contact us at **info@nzbri.org**

The Friends of the Brain Institute Golf Day is fully booked and raring to go on Friday 27 November. Last year this event raised $45,000 and the 31 teams had a fantastic day out at the Christchurch Golf Club at Shirley Links.

Save the Date! Unfortunately the Covid-19 lockdown put an end to our Opera Meets Art fundraising event earlier this year. We'll be back on **Saturday 8 May 2021** for a revamped evening of popular music in a new venue, The Piano on Armagh Street. This purpose-built concert hall has state-of-the-art acoustics that will make for an exceptional musical experience. We'll keep you up-to-date when tickets go on sale.

The Pegasus Bay Vine Run is on Sunday 31 January 2021. With 6km, 10km and 18km options, as well as a festival atmosphere, there is something for everyone. It's a great day out, so join in the fun and run or walk amongst the picturesque hills, valley and vineyards of Pegasus Bay to support the New Zealand Brain Research Institute. Register at **vinerun.co.nz**. The link between wine and brain research is Professor Ivan Donaldson, a man of many talents. Ivan was the first neurologist based in Christchurch, he is a board member at the New Zealand Brain Research Institute and is also owner of Pegasus Bay Winery. Ivan's family all work at the winery and with the amazing team at Pegasus Bay, the 2020 Vine Run raised $27,000 for brain research.

A great day out amongst the stunning vineyards of Pegasus Bay.

Coming Up

We'll be celebrating brain month in March 2021 with a range of public talks.
Make sure you are on our database by emailing **info@nzbri.org**, or follow us on Facebook at **facebook.com/nzbri**

Yes! I would like to support the New Zealand Brain Research Institute

Name: _____
Address: _____
_____
City: _____ *Postcode:* _____
Phone: _____
Email: _____

My gift: $ _____

Credit Card *Name on Card:* _____

Card Number: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ *Expiry* ____ / ____

If you would like to support neurological research by internet banking, please transfer your donation to New Zealand Brain Research Ltd, account number: ***01-0797-0631546-00*** *with your name and initials in the particulars line.*
Please email us at ***info@nzbri.org*** *or call us on 03-595-6800 so we can send you a tax receipt.*
Alternatively, visit ***nzbri.org/Support/Donate/*** *to make a donation directly online.*
If you have any questions, or would like more information on how to support neurological research, please contact our team on 03-595-6800.

Charities Commission No. CC20457

Your donation can be sent to: ***NZBRI, 66 Stewart Street, Christchurch 8011***