BRAIN*waves*

The Newsletter of the Brain Foundation *Summer 2008-2009*

2008 Research Grant Awards

On Wednesday 1 October 2008, the Brain Foundation held its annual research grant awards ceremony at the Great Hall in the University of Sydney. The Governor of NSW, Her Excellency Professor Marie Bashir AC CVO presented the awards to the fourteen recipients of the 2008 Brain Foundation Research Grants. The evening commenced with a recital by international concert pianist, Ambre Hammond who kindly donated her time to play at the awards ceremony.

The Brain Foundation would like to thank the members of the Brain Foundation Scientific Committee, who all volunteered their time to review and assess a record number of grant applications all with the potential to advance understanding and techniques in neurosurgery, neurology and neuroscience. The members of the 2008 Brain Foundation Scientific Committee are:

- Professor Nicholas Dorsch
- Associate Professor Richard Gerraty
- Professor Michael Halmagyi
- Associate Professor Matthew Kiernan – Chairman
- Professor Pamela McCombe
- Professor John Willoughby
- Associate Professor Stephen Robinson
- Professor Elsdon Storey

These grants have been made possible through the generosity of our donors, corporate sponsors and through the ongoing legacy of generous people who leave the Brain Foundation bequests to fund further research into brain diseases, disorders and brain and spinal cord injuries. Without the generosity of these people the Brain Foundation would not be able to give these grants, nor would we have been able to fund brain and spinal cord research of over $20 million to date.

Brain Awareness Week

Brain Awareness Week is an international effort organised by leading neuroscience organisations around the world to promote public awareness about brain and mind disorders and the benefits of brain research.

In 2009, **Brain Awareness Week is 16-22 March 2009** and planning for the week has already commenced. Visit our website www.brainaustralia.org.au for more details of how you can participate in Brain Awareness Week 2009.

Professor James Lance AO CBE – Service to the Brain Foundation

Professor James Lance AO CBE was one of the founding members of the Brain Foundation some 40 years ago and has continued to have a long and valued association with the Brain Foundation. At the 2008 Annual Awards presentation, the Brain Foundation was pleased to acknowledge the contribution Professor Lance has made to the organisation over the years, in particular the convening of the Brain Foundation's Scientific Committee.

Pictured with The Governor of NSW, Her Excellency Professor Marie Bashir AC CVO, are three generations of Convenors of the Brain Foundation Scientific Committee. From left to right, current convenor Associate Professor Matthew Kiernan, Professor James Lance AO CBE and Professor Michael Halmagyi.

Contact the Brain Foundation
PO Box 579, Crows Nest NSW 1585
Telephone: 02 9437 5967 or 1300 886 660
Fax: 02 9437 5978
Email: info@brainaustralia.org.au
Visit our websites www.brainaustralia.org.au and www.headacheaustralia.org.au

Award Winners and Projects

Dr Ernest Jennings
University of Melbourne

Co-Investigator: Dr Jason Ivanusic

Characterisation of a novel neural pathway involved in migraine

The Governor of NSW, Her Excellency Professor Marie Bashir AC CVO and Dr Ernest Jennings

Our lab, that has only recently been established, studies the mechanisms of pain originating in the head, including migraine headache. Population health studies suggest that approximately 12% of the population in Western countries suffer from migraine and the associated debilitating symptoms, which are disruptive to normal function in the home or workplace.

Although some factors that trigger migraine are known, the mechanisms are relatively poorly characterised. Migraineurs report pain and autonomic symptoms (e.g. nausea, sensitivity to light, crying or runny nose). The latter two symptoms are activated by a specific group of nerve cells located behind the eye – parasympathetic neurons in the sphenopalatine ganglion. In terms of the project currently funded by the Brain Foundation, we plan to further investigate the connectivity and control of these cells, as they are known to be active in some of the symptoms of migraine. To do this, we will use histological markers that are specific to migraine- allowing us to precisely visualise (using high-resolution confocal microscopy) the nerve cells and establish their connectivity. The data obtained from these preliminary studies will allow us to better understand the role of these nerve cells in these specific migraine symptoms. These data may also help to better understand the mechanisms of migraine more generally with the ultimate aim of developing better treatment outcomes for migraineurs.

Dr Geoffrey Lambert
University of NSW

Co-Investigator: A/Prof A.S. Zagami

The cortex, brainstem and migraine

Migraine is the most prominent chronic pain suffered by Australians and chronic pain itself is in the top three medical conditions in terms of socio-economic cost. The top two are cancer and cardiovascular disease.

The Governor and Dr Geoffrey Lambert

But migraine differs from cancer and heart disease in a very baffling way - there is no pathology. We cannot perform a brain scan or a blood test to determine if someone is suffering from a migraine. The only way we can be sure is to ask them. This has conditioned doctors to assume that migraine is not an organic disease, but a psychological one. Even patients often blame themselves. No way! Migraine is definitely an organic disease.

If we cannot find anything wrong inside the head of a migraine patient, what could be causing this excruciating pain? There are many trigger factors- bright light, wine, stress can all precipitate a migraine headache, but we don't know why or how. The pain appears to arise from the dura mater which covers and protects the brain from injury. We know that pain is a "warning signal" which tells us all is not well. Pain tells us to withdraw our hand from the hotplate or to visit the dentist. What is migraine pain warning us of?

We have concluded that the pain warning received during a migraine is a false alarm caused by an overly sensitive warning system. Just as you would protect your expensive assets with a sensitive alarm, so our brain is protected with a warning system of very high sensitivity.

We believe that the circuitry which sets the sensitivity of the migraine pain alarm system is buried deep in the brain- the brainstem. But the controls for that circuitry are higher up- in the cerebral cortex, the conscious part of the brain. Migraine triggers cause neurons in the cortex to become over-active. These over-active neurons affect the controls of the alarm circuitry and cause normal sensations from the head to be perceived as painful sensations- as a headache.

We have recently shown that such an alarm system actually exists and that migraine triggers activate it by cranking up its sensitivity. We are now moving ahead to investigate the 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 the false alarm. This would be the "magic bullet" that migraineurs have been seeking for 150 years.

Dr Stephen Tisch
University of NSW, St Vincent's Hospital

Brain adaptation underlying remarkable improvement in symptoms of Parkinson's disease after effective surgical and drug treatment.

The Governor and Dr Stephen Tisch

Can the brain "rewire" after effective treatment for Parkinson's disease?
Parkinson's disease is a progressive movement disorder which causes tremors, stiffness, slowness and difficulty walking. It affects 3 % of people over the age of 55 in Sydney. There is no cure for Parkinson's disease but oral medications which replace dopamine in the brain can help the symptoms. As the disease progresses the response to medications becomes uneven and patients may fluctuate between good and bad phases and develop involuntary movements. It is believed that fluctuations and involuntary movements develop because of abnormal rewiring (plasticity) within brain motor areas in response to the medications. Some newer treatments can help once oral medications fail. These include deep brain stimulation (DBS) surgery or continuous infusions of a medication called apomorphine. These treatments reduce the fluctuations and involuntary movements, providing more stable improvement. In some patients the improvement can be dramatic. This study will investigate how these treatments alter brain function in order to achieve the beneficial effects. The study will assess patients with Parkinson's disease before and after DBS surgery or apomorphine infusion using electrical tests of brain function. Some milder Parkinson's patients without fluctuations or involuntary movements as well as a healthy control group will also be studied for comparison. It is predicted that abnormal patterns of brain function will be present in patients with fluctuations and involuntary movements. These abnormal patterns may readapt to a more normal configuration after treatment with DBS or apomorphine infusion corresponding to improvement in the patients' condition. The overall aim of the study is to gain a better understanding of how these treatments work and the role of brain plasticity in this process. This study will further the understanding of Parkinson's disease and may help guide improved future treatments or tests to help predict responsiveness to therapeutic interventions.

Dr Benjamin Ross

University of Queensland

Development of Novel Disease-Modifying Drugs for the Treatment of Alzheimer's Disease

The Governor and Dr Benjamin Ross

Our research group is interested in the chemical biology of neurodegenerative diseases, especially the discovery of drugs and drug targets for the treatment of Alzheimer's disease. Alzheimer's disease is the most common neurodegenerative disorder and the most prevalent cause of dementia in the elderly. The increase in life expectancy means that by the year 2025 it is estimated that 22 million people worldwide will develop Alzheimer's disease. The drugs currently used for Alzheimer's disease therapy are symptomatic treatments that afford cognitive benefit only for the first several months of treatment. There is an urgent need for disease-modifying drugs that target the mechanism of Alzheimer's disease and prevent disease progression.

Aggregation of beta-amyloid is a key event in Alzheimer's disease pathophysiology and increased levels of free radicals are a major factor in the cytotoxic processes that underlie the disease. We are developing a novel dual-action drug that both prevents brain damage from toxic free radicals and binds the beta-amyloid peptide preventing fibrillisation and deposition of amyloid. Funding from the Brain Foundation enables us to synthesise a series of drug candidates and to determine the ability of the candidates to inhibit the aggregation of beta-amyloid and trap free radicals in vitro. A dual-action drug may become a valuable disease-modifying treatment for Alzheimer's disease.

Dr Corinna Van Den Heuvel

University of Adelaide

Co-Investigators: Prof Peter Blumbergs, Ms Frances Corrigan

Assessment of the neuroprotective properties of the amlyoid precursor protein (AAP) following brain injury

There is increased expression of the amyloid precursor protein (APP) following traumatic brain injury. A number of investigators assumed this increase to be detrimental as it may lead to the over-production of one of it's

The Governor and Dr Corinna Van Den Heuvel

cleavage products amyloid beta (Aß) and thus potentially lead to Alzheimer's Disease.

However, there is also evidence to suggest that APP has many beneficial effects within the central nervous system. Our previous studies showed that administration of APP shortly after trauma, in a biological laboratory head injury model, significantly protects against neuronal damage and improves outcome following traumatic brain injury. These results subsequently prompted a collaboration between the University of Melbourne scientists who have extensive expertise in APP biology with our University of Adelaide group who have expertise in experimental models of neurotrauma.

This study will be the first to directly examine the role of endogenous APP in traumatic brain injury by using APP knockout in a traumatic brain injury model to further support the role APP plays in protecting neurons following traumatic brain injury. We predict that the lack of APP expression in these models will make neurons more vulnerable to head injury and the biological model will have a poorer neurological outcome following traumatic brain injury. The second key outcome of these studies is to administer different regions of synthesized APP into the brain following traumatic brain injury in order to identify the active (neuroprotective) region of exogenously administered APP. This second aim will facilitate developing APP into a therapeutic agent for treating neurotrauma in humans by developing either peptide analogues or synthetic organic compounds that mimic the active region of the APP molecule.

Dr Rainer Haberberger

Flinders University

Co-Investigators: Ian Gibbins and Robyn Flook

Novel pain pathway in human spinal cord

Our pulmonary neurobiology group has two major areas of interest.

I. The perception of pain is signalled from the periphery to the central nervous system via unmyelinated or light myelinated nerve fibres (nociceptive fibres) that originate from sensory neurons situated within dorsal root ganglia (DRG). The central projections of these neurons terminate within different laminae of the dorsal horn of the spinal cord.

The Governor of NSW and Dr Rainer Haberberger

We are interested in the function of these peripheral nociceptive neurons in health and disease. In the last years we could demonstrate that nociceptive neurons express multiple receptor subtypes specific for the neurotransmitter acetylcholine and that activation of the receptors is able to modulate the intracellular calcium concentration within the nociceptors as well as the threshold for painful stimuli. Currently, we are interested in the function of sphingolipids and their influence on the pain processing in peripheral nociceptors and in spinal cord.

II. Neural monitoring of the internal environment of the lung is essential for airway function and survival of terrestrial animals Sensory neurons serve here as the input elements of a complex brain network, which integrates the regulation of airway smooth muscle tone during the control of ventilation

We are also interested in how the peripheral lung function is regulated by sensory DRG neurons, and how the neural sensory systems might be involved in the lung inflammation. Up to now we were able to demonstrate that the lung is in addition to the vagus nerve also innervated by DRG neurons and could neurochemically characterise lung projecting neurons.

Dr Brian Owler

Children's Hospital Westmead, University of Sydney

Co-Investigator: Dr Dongwei Wang

Hydrocephalus and the role of brain water channels

The Governor and Dr Brian Owler

Hydrocephalus is an important neurosurgical condition in which cerebrospinal fluid accumulates in the ventricular system of the brain. It affects all ages and is the most common reason for paediatric neurosurgical

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admission besides trauma. Hydrocephalus may be congenital but is also a common sequalae of a variety of conditions including intracranial haemorrhage, meningitis and surgery. Unless treated it causes delayed development and/or neurological impairment. It may cause death. Current treatments are surgical and usually involve a CSF shunt or endoscopic third ventriculostomy. Shunts commonly fail (30% with 1 year) due to blockage and infection resulting in shunt revision surgery. Alternative effective medical treatments are needed. This requires an improved understanding of CSF physiology.

Hydrocephalus occurs when CSF production exceeds CSF absorption capacity (eg scarring of arachnoid villi or subarachnoid space secondary to haemorrhage or infection) or where there is an obstruction to CSF outflow (eg intracranial neoplasm). The choroid plexus is a vascular structure located within the cerebral ventricles where the majority of CSF production occurs. Aquaporins are a family of water channel forming proteins. Aquaporin 1 (AQP1) is found in the apical membrane of choroid plexus epithelial cells and is considered to have a role in CSF production.

Our laboratory has developed a cisternal kaolin model of hydrocephalus in a biological model. The aims of this project are to characterise this model in terms of its neuropathology and to determine whether choroidal AQP1 is altered in hydrocephalic models compared to controls. In addition, we aim to determine whether AQP1 knockout protocols develop hydrocephalus after cisternal injection of kaolin. It is anticipated that this project will define the importance of choroidal AQP1 in the development of hydrocephalus and its potential as a therapeutic target.

Dr Jonathan Sturm

Gosford Hospital

Co-Investigators: Dr Maree Hackett, A/Prof Greg Carter and Dr Denis Crimmins

Improving psychosocial outcomes after stroke

The Governor and Co-Investigator Dr Maree Hackett

Depression after stroke is common and is associated with poor quality of life. Effective strategies to prevent the development of depression after stroke may also reduce anxiety, increase participation in rehabilitation programmes, and improve physical function and quality of life. A cost effective, simple yet practical prevention strategy has been identified as a potentially suitable intervention. As the study is in progress and participants are not made aware of the nature of the intervention details of this intervention cannot be described in this report.

In two clinical trials this intervention was effective in reducing death by suicide in depressed psychiatric inpatients, and nearly halved repeat episodes of deliberate self poisoning following general hospital treatment. In this current pilot study we will recruit patients with stroke from Gosford Hospital and randomise them to either receive this intervention from their treating stroke unit doctors after stroke or to receive usual care. We will assess mood and quality of life at 6 months post-stroke. If the intervention shows evidence of effectiveness we will proceed with a large-scale multicentre trial.

This is a collaborative trial co-ordinated jointly by independent investigators at The George Institute for International Health (Dr Maree Hackett), Central Coast Stroke Services (Dr Jonathan Sturm, Dr Denis Crimmins), and The Department of Liaison-Psychiatry at Calvary Mater Newcastle Hospital, Brain and Mental Health Priority Research Centre, University of Newcastle (A/Prof Greg Carter).

Dr Mark Bellingham

University of Queensland

Co-Investigator: Dr Peter Noakes

The basis of hyper-excitability in upper motor neurons in a model of motor neuron disease

Dr Mark Bellingham

Evidence from human motor neuron disease patients and from laboratory models of motor neurone disease suggests that both upper and lower motor neurones may generate higher than normal levels of activity, and this hyperactivity may play a role in neuron death in motor neurone disease. In contrast to the extensive research carried out on lower motor neurones in biological models of motor neurone disease, little is known about changes in activity in upper motor neurones in these biological models. One reason for this is that upper motor neurones are only a fraction of cortical neurones, and it is consequently difficult to positively identify the upper motor neurones in experimental research. My research has already shown that lower motor neurones show hyper-activity from birth in a biological model of this disease, and this hyper-activity is associated with an increase in a specific type of sodium current and with increased levels of several sodium channel genes. Whether this early hyper-excitability also exists in upper motor neurones is unknown. The aim of this grant is to develop a novel biological model, in which upper motor neurones are positively identified due to their selective expression of a fluorescent protein marker, and then to test the hypothesis that early hyper-excitability, due to this increased sodium current, is present in upper motor neurones in this novel biological model of motor neurone disease. The electrical activity of upper motor neurones and the levels of expression of sodium channel genes and proteins will then be measured for the first time in these novel laboratory models. This work will strengthen the evidence for hyperactivity as a factor in motor neurone disease, and may ultimately lead to novel therapeutic strategies.

EARLY CAREER RESEARCHERS

The following Brain Foundation Research Grant Awards were made to early career researchers. These grants were awarded to those researchers who are early in their careers and proposed projects with a high standard of scientific quality, significance and/or innovation that will enable them to qualify for much larger government grants.

Dr Stephen Reddel

Concord Repatriation & General Hospital, University of Sydney

Co-Investigator: Dr William D. Phillips

Does pyridostigmine (Mestinon) make myasthenia gravis worse in the long term?

The Governor and Dr Stephen Reddel

We will test the effect of pyridostigmine on the neuromuscular junction in a laboratory model with passively transferred myasthenia gravis. Pyridostigmine and related drugs increase the amount of acetylcholine in the neuromuscular junction synaptic cleft and are used for the treatment of myasthenia gravis. They provide a benefit within minutes.

Recent studies into synapse formation have shown that acetylcholine can promote active dis-assembly of postsynaptic acetylcholine receptors and dismantle the neuromuscular junction as a whole, while a second signaling pathway exists, where neural agrin, and the receptor MuSK, acts to stabilise the neuromuscular synapse during development and in later life. Since pyridostigmine works by prolonging the actions of acetylcholine at the synapse, it is important now to test whether pyridostigmine fosters disassembly of the neuromuscular junction with long term adverse consequences, notwithstanding its short term benefit.

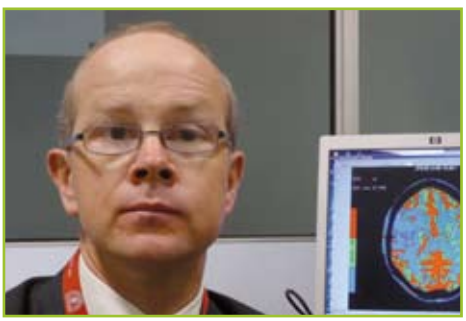
This research will have implications for many other disorders of the synapse, including Alzheimer's Disease where a related acetycholine esterase inhibitor, donepezil, is in widespread use. A role for the second stabilizing pathway agrin-MuSK has recently been demonstrated in the brain, although interestingly in concert with a different primary neurotransmitter, glutamate. It may be a common motif of synapses that increasing the amount and duration of the primary neurotransmitter has long term downregulatory effects on the post synaptic apparatus, and that a second supportive regulatory pathway exists at all synapses. In this case, stabilisation of the post synaptic apparatus via the second signalling pathway may be a more effective way of treating disorders where reduced synaptic signaling is present, which includes many neurodegenerative disorders such as Alzheimer's Disease and Motor Neuron Disease. If our hypothesis is confirmed, it will suggest that the use of pyridostigmine in myasthenia gravis should be limited or curtailed to occasional use, and that upregulation of the post synaptic structure via a search for agrin MuSK small molecule agonists may provide a more effective therapy for all disorders of the neuromuscular junction.

A/Prof Richard Gerraty

Alfred Hospital, Monash University

Co-Investigators: Dr Anoop Madan, Dr Helen Kavnoudias and Mr Philip M Lewis

Neck artery trauma and microclots to the brain



A/Prof Richard Gerraty

Head trauma may cause damage to the neck arteries, an injury called dissection. Clots breaking free of the dissected arterial lining may cause stroke, usually some days after the head injury. These dissections are frequently detected in the emergency department by computed tomography angiography (CTA), now a routine protocol in certain trauma patients. Intravenous anticoagulation is standard treatment for traumatic dissection, but is unproven and has not been shown to be superior to aspirin. Furthermore, heparin cannot be given safely in up to 50% of trauma patients. Transcranial Doppler ultrasound (TCD), an ultrasound test of the brain arteries, can detect tiny clots (microemboli) coming from dissected neck arteries. These can be recorded by computer and reliably counted electronically. By correlating microemboli counts with the grade of arterial injury as detected by CTA, and also the severity of the neurological injury, the patency of the intracranial arteries and the different treatments, heparin, aspirin or no treatment, the risk profile of different types of injury can be compiled. A low risk group may be identified who could be treated with aspirin or no therapy. For a sub-group potentially at high risk of stroke, this research will also be essential in planning a randomised trial of therapy, with the hope that serious stroke could be prevented in survivors of traumatic head injury who might otherwise make a good neurological recovery.

Dr Miriam Welgampola

University of Sydney

Co-Investigator: Prof Brian L. Day

Vestibular-postural responses in pre and post operative follow-up of cerebellopontine angle tumours

The Governor and Dr Miriam Welgampola

Vestibular schwannomas are slow-growing tumors arising from the vestibular nerve. They can be incidentally discovered or may present with hearing impairment, tinnitus, or imbalance. Their natural history ranges from spontaneous involution to rapid growth. Since the tumor may remain unchanged in size for years following diagnosis, a careful follow-up by MRI ("wait and scan") approach has emerged towards patients with small and medium-sized tumours. In this study, we first seek a physiological measure that will be a useful follow-up tool for longitudinal assessment of patients with schwannomas who are being managed conservatively.

Upon surgical removal of a schwannoma, there is partial or complete section of the vestibular nerve. A proportion of patients develop post-operative vertigo and disequilibrium. Symptoms are severe for patients who had smaller tumors and relatively intact vestibular nerves (who face a precipitous change in vestibular function due to surgery); in contrast, subjects with larger tumors in whom the vestibular nerves were slowly destroyed due to the schwannoma are relatively asymptomatic. Overall, early post-surgical rehabilitation promises a good outcome in terms of postural stability.

A low intensity (0.5-1mA) cathodal electrical pulse delivered over the mastoid process activates the terminal endings of the vestibular nerves. An increase in the firing rate of the nerve produces a sensation of falling in the direction of the stimulated ear. A compensatory body sway occurs in the opposite direction. The direction and magnitude of body sway can be quantified in 3 dimensions. Galvanic vestibular stimulation offers a safe and simple means of testing vestibulospinal pathways to the trunk and limbs.

Although a few centers offer brief in-hospital pre- and post-surgical rehabilitation (lasting the duration of stay), it is not feasible to refer all patients undergoing shwannoma surgery for intensive rehabilitation lasting weeks. This project will develop a reflex measure that will identify an "at risk" population for post surgical disequilibrium who can be offered intensive rehabilitation. Vestibular schwannomas also provide an excellent disease model for studying selective vestibulopathy affecting the superior and inferior vestibular nerves. Our work will help validate a quantitative and lateralizing test of the vestibular projections to the trunk and limbs. This technique will be useful in the assessment of disorders of stance and gait which are a debilitating manifestation of vestibular disease.

Dr Arun Krishnan

Prince of Wales Medical Research Institute

Investigating the causes of diabetic neuropathy

The Governor and Dr Arun Krishnan

Australia has one of the highest rates of diabetes in the world. Diabetes may be complicated by the development of neuropathy, causing symptoms such as weakness and pain in the upper and

Award Winners and Projects

lower limbs. Diabetic neuropathy leads to considerable disability and high social and economic costs. Despite the advances that have been made in possible treatments, the cause of diabetic neuropathy still remains unclear. Further progress has also been hampered by our inability to detect neuropathy in its early stages. The current study proposes to address these difficulties by assessing whether novel nerve excitability techniques may represent a more sensitive method of detecting diabetic neuropathy. These cutting-edge techniques are non-invasive, well tolerated, and can be applied to patients at the bedside. We will compare the utility of these techniques to those used in routine clinical practice. If nerve excitability techniques prove to be more sensitive than current techniques in the detection of early neuropathy, a significant advance will have been made in our ability to diagnose early neuropathy. Moreover, the insights provided by these novel techniques may allow new treatments and preventative strategies to be trialled in cases of early nerve dysfunction, before irreversible nerve injury has occurred.

Dr Stacey Jankelowitz

Royal Prince Alfred Hospital,
University of Sydney

Co-Investigator: Professor David Burke

Nerve excitability in Long QT Syndrome

The peripheral nerve, i.e. the nerve in the arm or leg, has various ion channels that may be affected as the primary cause, or as a secondary result, of disease. Changes in these channels may produce the symptoms of disease and/or provide targets for treatment. Long QT syndrome is a cardiac disorder in which patients may have no symptoms, may faint frequently, may have abnormal heart rhythms or experience sudden, unexpected death. Recently, the genes and associated ion channel abnormalities in the heart muscle have been described for long QT syndrome. Similar ion channels exist on the human peripheral nerve but these have not been studied in patients with long QT syndrome.

The Governor and Dr Stacey Jankelowitz

Research Grant Progress Report

Brain demyelination in children: development of a novel auto-antibody method to detect antibodies against cell surface proteins.

Chief Investigator – Dr Russell Dale
Co-Investigator – Dr Fabienne Brilot

Infectious illnesses such as colds and influenza are common, and are an unavoidable part of life on earth. Most of the time our immune system deals with infectious micro-organisms without problem and we make a full recovery without complications. On some occasions our bodies can over-react to micro-organisms and our immune system can attack itself (autoimmunity). One of the most common examples of autoimmunity is when the immune system attacks the white matter of the brain resulting in demyelination. In adults, the most common outcome is a chronic progressive condition called multiple sclerosis.

There are two different brain demyelination events in children (Figure 1):

1. A sudden attack after an infection associated with unconsciousness. This is called ADEM (acute disseminated encephalomyelitis). These patients usually fully recover with treatment and do not have further attacks.
2. A first attack without unconsciousness, called CIS (clinically isolated syndrome). These patients have a higher risk of progression to further attacks, and therefore multiple sclerosis.

Investigation of this autoimmune reaction in adults has been hindered because investigation often occurs many months or years after the disease began. When there is this time delay, the autoimmune reaction can alter and become less specific. However, the paediatric patients present symptoms very rapidly after induction of disease. These paediatric patients offer us an opportunity to examine the abnormal immune reaction early in its course when it is more specific.

Some of the most common proteins in the white matter are called myelin proteins. The myelin insulates the nerve cells, and allows normal electrical conduction within the brain. These myelin proteins have been considered an important target for the autoimmune reactions against the brain. One myelin protein of particular interest is called myelin oligodendrocyte glycoprotein (MOG). Our Brain Foundation grant allowed us to measure antibodies that bind to MOG using a specific system that allows the MOG protein to exist exactly how it does in human brain. This assay has found that 50% of childhood ADEM and CIS patients have extremely high levels of antibodies against MOG. Only 1% of adult multiple sclerosis patients have high levels such as this. This fascinating finding suggests that children with brain demyelination have much more extreme autoimmune reactions against MOG. Some of these patients have gone on to develop MS. We believe that these patients offer an important opportunity to examine the very earliest autoimmune reaction. This study therefore has implications not just in children, but also adults with MS. It is hoped that recognition of patients with high levels of antibodies against MOG will allow tailored treatments to patients in the future.

Russell Dale and Fabienne Brilot work within the neuroinflammation group at the Children's Hospital at Westmead.

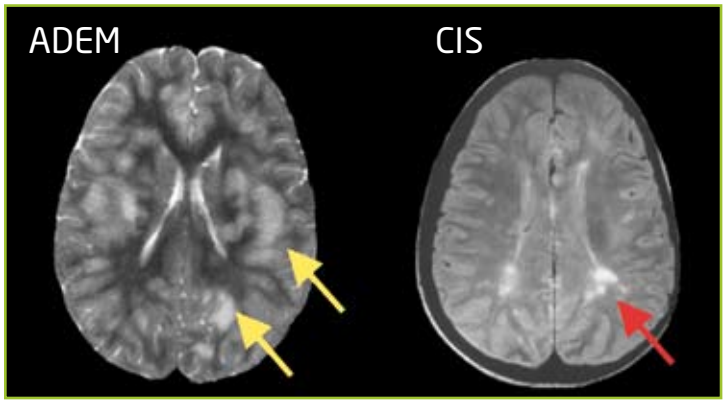


Figure 1. Comparison between magnetic resonance imaging in ADEM and in CIS. A child with ADEM (left) presented symptoms suddenly with unconsciousness and large patches of inflammatory demyelination in the white matter (yellow arrows). An adolescent with CIS (right) displayed symptoms more slowly with abnormal sensation in one arm (CIS) and had smaller white matter lesions (red arrow). This patient (CIS, right) progressed to multiple sclerosis.

This study will investigate whether there are changes in ion channel function on the peripheral nerve of patients with long QT syndrome using the techniques of axonal excitability testing. Electrical impulses of variable duration and strength are applied to the nerve in various combinations and at different time intervals. The change in threshold for the required response and the change in the response itself, provide information with respect to the different ion channels along the nerve. Patients with long QT syndrome will be compared with age-matched control subjects to determine the presence of alterations in ion channel function. If changes in ion channel function are detected, further studies will be performed to determine whether these changes are in anyway protective against neurotoxins and disease or whether they increase the susceptibility to peripheral nerve disease.

THANK YOU TO ALL OUR DONORS AND BEQUESTORS WHO MADE THESE AWARDS POSSIBLE

The Brain Foundation would like to thank all of our generous donors through their continued support of the Brain Foundation and the following bequestors who have made these research grants possible:

Grace Jeanie ADMANS
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Kathleen TOY
Claire Lilia WOOTON
Frank & Morphyn YOUNG

Headache and Migraine

Each year the Brain Foundation funds research into chronic headaches and migraines, however we believe that the funding is not enough for this complex area of neurology. To increase awareness and research funding for chronic headaches and migraines, Headache Australia is compiling a register of chronic headache and migraine sufferers. This register will be used to gain more funding for chronic headache and migraine research to end the suffering and reliance on medication. You can register your suffering by completing the questionnaire on www.headacheaustralia.org.au

Medication Overuse Headaches

Pain-relieving medicine, if taken too often can itself lead to a type of chronic daily headache – Medication Overuse Headache.

As the body gets accustomed to medication, it craves for more. When the medication wears off, a headache is triggered which causes a person pain and leads them to take more medication. This leads to a vicious cycle of taking medication to relieve a headache that in itself is caused by taking medication.

How do I know if I am suffering from Medication Overuse Headache?

- Daily or almost daily headache, with daily use of analgesic medication.
- Preventative medication becomes ineffective.
- The headache is often at its worst in the morning and becomes more severe after physical activity.
- Headache temporarily worsens if medication is stopped.
- There is often a history of other headache, including migraine-type headaches.
- Depression and sleep disturbances usually exist.
- There may be nausea, forgetfulness and/or restlessness.

What should I do if I think I have a Medication Overuse Headache?

You should consult with your doctor if you think you are suffering from medication overuse headaches.

Early intervention is important because the long-term prognosis depends on the duration of the medication overuse.

Introducing Dr Bronwyn Hooker, Medical Specialist Liaison

Dr Bronwyn Hooker has recently joined the Brain Foundation as our Medical Specialist Liaison. Bronwyn's primary role is to meet Neurologists and Neurosurgeons within NSW and update them on the work of the Brain Foundation and familiarise them with our bequest program. As a charitable organisation bequests are one of the ways in which the Brain Foundation generates funds for research, such bequests are recognised each year in our Annual Awards.

Bronwyn is shown here on the right accepting a supporters' artwork from Zoe Checketts (left) from the Hunter Medical Research Institute in recognition of the 2007 research grant given by the Brain Foundation to Associate Professor Chris Levi for his project *A randomised controlled trial of mild hypothermia in acute isachaemic stroke*. Also pictured is Gerald Edmunds, CEO Brain Foundation.

In Memoriam

The President, Directors and Staff pass on their condolences and gratefully acknowledge gifts in memory of the following people since the last Brainwaves Newsletter.

- John Ciccone
- Robin Burbidge
- Andre Jacques Catteau
- Valda June Robins
- Colin Bond
- Selina "Sally" Stellar
- Florence Bloomfield
- Janet McSwain

We continue to revere the memory of those for whom gifts have already been made and especially those who kindly made bequests to the Brain Foundation.

How YOU can help fund BRAIN RESEARCH

You can help fund brain research by:

- Making a donation
- Giving the gift of Brain Research instead of a birthday present or a wedding gift.
- Make a bequest to the Brain Foundation in your will
- Use the Everyday Hero site www.everydayhero.com.au or the Mycause website www.mycause.com.au for an easy way to create a hero or events page to both advertise and collect the donations.
- Workplace giving
- Funeral Tributes

The Brain Foundation is self funding so **100%** of your donation or bequest goes directly to the **research fund.**

Special Gifts

The Gift Of Research

Mr Paul Ainsworth has made a donation in the form of a research grant to be used for research into Dystonia. The grant will be known as the Paul Ainsworth Dystonia Research Grant.

Dystonia is a neurological condition – one of the movement disorders – in which involuntary muscle contractions cause twisting or repetitive movements, or abnormal body postures. Any part of the body may be affected, in some cases only a single muscle is involved, while in others, a group of muscles (e.g. in the arm or leg), or the entire body may be affected.

"There are many thousands of people in Australia with Dystonia and many more affected by it. I hope the research grant will contribute to developing better treatments or, one day, a cure" Mr Ainsworth said.

I would like to support brain research

Please complete this form and return it to the Brain Foundation at
PO Box 579 Crows Nest, NSW 1585, or fax to 02 9437 5978, or contact the Brain Foundation on 02 9437 5967.

Name _____

Address _____

_____

State _____ Postcode _____

Telephone ( ) _____

Mobile _____

Email _____

I would like further information about:

❑ Workplace giving | ❑ Making a bequest

I would like to receive the bi-annual BRAINwaves 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 _____ / _____

Name on Card _____

Cardholders signature _____

Thank you for supporting brain research through the Brain Foundation