brainWAVES

The Newsletter of the Brain Foundation. *Summer 2010*

Summer and Christmas Edition

To all our valued members, the directors and staff of the Brain Foundation extend our best wishes for a very happy Christmas and a safe and relaxing New Year and holiday season. We hope that you enjoy reading about our recent successes and awards.

Faulty gene causing migraines!

Recent research has found that migraine with aura (accompanying visual disturbances) is caused by a faulty gene.

The study, undertaken by Griffith University researchers in Queensland in collaboration with Oxford University in the UK, University de Montreal in Canada and other research organisations, was published in the prestigious medical journal Nature Medicine in September this year.

The study found when the gene KCNK18 is not switched on, it inhibits a protein, called TRESK, which regulates the threshold of sensitivity of pain centres in the brain.

Griffith Health Institute Director, Professor Lyn Griffiths, said while previous studies found genes associated with migraine, this faulty gene directly caused migraine.

"For the first time, we have found a clear inheritance pattern in the gene and know it is the cause behind this debilitating condition," Professor Griffiths said.

The team compared the DNA of people who suffer from migraines with that of people who do not. They found that one large family of sufferers of migraine with aura carried the mutation.

"We traced a family over four generations and found that all people in the family with the gene mutation suffered from migraines and it was a dominant gene, so that a single copy of the mutation led to the painful disorder."

TRESK, which plays an important role in nerve cell communication, and its pathways provide important clues for migraine treatment.

"This finding will give us a real opportunity to find a new way to fight migraines and improve the quality of life for those suffering."

"Further research needs to investigate how commonly people with migraine and aura are affected by the mutation."

Migraine is a common recurrent headache disorder, with an annual prevalence estimated at 18.2 per cent in females and 6.5 per cent in males.

The World Health Organization rates it as a leading cause of disability worldwide and it is also thought to be the most costly neurological disorder in Europe.

One third of attacks, which can last from four to 72 hours, have accompanying neurological disturbances known as aura.

These are commonly visual, such as hallucinations and black spots.

The Brain Foundation would like to invite all migraine and chronic headache sufferers to register on the Headache Australia web site if you have not already done so. The web site posts information about research projects and invites members who fit the criteria to apply should they wish to participate. The web site also hosts a forum in which members can ask questions or share their experiences with others.

www.headacheaustralia.org.au or www.brainfoundation.org.au

Contact the Brain Foundation
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Email: info@brainfoundation.org.au
Visit our websites www.brainfoundation.org.au and www.headacheaustralia.org.au

Events

Zombies turn out in force in Brisbane

Where do all the Zombies in Brisbane hide?

The 5th Brisbane Zombie walk took place on Sunday 24th October in glorious sunshine. With a larger than expected crowd of around 12,000, the Zombies were obviously not put off by the sunny weather!

Many Zombies arrived early, and the crowd of extravagantly made up people continued to grow until, by 3.00 pm, Wickham Park was completely full. There were family groups and smaller groups of friends over a very wide age range, all united by the opportunity to enjoy the occasion to "dress up" in an outlandish and gruesome way for the fun of it, and to raise money for the Brain Foundation.

Leaving Wickham Park for a walk to Centenary Place in the 'Valley' the parade entertained and attracted large crowds of onlookers in the city. Marshalls were kept busy collecting donations for the Zombies as they passed by and it took over 2 hours for the entire group to cover the 3kms to the final destination where refreshments and pizza, courtesy of Hell Pizza, awaited. With strong support from the sponsors, Dracula's on the Gold Coast, CrazyContacts, 24 Hour Wristbands and Hell Pizza donations and sales from merchandise the event raised over $13,000.

The Brain Foundation would like to sincerely thank the organisers – Cara Westworth, Anthony Radaza and Sarah Keogh for their tireless work to organise this event every year. Is Brisbane the Zombie capital of the world? We think it might be.

Second Annual Golf Day

Golfers supporting the Brain Foundation were out early on a lovely spring day in September at the Pymble Golf Club for a morning of play organised and managed by Gary Dawson and Matthew Laverty of Bullant Sports, at no cost to the Brain Foundation. A fully catered breakfast gave the 64 Golfers a good start to the day and while it was very unfortunate that 14 of the greens were out of play, this only added to the challenge as the temporary greens were harder to read and play.

The day was made possible due to the dedication and abilities of Brain Foundation Director, Val Gibson. She recruited the players and also made her Surfers Paradise Unit available for a week as an auction prize. Other auction items were available courtesy of Gary Dawson and raffle items were donated by The Constant Reader, Burlington Restaurant and Stuyvesant's House, Crows Nest, Club Mac Hair Design, West Pennant Hills, and also by Gary and his connections.

Bullant Sports also support a number of other charities in this way in between their main business of conducting Golf Days for staff and clients of major corporations. They add to the funds raised from each Golf Day by having a combined Charity Gala Dinner at the end of the year at the Sydney Hilton Hotel.

Val Gibson and Gerald Edmunds (right) are pictured with the winning men's team.

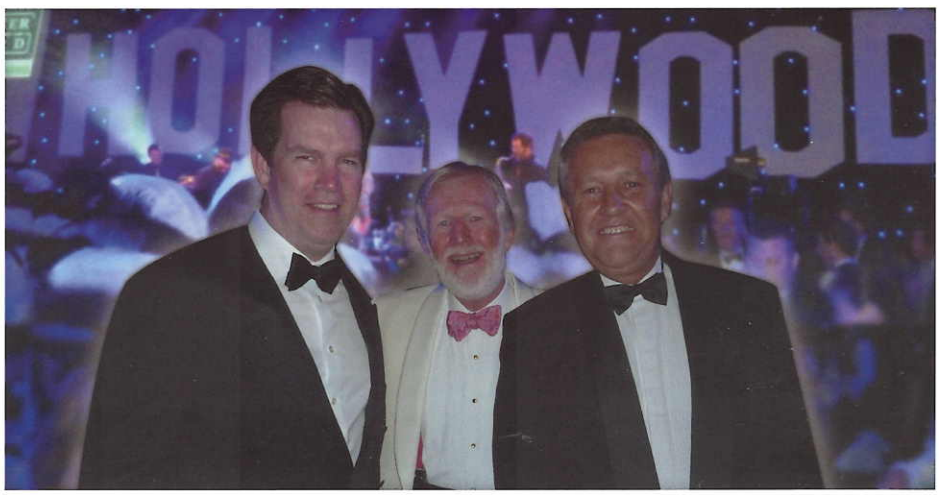
Hollywood comes to the Gold Coast at the Ray White Surfers Paradise Annual Charity Ball

"Hollywood" was the theme and the Sheraton Mirage on the Gold Coast was the venue for the 15th Annual Ray White Charity Ball. Organised by Andrew and Greg Bell, Directors of Ray White Surfers Paradise, the committee, led by Selena Carson, put in an enormous effort promoting and running the Ball and arranging Marcia Hines as the entertainment.

This successful event raises funds for Muscular Dystrophy and lifts the profile of the Brain Foundation in the region. All tables were booked well in advance, giving a total attendance of 600 people. There was a wide range of highly desirable items for the silent auction and the open auction attracted spirited bidding.

The Brain Foundation's 2010 Grant for research into Muscular Dystrophy linked to this event was awarded to Dr Sandra Cooper of the Children's Hospital at Westmead and the University of Sydney (see summary this newsletter).

Secretary General, Gerald Edmunds is pictured with Karl Morris of Ord Minnett (right), and Andrew Bell (left).



2010 Award Winners and Projects

The highlight of the Brain Foundation's year is the formal presentation of research awards. Held in the Great Hall at Sydney University, this year's Guest of Honour was Mr Alan Jones AO and once again our guests were treated to a recital by international concert pianist, Ambre Hammond.

This edition of Brainwaves provides a showcase for the successful applicants and their projects. Without the support of you, our donors, these awards would not be possible.

Memory function in temporal lobe epilepsy

Dr Julia Hocking

Co-Investigator: Professor David Charles Reutens

Mesial temporal lobe epilepsy is the most common form of adult-onset epilepsy, and patients unresponsive to drug treatments for epilepsy may require surgical removal of brain tissue to prevent life-threatening seizures. The brain structures affected in mesial temporal lobe epilepsy play a pivotal role in long term memory, and memory dysfunction is the chief cognitive issue in this group of patients.

Measureable memory decline is also a common consequence of temporal lobe resection, used to treat mesial temporal lobe epilepsy refractory to medication. Between 33- 55% of patients are reported to show significant post-operative verbal memory decline and severe amnesia is one of the most feared complications of surgery.

The assessment of pre-operative memory function and of the structural and functional integrity of key brain structures subserving memory forms an important part of pre-surgical evaluation, and informs assessment of the risk of post-operative memory decline. Functional MRI (fMRI) is being used more frequently to predict the impact that surgery may have on cognitive functioning of patients with intractable temporal lobe epilepsy, however there is no gold standard for accurate prediction of potential post-surgical cognitive deficits.

The aim of the research to be funded by the Brain Foundation is to investigate a new method for assessing post-operative memory function, and to assess the differential effect that lateralisation of damage and/or surgery (i.e. left versus right temporal lobe) has on memory function outcome.

Functional brain imaging techniques will be used in patients with left and right mesial temporal lobe epilepsy, with the ultimate aim of developing a new method to assist in pre-surgical evaluation and to minimise post-operative cognitive dysfunction in this group of patients.

A multi-disciplinary approach towards behavioural dysfunction in motor neurone disease (MND)

Dr Michael Hornberger

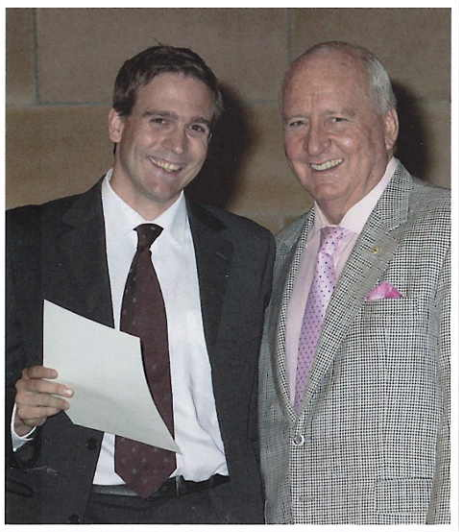
Co-Investigators:
Dr Eneida Mioshi, Dr Patricia Lillo

Motor Neurone disease (MND) is a devastating disease which affects up to 1300 patients in Australia at any given time and is the most common neurodegenerative disease at a young age. Patients usually show a range of a progressive loss of muscle control, which has been extensively studied.

Much less is known of other symptoms MND patients have. For example, up to 40% of MND patients can, in addition to their motor problems, present with changes in behaviour. These behavioural changes can complicate the diagnostic distinction from other neurodegenerative diseases, such as frontotemporal dementia and may influence the progression of the disease. In addition, it is known from other diseases that such behavioural changes can cause great distress to the patients as well as their carers and families, which need to be addressed.

The aim of our current study is to investigate such behavioural changes in MND in more depth via a multi-disciplinary approach. First of all, behavioural problems will be characterized in a group of MND patients via clinical questionnaires and interviews, which will determine which behavioural changes are most likely to occur in MND. Second, the underlying brain changes associated with the behavioural disturbances are identified via brain imaging techniques to help clinicians identifying patients that are more likely to have behaviour problems and offer appropriate treatment options. Finally, we investigate whether behavioural changes have an equal or greater impact than the motor problems on the carers and families of MND patients. The last part of the project will therefore disambiguate the behavioural and motor problems seen in MND patients.

Taken together, the findings of the Brain Foundation funded project will inform MND patients and their clinicians of the likelihood of behavioural changes during the disease, which in the long-term will allow better management and treatment options in MND.

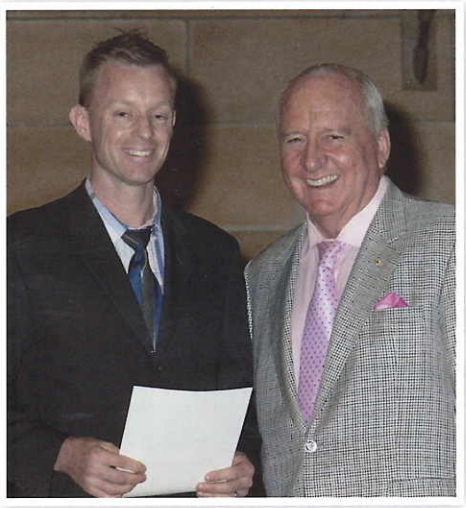


2010 Award Winners and Projects

Targeting TDP-43 to treat neurodegenerative disease

Dr Peter Crouch

Co-investigators: Dr Anthony White, Dr Qiao-Xin Li, Dr Paul Donnelly, Associate Professor Kevin Barnham



Although neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and motor neuron disease are becoming more and more prevalent in our society, the sad reality is that effective therapeutics to treat these diseases do not exist. Our research team is trying to rectify this problem, and funding from the Brain Foundation will help us continue our research efforts.

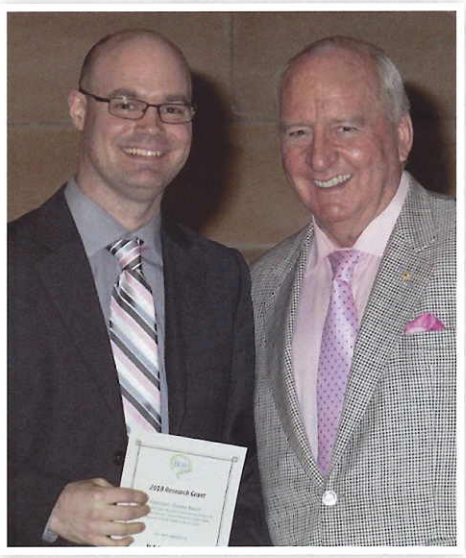
A major obstacle in trying to develop therapeutics for neurodegenerative disease is the fact that their fundamental causes are not yet fully understood. In 2006 considerable excitement was generated when it was identified that abnormal changes to a protein known as TDP-43 are a consistent feature of different neurodegenerative diseases. This finding suggested that different neurodegenerative diseases share more in common than previously thought, but further to this, it suggested that abnormal changes to TDP-43 may be an important a causative factor in the development of neurodegeneration. Supporting this, experimental mice have been created to mimic many features of abnormal changes to TDP-43. These mice develop physical symptoms reminiscent of neurodegenerative disease in humans, including decreased cognitive capacity (i.e. decreased short-term memory) and impaired locomotive capacity (i.e. decreased ability to walk).

Our team has recently gained access to these TDP-43 mice. The focus of our current work is to use these mice to test the efficacy of compounds we have under development as potential therapeutics for neurodegenerative disease. The testing we have already completed indicates our compounds have good therapeutic outcomes. Showing their efficacy in TDP-43 mice will provide strong data to indicate whether our compounds have the potential to treat a broad range of neurodegenerative diseases.

Protein recycling is disrupted in Parkinson's disease

Dr Anthony L Cook

Co-investigators: Dr Stephen Wood, Professor Alan Mackay-Sim



Parkinson's disease is an incurable neurodegenerative brain disorder affecting many older Australians, recognisable by the characteristic tremor observed in patients. The reasons why nerve cells in Parkinson's disease patients die is not yet well understood. However, there are a number of recurring themes.

One suggests that nerve cells in Parkinson's disease patients are in a state of stress, due to an inability to adequately cope with the damaging effects of molecules called oxidants. This has led many researchers to speculate that activation of a cellular communication process known as the "anti-oxidant response" will be of therapeutic benefit.

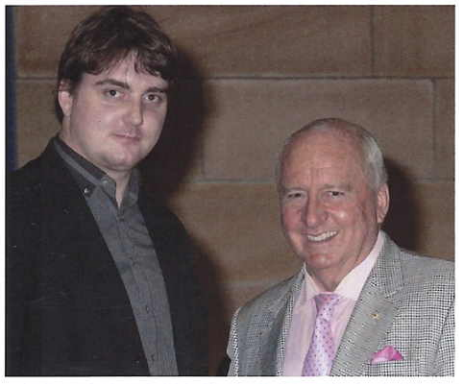
A second theme is the presence of abnormal protein aggregations within Parkinson's disease Patient cells. These protein aggregations are not found in healthy cells as they are efficiently degraded by another cellular process called "autophagy" (which literally means "self-eating"). Recent scientific data has suggested the anti-oxidant response and autophagy are regulated via the co-ordinated actions of proteins that control either process.

Organs other than the brain are also affected in Parkinson's disease. One of these is the olfactory mucosa, an organ within the nose responsible for our sense of smell, loss of which is as common a symptom in Parkinson's disease as uncontrolled movement. Our current research centres on olfactory mucosa cells which can be grown in the laboratory, and has revealed several unique differences between cells from Patients with Parkinson's disease compared to healthy Control donors. We have found that mechanisms which control autophagy malfunction in Parkinson's disease Patient cells when the anti-oxidant response is activated. Because the anti-oxidant response is considered a potential therapeutic target for Parkinson's disease intervention, any unexpected side-effects (such as loss of proper autophagy control) will have important implications for therapeutic development. Our aim is to understand the normal co-ordination of these processes in Control donor cells, and to identify how they become non-functional in Parkinson's disease Patient cells.

Lipids and cognition in postmenopausal women

Dr Cassandra Szoeke

Co-investigators: Professor Lorraine Dennerstein, Professor David Ames



Dementia and cognitive impairment cause significant disability, morbidity and mortality within our ageing community and current therapies are inadequate. The emerging therapies will be limited by both cost and side effect profiles. For this reason population-based prevention strategies are required now more than ever to reduce the burden of disease in our community.

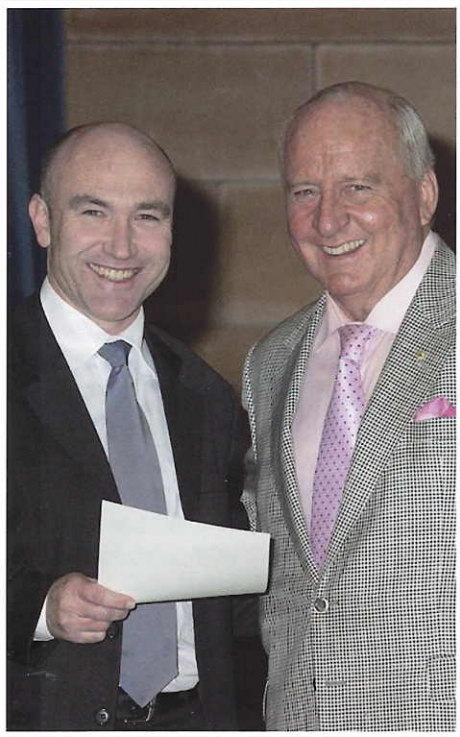
Early work from our group examining a single episodic memory task in 1999 showed an association between memory and lipid levels. Examining lipid measures from 1991-1999, showed that serum concentration measures closer to the time of memory testing showed a stronger association than those measured three years before. The proposed study will analyse lipid measures in 2002 (the year full cognitive test battery were applied) in order to examine the relationship between memory scores and lipid levels. This dataset has other cardiovascular risk factors (hypertension, blood sugar levels, BMI, smoking, diagnosis of hypertension, diabetes, heart disease) already available and therefore analysis can examine these variables.

We will examine the potential strategies for prevention by addressing midlife cardiovascular risk factors and cognition. Studying healthy ageing people earlier in their life is important to pick up factors, which may be targets for prevention of later life disease. For this reason our study examines a population of healthy ageing women who have been followed for more than a decade as part of a larger study of the menopausal transition. We will examine the relationship between cardiovascular risk factors (including high blood pressure, weight, diabetes, heart disease, smoking, cholesterol levels) and memory. The results of this study would fill a significant gap in our current knowledge on the role of lipids, a potential avenue of treatment, PRIOR to the postmenopausal phase of women's ageing. The assessment of risk factors would provide direction to potential preventive strategies to be instituted in the mid-life period to improve cognitive outcomes in ageing and targets for screening to achieve earlier detection. Outcomes of this study will inform healthcare practice in terms of preventive strategies and treatment of mid-life risk factors.

Advanced analysis of the (non-invasive) brainwave recording to identify where in the brain the seizure starts when there is either no lesion or multiple potential culprit lesions visible on the patient's MRI brain scan

Dr Chris Plummer

Co-Investigators: Professor Mark Cook, Dr Simon Harvey



Epilepsy is a leading cause of morbidity in Australia, particularly in the young and the elderly. There is a burgeoning gap between the increasingly technical methods of seizure rhythm analysis in epilepsy (termed EEG Source Modelling, or ESM) and the extent to which these promising methods have been tested in the routine clinical setting. This gap should be bridged because there is a pressing need for better, non-invasive ways of locating the source of the seizure in the brain of the sufferer.

Our pilot study will examine the clinical application of ESM when there is no clear guide from the patient's MRI brain scan (i.e. when there is no visible lesion or when there is more than one possible culprit lesion giving rise to seizures).

The benefit of ESM is that it reflects source characteristics on the same millisecond scale as invasive, intracranial EEG. However, the latter is hazardous (morbidity, mortality risk) and it is not a genuine gold standard (only limited parts of the brain surface can be sampled).

Findings from this work will hopefully open the way for a larger scale study that aims to improve the accuracy of seizure localization in patients with epilepsy. This can lead to better medical and surgical treatments for our patients, particularly those with difficult to control epilepsy syndromes.

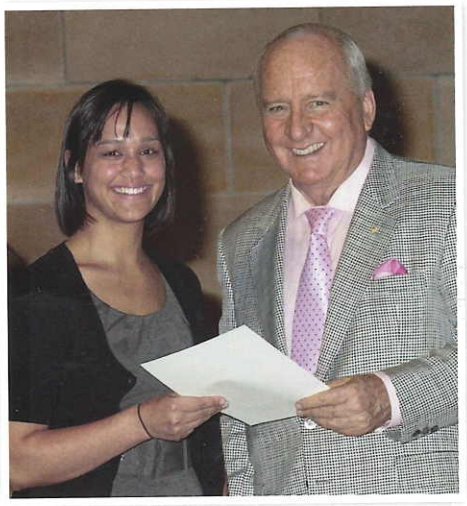
2010 Award Winners and Projects

A novel platform for studying brain injury in vivo

Dr Jyoti Chuckowree
Co-Investigator: Dr Tracey Dickson

Traumatic brain injury (TBI) is currently a leading cause of death and disability in developed nations such as Australia. The incidence of TBI is highest in people during the most productive years of their lives and frequently results in ongoing neurological impairment. TBI costs the nation several billion dollars each year and has been implicated in the development of other disorders, such as Alzheimer's disease and post-traumatic epilepsy, further intensifying the socio-economic and medical burden of this condition. There are currently no effective treatments or cures that can reverse the primary damage and complex secondary pathologies that develop following a TBI.

It is crucial that we understand the mechanisms by which the brain responds to injury before we can develop effective strategies to promote functional recovery. Until recently the predominant method for studying brain injury was to examine brain tissue harvested post-mortem from experimental animal models or human donors. A major limiting factor of these studies was that they only provided a 'snap-shot' of what was occurring in the intact brain. An exciting new imaging technology, in vivo two-photon laser scanning microscopy, now allows individual nerve cells within a whole living system to be imaged. By combining this imaging technique with models of experimental brain injury in mice we will develop a novel, clinically relevant model for studying brain injury in real time. This platform will allow us to investigate the neural response to trauma within the complexity of the intact brain in a whole living system. This approach will also provide an ideal system in which to test potential therapeutic agents and will



be adaptable to studying a range of neural injury and disease models. We would sincerely like to thank the Brain Foundation for generously providing us with the funding to initiate this project.

Finding the key to the migraine riddle

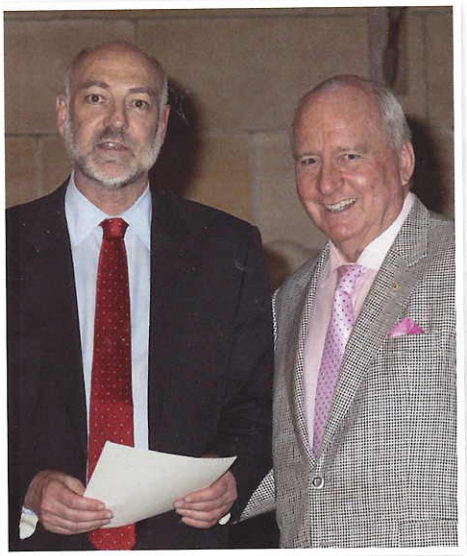
Dr Geoffrey Lambert
Co-Investigator: Professor Alessandro Zagami

One-third of women will suffer from migraine at some stage of their life and, across the population about 1 in 6 people are migraineurs. But migraine is mysterious in a special way- differs from cancer and heart disease in a very baffling way- there is no pathology. You can't perform a brain scan or a blood test to determine if someone is suffering from a migraine. The only way you can be sure is to ask them.

Migraine is definitely an organic disease. But, if we can't find anything wrong inside the head of a migraine patient, what could be causing such an excruciating pain? We know that many trigger factors- bright light, wine, stress can precipitate a migraine headache, but we don't know why or how. The pain of migraine APPEARS to arise from the dura mater which covers and protects the brain from injury. We all probably know that pain is a "warning signal" or alarm that tells us all is not well. Pain tells us to withdraw our hand from the hotplate or to visit the dentist. So... what is migraine pain warning us of? After many years of research, we have concluded that the pain warning which we receive during a migraine headache is a false alarm caused by an overly sensitive warning system.

We believe- that the circuitry which controls the sensitivity of the migraine pain alarm system is buried deep in the brain, but the controls for that circuitry are higher up- in the cerebral cortex, the conscious part of the brain. When a migraineur encounters one of her trigger factors, some neurons in the cortex become over-activated. These over-active neurons affect the controls of the alarm circuitry, which then causes normal sensations from the head to be perceived as painful sensations- that is to say, as a headache.

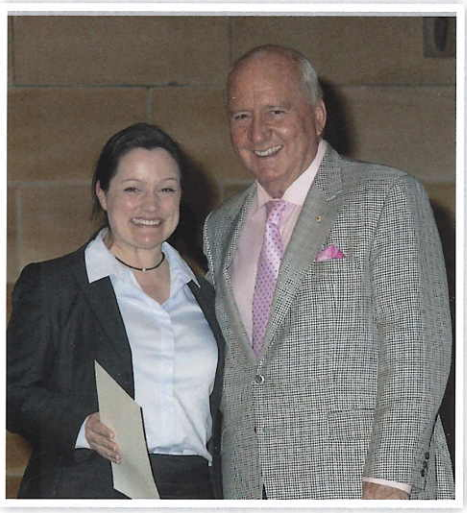
So far, we have been able to show that the brain contains just such an alarm system and that migraine triggers can indeed activate it by cranking up its sensitivity. We are now moving ahead to investigate the precise mechanisms by which this tweaking



of the alarm system occurs. If we can discover this mechanism, we may be able to prevent migraine by preventing excitation in the cerebral cortex or by stopping the excitation from reaching down into the brainstem to generate a false alarm. This would be the "magic bullet" that migraine researchers and migraineurs have been seeking for 150 years.

Epilepsy and Bones - Cellular Electrophysiology

Dr Sandra Petty
Co-Investigators: Professor Eleanor Mackie and Dr Chris French



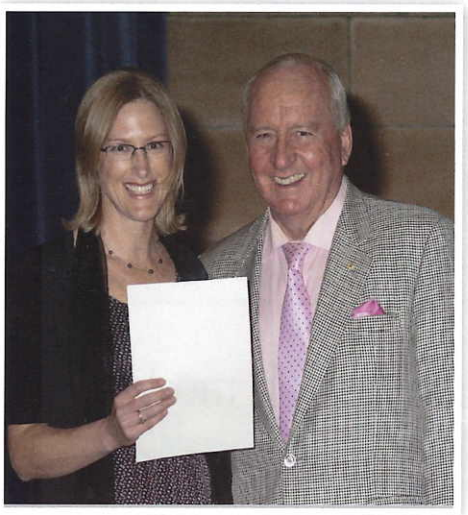
Patients with epilepsy have double the fracture risk of the general population. There is currently no unifying theory to explain this increased fracture rate. However, as almost all anti-epileptic drugs (AEDs) have been implicated, the mechanism appears common across AEDs (which often act upon ion channels to prevent seizures).

In bone, ion channels are likely to convey signals from sites of stress which require bone remodeling to maintain maximum strength and resistance to fracture. Alteration in bone cell ion channel excitability from epilepsy or AED use may potentially impede such a targeted remodelling process.

This novel proposed mechanism will be studied assessing bone cell ion channel activity in response to AED using a technique called patch clamping. The results may identify an explanatory mechanism for why patients with epilepsy have increased fracture risk, and potentially establish improved therapeutic targets for this clinically important problem, with the long-term aim to reduce the risk of fractures in patients with epilepsy.

Dysferlinopathy: A rare disease sheds light on the mechanism of membrane resealing

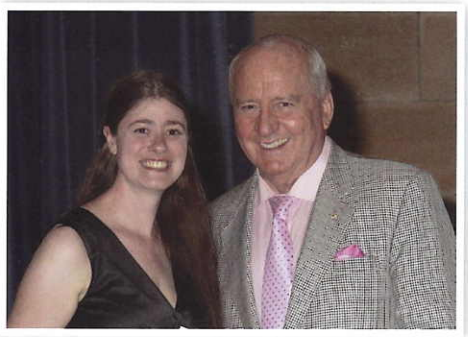
Dr Sandra Cooper
Co-Investigator: Professor Kathryn North



Dysferlin is a muscle membrane protein that is mutated in a form of inherited muscular dystrophy. Dysferlin has been shown to be essential for muscle cells to repair acute damage to their surface membrane, and is the first identified component of membrane repair machinery. We have been studying the biology of dysferlin in muscle cells; where it goes, how it behaves, and exactly what role it plays in muscle membrane repair. Dysferlin has many calcium-binding domains, and is thought to play a key role in the calcium-activated fusion of vesicle 'patches' that seal off membrane lesions. Using dysferlin as the key, we want to unlock the molecular steps required to survive a membrane injury. We have developed novel assays to test therapies that improve recovery from membrane injuring events. Our goal is to understand membrane resealing, and learn how to improve cell survival from membrane injury for therapeutic treatment of neuromuscular disease, and of other conditions characterised by membrane damage and repair, such as surgery, injury, cardiac ischaemia and stroke.

Understanding why some nerve tissue is more likely to die following a stroke

Dr Neil Stratt
Co-Investigator: Professor John Andrew Paul Rostas



Stroke is the second leading cause of death and leading cause of adult disability in Australia. Although there have been a number of important treatment advances in the last few years, many patients continue to die or be left significantly disabled by stroke. During a stroke there is loss of blood supply to part of the brain. Brain cells in this area often emit electrical and chemical discharges which increase their energy requirements, just at the time when these energy sources (in the form of oxygen and glucose) have decreased. This may result in a cascade of molecular events that hastens the death of the brain tissue. Manipulating aspects of this cascade may provide an opportunity to protect brain tissue and reduce injury (neuroprotection). The aim of this project is to investigate how changes in the signaling protein CaMKII (Calcium-calmodulin stimulated protein kinase II) can alter stroke-induced brain cell death.

Work of ourselves and others indicates that CaMKII activity is a major determinant of brain cell death after stroke. A critical target of CaMKII may be part of the receptor for the main excitatory chemical in brain, known as the glutamate receptor type I (GluR1). Our group have recently identified two potential targeting pathways by which CaMKII may regulate GluR1 through a process known as phosphorylation. Using a genetically modified mouse that lacks one of these targeting pathways, this project will determine the relative importance of the two targeting pathways in determining stroke susceptibility of brain. We and others have shown that the targeting pathways control not only activity, but also location within the cell. If our hypothesis for the role of these pathways in stroke injury is proven, manipulation of these pathways with medication could therefore provide a tolerable means to improve outcome for stroke patients.

2010 Award Winners and Projects

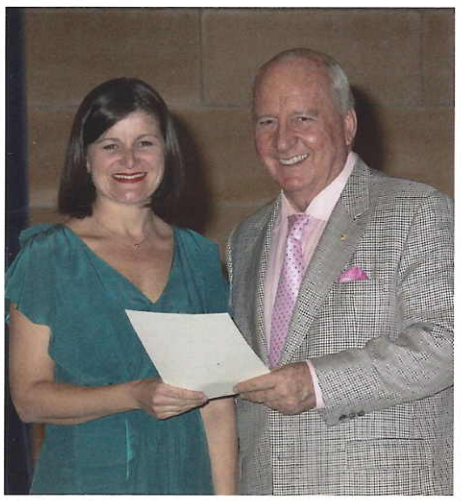
Exercise: can it help the brain change itself?

Dr Michelle Nadine McDonnell

Co-Investigators: Associate Professor Michael Ridding, Dr John Semmler, Associate Professor Jon Buckley

As the leading cause of disability in Australia, stroke presents many challenges for our healthcare system. As the blood supply to the brain is interrupted, nerve cells die and nerve pathways are damaged, resulting in weakness and other deficits such as affected speech and language abilities. After such an injury, rehabilitation is required to strengthen weak muscles or improve walking, but the ultimate goal of any physical therapy is to encourage the brain to make new connections between nerve cells to allow improved function. Although the brain can't regrow the damaged cells, it can adapt to the damage by way of altering connections between nerve cells, which is known as plasticity. Our research team has been interested for many years now in ways to encourage the brain to change itself and improve function through plasticity, and we have sought ways to increase plasticity in the motor parts of the brain of healthy young and elderly adults and patients with conditions such as stroke.

We have shown that healthy individuals who are very physically active have a greater potential for plasticity, or re-wiring within the brain when compared to those who are very sedentary. The likely mechanisms for exercise changing the brain are changes in blood flow, secretion of important chemicals within the brain which help new brain cells to grow and survive and increased activation of certain parts of the brain. This grant from the Brain Foundation will allow us to investigate whether a single session of aerobic exercise, for example cycling on an exercise bike, can promote brain plasticity. Our vision is that aerobic exercise could be rehabilitation's silver bullet; a simple intervention which makes further exercise and training much more effective due to increased potential for beneficial change within the brain. This would revolutionize



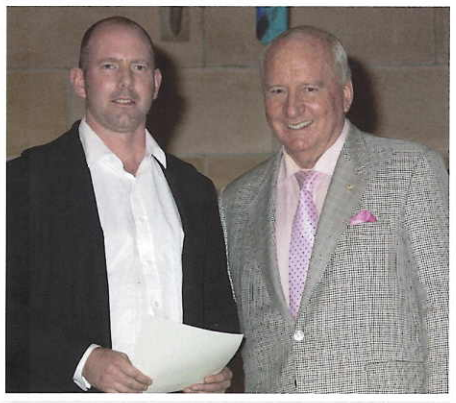
the way that we approach rehabilitation, and may reduce the devastating impact of stroke and other disorders affecting the brain.

Improving modern therapy for treating adult brain cancers

Dr Angus Harding

Co-Investigators: Associate Professor Brian Gabrielli, Deputy Director of Neurosurgery Sarah Olson

Glioblastome multiforme (GBM) is the most common primary brain tumour in adults. Patients with GBM present with a variety of symptoms, including headaches, seizures, confusion, memory loss and personality changes. Most cases of GBM arise spontaneously without any preceding history of low-grade disease, and in the majority of patients there are no family genetic abnormalities that are known to cause GBM disease. Current treatment for GBM combines maximal surgical resection followed by radiotherapy and chemotherapy. Despite this aggressive therapy regime, patients diagnosed with GBM have median survival times of 14 months after diagnosis. Importantly, very recent studies show that mutations caused by the current therapy are directly responsible for the development of therapy resistant tumour cells, which then drive disease relapse and ultimately kill GBM patients. Increasing the effectiveness of current therapies will decrease therapy-induced mutations in tumours to extend patient lifespan and improve patient quality of life. We have identified a therapeutic strategy that increases the effectiveness of current therapy ten-fold in our experimental systems. The aim of our project is to confirm this important finding in tumour cells derived from a large number of patient tumours, and then generate the pre-clinical data necessary to establish a Phase I clinical trial. If the pre-clinical data supports our hypothesis we will apply for funding to establish a Phase I clinical trial at the Princess Alexandra Hospital in a follow-up grant in 2012. The funding provided by the Brain Foundation has the potential to significantly improve the clinical outcome in brain cancer patients. In addition, as the experimental work will be performed by a

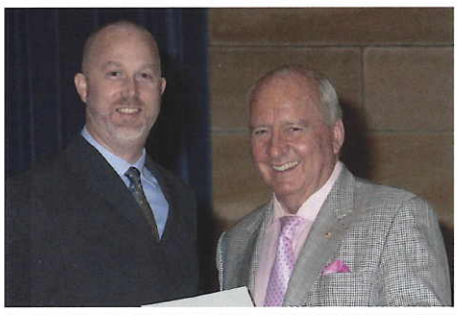


trainee neurosurgeon, the Brain Foundation is directly contributing to the training of the next generation of physician-researchers who will be spearheading translational medicine in the future.

Molecular imaging in brain AVMs

Dr Andrew Davidson

Co-Investigators: Professor Marcus Stoodley, Professor Michael Morgan



Arteriovenous malformations (AVMs) of the brain are complex vascular lesions that most commonly present with stroke. Bleeding from AVMs accounts for only 2% of all strokes, but is over-represented in young patients, being responsible for 38% of brain hemorrhages in patients aged 15-45 years.

The surgical management of small AVMs is highly effective, and can be achieved with low risk. However, the management of large AVMs is plagued with difficulty. Surgery is associated with high complication rates, and other treatments are largely ineffective. Changes in AVM blood vessels have been demonstrated following radiotherapy; however, a major limitation of radiotherapy in AVM management has been the high dose required to treat large lesions. As a result, a significant number of young patients harbour large AVMs that remain untreatable using current techniques.

Some of our group's earlier work has been directed at understanding the intrinsic molecular changes found in AVMs, as well as the additional changes induced in AVM endothelial cells by the application of various targeted external stimuli (such as focused irradiation, or heat energy). Ultimately, it may be possible to 'prime' the endothelial cells of human AVMs by the non-invasive application of heat energy, through the use of high-intensity focused ultrasound. This could then be followed by the administration of a vascular targeting agent directed specifically at these molecular changes, which could result in obliteration of the abnormal AVM vessels.

Our most recent work has been directed at demonstrating the gene and protein expression changes that occur in endothelial cells after heating with focused ultrasound, using both tissue culture and an animal model of AVM. The funding provided by the Brain Foundation will allow us to examine the precise anatomical location and temporal distribution of target molecules in our well-established animal model using the technique of in vivo molecular imaging. This is the next important step in the development of a systemic vascular targeting strategy against brain AVMs.

The results of this study have the potential to revolutionise the treatment of large, difficult to treat AVMs. Eventually, the entire treatment procedure may be performed non-invasively, and with a lower risk profile and greater efficacy than current treatments.

Is stroke neurodegenerative? A longitudinal study of changes in brain volume and cognition following stroke

Dr Amy Brodtmann

Co-Investigator: Dr Toby Cumming

Alzheimer's disease (AD) is the most common form of dementia. It is a progressive disease, and patients typically experience ongoing decline in memory, worsening confusion, language breakdown and often irritability and aggression. Certain proteins (amyloid and tau) are found in the brains of patients with AD. These proteins act to accelerate cell death in the brain, which has the effect of reducing brain volume over time, a process known as atrophy. Stroke occurs when blood supply to the brain is disturbed, either by a blocked or a burst blood vessel. Risk factors for stroke include high blood pressure, irregular heartbeat, smoking, diabetes, and high cholesterol. Historically, AD and stroke have been seen as separate entities. There may be reason to believe, however, that stroke has a role in the progression of AD. Dementia caused by problems in the brain's blood vessels (vascular dementia) often co-exists with dementia caused by AD. Research has shown that AD patients with a history of stroke had poorer cognitive function than those who had not suffered stroke. Furthermore, there is substantial overlap between the risk factors for stroke and the risk factors for AD. At present, there is no direct evidence and the question remains as to whether stroke can trigger progressive dementia and ongoing cell death in the same way as AD. In this project, we propose a simple way to answer this question. We will measure brain volume (using brain scanning) and cognitive function (using paper-and-pencil tests) in 20 stroke patients at several times over the first year after stroke. These results will be compared against healthy controls to determine whether stroke is associated with progressive reduction in brain volume and cognitive decline.

2010 Award Winners and Projects

A statewide study of Huntington Disease in New South Wales, Phase I

Dr Clement Loy

Co-Investigator: Dr Elizabeth McCusker

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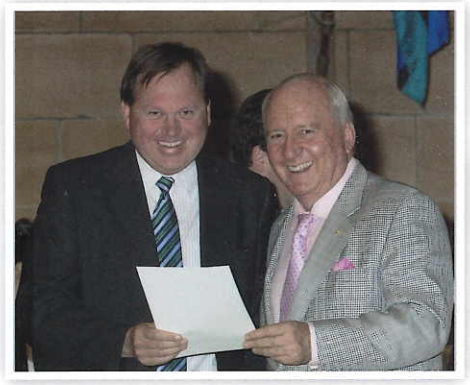
Development of a 68Ga-dopamine transporter PET tracer for brain imaging of Parkinson's Disease

A/Prof Roslyn Francis

Co-investigators: Dr Laurence Morandeau, Dr William MacDonald, Dr Rick Stell, Dr Julian Rodrigues



Parkinson's disease is a common progressive neurodegenerative disorder, which is primarily diagnosed on the basis of clinical features and response to dopaminergic therapy. In the early stages of the disease it can be difficult to distinguish from other causes of parkinsonism (e.g. drug induced parkinsonism, vascular parkinsonism, Multiple System Atrophy etc), and from other tremulous disorders such as Essential Tremor. As opposed to Parkinson's disease many of these conditions have normal presynaptic nigrostriatal function, which can be assessed by functional radiotracer based PET imaging. An accurate early diagnosis of Parkinson's Disease is crucial from a prognostic, therapeutic and neuroprotective perspective. Unfortunately, this imaging modality is not currently available in Western Australia nor is it widely available in other parts of the country. The WA PET service, in collaboration with R.A.P.I.D. laboratories, Medical Technology and Physics, SCGH, have experience in developing new tracers for functional imaging, using positron emission tomography (PET) technology. PET scans are very sensitive and allow the quantitation of functional processes.

We propose to radiolabel a dopamine transporter agent with a PET radionuclide in order to assess the dopamine transporter function in the brain, a measure of presynaptic dopaminergic integrity. Most PET agents are produced in a cyclotron, which are a scarce and expensive resource (there is only 1 cyclotron in Western Australia). The PET radionuclide we propose to use, Gallium-68 (68Ga), is however unique, as it comes in a generator, which lasts for 1 year. This will allow for easy access and is relatively inexpensive compared to cyclotron produced PET radionuclides.

Our project therefore aims to radiolabel a dopamine transporter agent, TRODAT, with Gallium-68. Multiple labelings will be performed to optimize the technique, under a range of conditions. Extensive testing of this product will be performed. At the end of the project we hope to have a product suitable for testing in human clinical trials.

2010 City to Surf
By Darren Fredrickson, Brain Foundation Everyday Hero

It was a very cool, crisp, clear morning and there was a real carnival atmosphere as the "Back of the pack" crowd steadily grew to tens of thousands in our holding bay at the south end of Macquarie St.

The two announcers tasked with providing an ongoing commentary of the mornings proceedings were skilfully bouncing information laced with anecdotes and comedic musing off each other. "Look at those guys!" said one veteran contender, rugged up in every piece of clothing they didn't want to take home again, waiting to shed it all on the side of the road for the Girl Guides to dutifully collect and donate to the Smith Family. They were motioning toward two brave souls who in the biting chill had stripped down to their "Tony Abbott's" and painting their bodies – one yellow, one orange. After about an hour we were informed the first starting gun had been fired and the race had begun.

We still had over an hour to wait for the unmistakable crack of our starting pistol. Whilst waiting we encountered super heroes, gorillas, pandas and all manner of masks and fancy dress. The next group were away, then the next, then we heard the race had already been completed and won by a New South Welshman in just over 40 minutes. And still we waited.

Then all of a sudden, a group of officials descended upon our starting line and the countdown began. 10, 9, 8..... 1, crack. A wave of bodies sprang from the starting line like a not so fizzy bottle of soft drink being opened. It was then several minutes of a strange mix of jogging, power walking, dancing and strolling before we reached what was the official start point. The timing tags then auto-magically set off some unseen timer and the race was on.

There was a very slight ramping up of speed for the joggers, power walkers, dancers and strollers as we flowed down William St. I remembered reading on a forum somewhere that turning around at the entry to the William St. Tunnel at Kings Cross and looking back up William St. toward Hyde Park was a sight to behold. I did so, and it was. I was smack bang in the middle of a community event, community spirit, that brought together thousands upon thousands of people in a common endeavour. The streets were lined with St. Johns ambulance volunteers, Ambulance Officers, Police Officers, Photographers, and onlookers. House parties were springing up all around, with people taking the festival spirit to its obvious outcome.

As we passed the first of many drink stations the noise of thousands of discarded plastic cups being trampled into the street was not unlike what I imagine being caught in an avalanche sounds like.

Then further on, a rock band covering Metallica on the roof of a hotel. At first I smiled at their obvious attempt at dressing up like an Eighties glam rock band – spandex, big hair, leopard prints etc. and then the smile withered ever so slightly when I realised they were making fun of me and my generation.

Further along there were jazz bands of varying styles, DJ's with massive speakers, vocal spectators and lurking news personalities looking for a story leading around their camera operators like leashed animals.

The much maligned Heartbreak Hill came and went without too much fuss and the last five or so kilometres took on a much more pleasant air as we wound our way through the suburban streets.

It was about this time when I started noticing the red, green, blue and even yellow bibbed individuals making their way back to who knows where after completing the run oh so long ago, looking at us poor sloths, jogging, power walking, dancing and strolling along.

And then all of a sudden, there it was, off in the distance, Bondi, and a truly seething mass of individuals. There was still quite a distance to cover, but it felt then like I'd made it. My inaugural City2Surf, performed using my very own designer power limp. Just a couple of k's to go. I picked up the pace as much as I could and powered my way through the crowd.

As I came toward the finish line I was sure none of the hundreds of photographers had a lens pointed in my direction. Walking over the finish line, the magical timer being stopped, and the pace deadening, I slowly, gingerly made my way through the corralling gates to collect my medal.

For many, that's when the party really started. For me, it was a long afternoon of lines. Toilets, food, buses, trains. That's the downside of any mass gathering and a small price to pay for the experience. I am so thankful to everyone who offered their support, to those who shelled out hard earned money to my charity of choice, the Brain Foundation, and to all the well-wishers. I couldn't have done it without you. I did do it, and I must say, I'm really proud of myself. Will I do it again next year? Just try and stop me.

North West Committee, Tamworth, 7th Christmas Fair

The Tamworth based North West Committee is again preparing for what will be their 7th Christmas Fair. To be held on Saturday the 20th of November at the Tamworth Race Course the market ranges from a flea market to up-market items and always features good bands and entertainment for children such as local identity, Rodney the Clown. Another feature is the local Pipe Band that somehow manages to march through the crowds and stalls with ease. If you are anywhere near Tamworth, be sure to visit on the day to support Pip Warner and her committee. They have raised tens of thousands of dollars for brain research by their efforts.

Fundraising

Fundraising for the Brain Foundation

Would you like to Fundraise for the Brain Foundation?

Fundraising is easy! The Brain Foundation is registered with Everyday Hero, My Cause and Go Fundraise. These companies make it easy for you to run your own fundraising event or to get sponsored in a public event like the City to Surf or the Melbourne Marathon. You can also register your special event such as an engagement or birthday to raise funds. Visit their web sites and discover how easy it is to set up your own home page and how easy it is for others to donate. Remember, the Brain Foundation can allocate your money raised to a specific area of research that is personal to you - such as Brain Tumours, Parkinsons or Muscular Dystrophy to name a few.

Some of our fabulous fundraisers in 2010 are:

Mr Adi Diner who ran in the Melbourne Marathon. Adi raised over $1,700 to go towards Migraine Research – which affects his wife. Adi's fundraising page was with My Cause.

Avril Cook, Shae Miller and Darren Fredrickson who all ran in the Sydney City to Surf and had their fundraising pages with Everyday Hero. Darren raised well over $3000 – a heroic effort – read his engaging story of what it is like to be a participant in the big race elsewhere in this newsletter.

Guy and Justine Olian who are currently raising funds with Go Fundraise to celebrate their engagement. Guy's father sadly passed away from Parkinsons Disease and all funds raised will go towards further research into this terrible disease.

www.everydayhero.com.au
www.mycause.com.au
www.gofundraise.com.au

In Memoriam

Guiseppe MUSA

Stephen Maxwell STEWART

Dr John DOYLE

Adam GILSON

George Ronald IRVINE

Geoffrey Keith FARRAR

Marion KILLEY

Dean Russell BOWMAN

Moyra PARKER

Agnes LUCKINS

Mr TJ EDWARDS

Peter MOUNTFORD

In Celebration

Engagement

Justine and Guy OLIAN

To make a donation, please complete this form and return it to the Brain Foundation using this reply paid envelope.

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Mobile _____

Email _____

ID Number _____

I would like further information about
❑ Making a bequest ❑ Workplace giving

I would like to receive the bi-annual Brain*WAVES* newsletter by ❑ Post ❑ Email

Please accept my tax deductible donation to the Brain Foundation:

❑ $200 ❑ $100 ❑ $50 ❑ Other _____

Regular donation:
I would like to make a regular donation to the Brain Foundation. Please debit my credit card for $ _____ per month until I notify you.

Please find my cheque payable to Brain Foundation enclosed
***OR* Please debit my** ❑ Mastercard | ❑ Visa | ❑ Amex

Card No. _____ / _____ / _____ / _____

Expiry Date: _____ / _____

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Thank you for supporting brain research through the Brain Foundation