brainWAVES

The Newsletter of the Brain Foundation. *Summer 2009 - 2010*

Summer and Christmas Edition

The directors and staff join in wishing all our readers a very happy Christmas and best wishes for the New Year.

This year, the Brain Foundation has joined with **MyCause** to make Christmas e-cards available online. The system also makes it possible to provide a gift for "someone who has everything". That is, a gift of a donation towards brain research and tax deductions apply.

See the link on the Brain Foundation web site for more details and to view the whole collection of e-cards available for all occasions.

Ray White Real Estate Surfers Paradise Charity Ball

Ray White at Surfers Paradise headed by CEO, Andrew Bell has promoted an annual Charity Ball to raise funds for Muscular Dystrophy (M D) for the last 14 years.

Through their efforts and the generosity of the local community, they have raised millions of dollars. This year, the Brain Foundation was included as it has a fund dedicated to research into M D and brings the additional government funding of up to 75% of money raised.

Pictured below are: Val Gibson, committee member, Dr John Corbett, Director of the Brain Foundation, Andrew Bell CEO of Ray White and Gerald Edmunds, CEO of the Brain Foundation.

The 2009 M D project was awarded to Professor Rick Jackson of Griffith University. His project is explained in the Grants Section.

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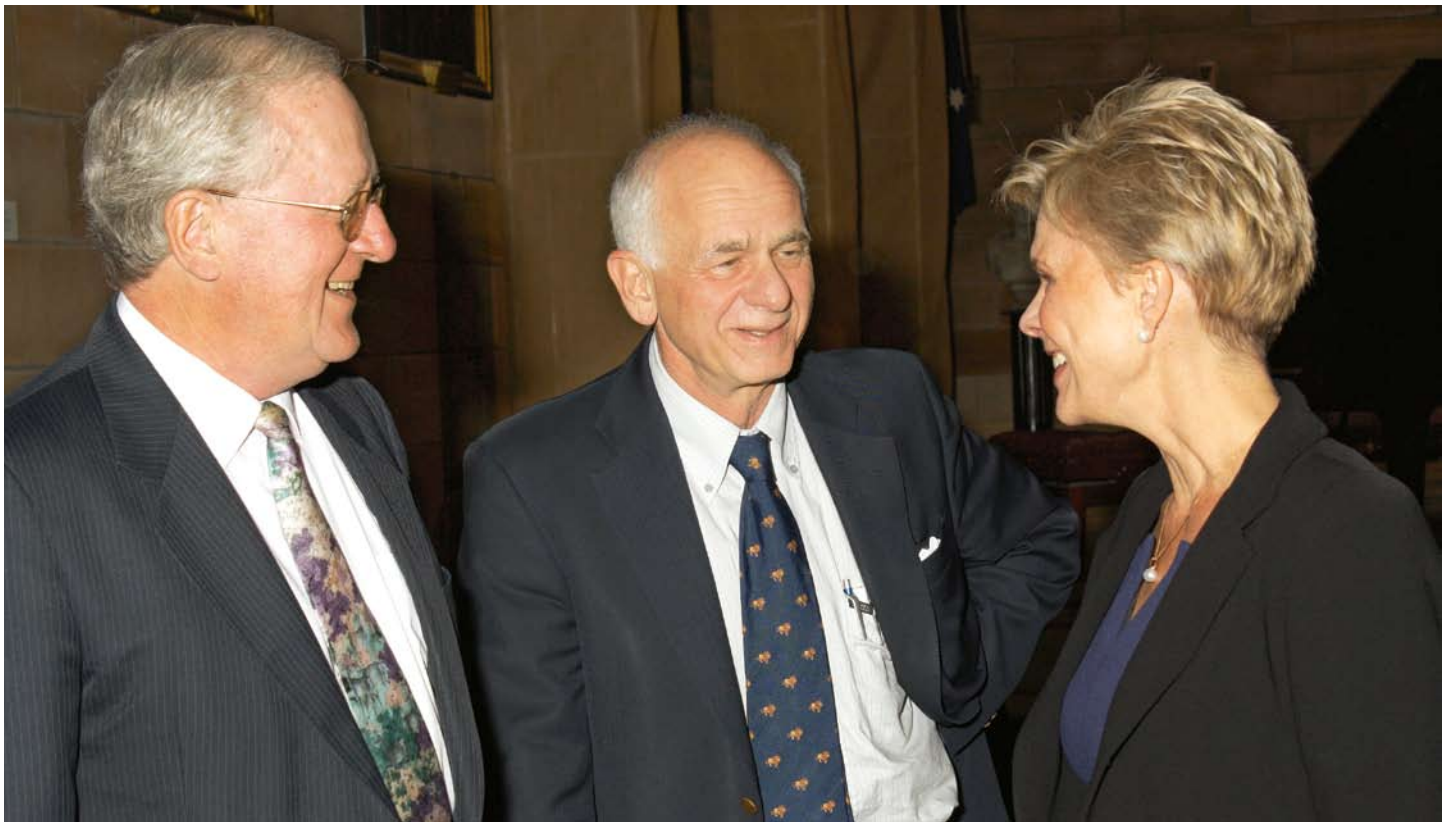
2009 Research Grant Awards

The highlight of the Brain Foundation's year is the occasion when research awards are formally presented.

This edition of Brainwaves is providing a showcase for the successful individuals and their projects because this is why we ask you to donate.

On Tuesday 29th of September, 2009, the Annual Research Grant Awards ceremony was held 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 2009 Grants. These projects were selected from a competitive national pool based on the potential of each one to make a difference by enabling an earlier diagnosis and also to advance the treatment of sufferers in the area being investigated. The evening commenced with recital by international concert pianist, Ambre Hammond who kindly donated her time to play at the awards ceremony. She has also nominated the Brain Foundation as a Charity that she supports in her promotional material. Ambre has recorded a number of CDs and they are available through this office with proceeds going to the Foundation.



Professors Nick Dorsch, Michael Halmagyi and Kathryn North at the Annual Award Presentation.

The Brain Foundation would like to thank the members of the Brain Foundation's National Scientific Committee, who all volunteered their time to score a record number of grant applications and selecting those Applicants with the greatest potential to advance understanding and techniques in neurosurgery, neurology and neuroscience were selected.

The members of the 2009 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 you, our readers and donors, some corporate sponsors and though the ongoing legacy of generous people who have left the Brain Foundation bequests.

There have been significant advances from the projects that have been funded.

Some examples are:

- Brain imaging
- Genetic structure implicated in migraine
- Grafting adult neural stem cells into the brain and spinal cord to repair damaged neurons; and
- Intravascular cooling to limit the damage to brain tissue after stroke

Without such generosity, the Brain Foundation would not be able to give these grants, nor would we have been able to fund brain and spinal research of over $20 million to date. The Commonwealth Government now supplements what the Brain Foundation provides. This year the value of grants will increase by up to 75%.

Award Winners and Projects:

A study on the tolerance of the brain to the kinds of forces encountered in an impact to the head.

Dr Robert Anderson

Centre for Automotive Safety Research, University of Adelaide

Co-Investigator: Professor Robert Vink

The development of safer vehicles and protective devices such as helmets is based on estimating the risk of injury in an impact. Right now, in the development of these safety systems, the measure of risk to the head is based on deceleration signal produced in a crash test dummy during a test.

In the future injury risk will be measured using methods that better reflect the mechanisms of injury in an impact. Increasingly, these mechanisms are being investigated using computer simulations of head impact. However, quite how these simulations should be calibrated is unknown – it has been difficult to determine what magnitude of physical stress is required to injure the brain.This project will seek to investigate this.

By examining the response of the sheep's brain to a controlled indentation, we can examine how the function of the brain is altered by physical stresses, and what level of stress is required to trigger an injury response. The results will allow criteria to be developed for use with computer simulations of head injury, which in turn will allow better measurement of head injury risk in any given situation.

Our hypothesis is that a quantitative relationship exists between mechanical forces induced in traumatic brain injury (TBI) and the resultant brain pathophysiology. Accordingly, the objective of this project is to characterize the relationship between mechanical strain and brain injury in a sheep model of human TBI. This will be achieved through a detailed study of the pathophysiological response of the brain to direct load. Imaging and histology will be used to quantify the injury response, and a computer model of the experiment will be used to quantify the mechanical strain.

This project is a collaboration between Dr Robert Anderson at the Centre for Automotive Safety Research at the University of Adelaide, Professor Robert Vink, Professor of Neurosurgical Research, the Head of School of Medical Sciences, and the Deputy Executive Dean of Health Sciences at the University of Adelaide, and will also involve Associate Professor Tetsuya Nishimoto of Nihon University, Japan.

Testing anti-migraine drugs in normal and hypoxic conditions.

Dr Svetlana Shabala

Menzie Research Institute, University of Tasmania

Co-Investigators: Professor Adrian West and Dr Roger Chung

Dr Shabala is a Research Fellow in a NeuroRepair group of the Menzies Research Institute in Tasmania (leaders Dr R. Chung and Prof A. West). In her work she uses an electrophysiological approach to study mechanisms of membrane transport processes in neural populations.

This includes measurements of net ion fluxes non-invasively using microelectrode ion flux measuring (the MIFE) technique that was developed at the University of Tasmania. This technique was successfully used to address different aspects of membrane transport processes in plants, yeast, and bacteria. Dr Shabala has recently extended its application to mammalian tissues and cells proving its applicability and high predictive power in mammalian cell research. In the project funded by the Brain Foundation, Dr Shabala will use the MIFE technique to study mechanisms underlying migraine. Migraine is a complex, disabling disorder of the brain that manifests as attacks of often severe head pain with sensory sensitivity to light, sound and head movement. Migraine prevalence is 12% of the population and it has a substantial economic and societal impact. Despite relatively extensive research in the area, the cause of migraine headache remains unknown. Cortical spreading depression (CSD) has been implicated in migraine and as a headache trigger with ion homeostasis being strongly associated with generation and propagation of CSD. Dr Shabala will use the MIFE technique to observe the kinetics of the key ions in response to factors that initiate CSD. The project is aimed to establish models of CSD in normal and hypoxic conditions in vitro to assess differences in their mechanisms. The researchers will also test whether increases in oxygenation can abrogate CSD. Using the models they will test drugs used in migraine treatment for their efficacy in prevention of normoxic and hypoxic CSD.

Award Winners and Projects:

Investigation of the ABCG2 pump in radiation.

Dr Andrew Hallahan

Department of Paediatrics and Child Health, University of Queensland & Haematology/Oncology and Stem Cell Transplant Unit, Royal Children's Hospital Brisbane

Co-Investigator: Dr Wendy Ingram

Brain tumours are the leading cause of cancer related death and disability in children. The Royal Children's Cancer research laboratory is focused on improving our understanding of medulloblastoma, the most common malignant brain tumour of childhood.

This is cured in 50-75% of cases with a combination of surgery, radiation and chemotherapy. For those who relapse the prognosis is bleak, with fewer than 10% achieving long-term survival. Survivors typically have long-term disabilities, both due to direct effects of the tumour and the side effects of treatment, particularly radiation, on the normal brain. Therapeutic advances have been limited in the past decade and medulloblastoma remains a significant cause of cancer related death and disability in children.

The Children's Cancer Research Laboratory is a team of scientists and clinicians focused on improving our biologic understanding of malignant brain tumours. We have established innovative models to study primary tumours collected after surgery in addition to established cell lines. Our focus is on elucidating the biology of relapsed, radiation resistant tumours for which there are no effective current treatments. We are particularly interested in possible links between resistance and stem-like features of tumour cells. Our studies have shown that radiation resistant medulloblastoma cells have increased amounts of a potentially critical drug transporter protein called ABCG2. This may be an important way in which these tumour cells survive and blocking it may increase the efficacy of radiation and chemotherapy.

Funding from the Brain Foundation provides critical support for us to determine the role of the ABCG2 protein in radiation resistant medulloblastoma. It will substantially improve our knowledge of this very challenging disease. We aim to establish if ABCG2 inhibition is a potential new approach to treatment for children whose disease returns after treatment. Our vision is to develop better biologically based therapies that will cure more children with fewer side effects giving them the lives they deserve.

Circulating endothelial cells in brain tumours.

Dr Andrew Morokoff

University of Melbourne & Department of Neurosurgery and Surgery, Royal Melbourne Hospital

Co-Investigators: Dr Nicholas Schaerf, Dr Katharine Drummond, Professor Andrew Kaye and Professor Mark Rosenthal

The most common brain cancer, high grade glioma, still has a terrible prognosis of only 12 months and requires better ways to monitor treatments and make clinical decisions.

These decisions can include whether and when to instigate interventions such as specialised imaging, chemotherapy or repeat surgery. Angiogenesis, the process of tumour blood vessel formation and growth is known to be extremely active in high grade brain tumours. The main current method of monitoring tumour progression currently is contrast-enhanced MRI but this has limitations, especially with the use of newer drugs such as anti-angiogenesis inhibitors, that reduce the appearance of enhancement. Circulating endothelial cells (CECs) are blood vessel lining cells circulating in the bloodstream that may correlate with the degree of blood vessel activity in the tumour. The aim of this project is to determine if the level of CECs determined by a simple blood test, can provide an accurate "biomarker" for either the prognosis and or progression of gliomas. We plan to recruit 200 patients with high grade gliomas and take blood at at least six time points during the course of their illness. The CEC level will be assessed by flow cytometry in the laboratory. Clinical data will be collected concurrently, with the assistance of the Biogrid initiative for clinical database analysis. CEC levels will be analysed to determine if there is a statistically significant correlation with 'true' tumour burden, response to treatment, MRI appearance, tumour grade and patient outcome. If valid, this test could become a valuable, simple, cost-effective tool to help guide more accurate treatment decisions in patients with brain tumours and to guide future clinical trials.

Investigating methods of measuring the response

Dr Katya Kotschet

Centre for Clinical Neurosciences and Neurological Research, St Vincent's Hospital Melbourne & Howard Florey Institute Melbourne

Co-Investigators: Dr Noel Lythgo and Professor Malcolm Horne

We thank the Brain Foundation for this 2009 research grant award, which will further our clinical studies in the area of cervical dystonia, or involuntary abnormal posturing or tremor of the neck.

As recently as the 1970s, CD was thought to have a psychological basis of hysteria, but in the past 3 decades the neurophysiological basis has been identified, and treatment with botulinum toxin injections into selected neck muscles has been adopted as standard practice.

The clinical problem is in choosing which of the more than 30 different paired neck muscles to inject. With current selection methods (muscle hypertrophy on palpation, neck positioning, EMG assessment), we are only 60-75% effective in getting the treatment to the ideal muscles, and this limits treatment efficacy. This research will examine novel techniques we have recently developed to improve target muscle identification, using MRI scanning (for muscle enlargement) and specialised movement analysis (for neck deviation and tremor). We will look at treatment naïve patients, and follow their response to standard injection treatment. The overall aim of the research is to improve the efficacy of botulinum toxin treatment by better target muscle selection, and also to gain a better understanding of the basis of CD and the way in which botulinum toxin may exert its effects. My co-investigators are Dr Noel Lythgo (University of Melbourne) and Professor Malcolm Horne (Florey Neuroscience Institutes).

The role of platelet-released factors on brain injury during stroke.

Associate Professor Robert Medcalf

Australian Centre for Blood Diseases, Monash University

Co-Investigators: Dr Andre Samson and Ms Amanda Au

Stroke is the second leading cause of death and the leading cause of disability in Australia. It is predicted that 60,000 Australians will suffer from a stroke in 2009. Indeed, the morbidity and mortality associated with stroke places a heavy socioeconomic burden on our nation, costing over $2.14 billion each year. As such, there is an urgent need to improve the current clinical practices used to prevent and treat patients suffering from stroke.

An ischaemic stroke occurs when there is a prolonged disruption of blood flow to the brain. Such a stroke typically arises when a blood clot obstructs a major cerebral artery and deprives the brain of essential nutrients. This in turn, results in rapid, substantial and irreversible brain damage.

One type of blood cell – known as a platelet, promotes the formation of stroke-causing blood clots. It is well-established that platelets become "activated" and accumulate within blood vessels causing clots to form and subsequent stroke development. Upon their activation, platelets release many bio-active molecules some of which have unknown effects. No study has directly assessed whether molecules released from activated platelets have any influence on the extent of brain injury during stroke.

Our laboratory has shown, unexpectedly, that activated platelets release a factor(s) that protect brain cells from "excitotoxic" injury (a form of brain injury that occurs during stroke). We intend to identify and further characterise these platelet-derived brain protective agents and explore further their mechanism of action

In summary, although activated platelets are clearly harmful in that they promote the formation of stroke-causing blood clots, platelets also release natural, unidentified factors that protect the brain from stroke injury. We believe that further research into the influence of platelet-released factors on brain injury will lead to the development of novel and innovative stroke therapies.

Award Winners and Projects:

Investigating freezing of gait in Parkinson's disease.

Dr Simon Lewis

Brain & Mind Research Institute, University of Sydney

Co-Investigator: Dr Hamish MacDougall

Parkinson's disease (PD) costs nearly $300 million per annum in Australia and half of this cost results from the requirement of nursing home placement, which is commonly due to the development of falls. Falls in PD are frequently due to the phenomenon of freezing of gait (FOG) where patients suffer paroxysmal arrests in their walking and become unsteady. Current treatments for PD only afford limited benefits for FOG and the mechanisms underlying this symptom are not well understood.

Our research group has recently proposed a novel model explaining the processes that account for the clinical manifestations of FOG. We believe that these processes are not unique to gait and that FOG can be accurately modelled using other tasks, which do not involve walking per se. Our preliminary data, utilising a computer based testing paradigm has confirmed the major assertions of this proposed hypothesis and we now intend to combine this technique with the novel approach of recording FOG in patients in their home environment utilising ambulatory gait recorders.

If we can demonstrate that results on our computer based testing paradigm accurately reflect FOG behaviour recorded in patients in their home environment, we will be able to utilise this paradigm in future functional brain scanning experiments. The results of such studies could identify the pattern of brain activity underlying FOG in PD.

Improving our understanding of this important clinical problem will hopefully lead to the future development of improved therapies for patients.

Sharon Naismith – Representative for Dr Simon Lewis

Live Video recording of cell abnormalities

Associate Professor Carolyn Sue

University of Sydney & Department of Neurology and Neurogenetics, Kolling Institute of Medical Research, Royal North Shore Hospital

Co-Investigator: Dr Jin-Sun Park

Over the last decade, 6 genes have been confirmed to be causally associated with PD. There are four autosomal recessive (AR) genes (Parkin, PINK1, DJ1, ATP13A2) and 2 autosomal dominant (AD) genes (SNCA and LRRK2). The most recent gene to be causally linked to PD is known as the ATP13A2 or PARK9 gene (Ramirez et al., 2006). Although the function of this gene is not entirely understood, it is thought to impair lysosomal function, a pathway that is involved in clearing degraded proteins from the cell. The discovery that mutations in PARK9 are causative of PD implies that enhancement of lysosomal clearance of degraded proteins may offer a new mode of treatment for patients that suffer from PD.

We have identified a new family with young onset PD that has pathogenic mutations in the ATP13A2 (PARK9) gene. We performed confocal microscopy of COS7 cells transfected with plasmids containing fluorescent-tagged PARK9 and have found that the normal (wild-type) hPARK9 is located in the lysosomal membrane, whereas abnormal (mutant) PARK9 is not found in lysosomal membrane. These data indicate that mutant PARK9 is localised or targeted elsewhere in the cell. Mutant PARK9 may act or be degraded using alternative pathways.

Overall these studies will bring us closer to understanding the role of lysosomal function and thus lysosomal protein clearance in the aetiology of Parkinson's disease. Studying its characteristics will allow us to discover the underlying malfunction(s) in patients with both PARK9 mutations as well as those who suffer the sporadic form of PD.

If we establish that hPARK9 mutations cause lysosomal dysfunction, this will improve our understanding of the disease process in PD and direct the identification of novel targets that could be used for therapeutic intervention.

Figure legend: Research staff from the Department of Neurogenetics with John Howard during his visit to the Kolling Institute on August 6th, 2009.

Investigating a Genetic Risk Factor for Developing Abnormal Involuntary Movements in Parkinson's Disease.

Associate Professor David Williams

Van Cleef Roet Centre for Nervous Diseases, Monash University & The Alfred Hospital

Co-Investigator: Ms Perdita Cheshire

Parkinson's disease (PD) is caused by degeneration of dopamine-releasing (dopaminergic) neuronal circuits in the brain. Treatment involves dopaminergic medications, but the effectiveness of these medications is drastically limited by the onset of abnormal involuntary movements (dyskinesias) in more than 50% of patients. Dyskinesias severely compromise quality of life and offset the benefits of anti-parkinsonian medication. Once dyskinesias develop there are few treatment options available, short of reduction in medication or neurosurgery.

A recent clinical study on PD patients has implicated a genetic risk factor for the development of dyskinesias. Patients homozygous for the "met" allele of the brain derived neurotrophic factor (BDNF) gene were shown to be at greater risk of developing dyskinesias than those carrying the alternative "val" allele. Although this study provides compelling evidence for the "met" allele as a potential risk factor for developing dyskinesias, it is limited to a single centre without pathological confirmation of PD.

Other studies have shown that long term adaptive changes in synapses in the brain are a hallmark of dyskinesias in animal models and it is has been suggested that these changes can be directly related to dopaminergic medication administration, but this has yet to be tested in humans. We hypothesise that if BDNF genotyping correlated with these biochemical markers of synaptic changes, this would provide compelling evidence to support long term adaptation as the pathophysiological mechanism by which BDNF genotype may indicate a risk factor for dyskinesia.

In order to develop therapeutic approaches to dyskinesias, these hypotheses from animal models or small human studies with retrospective clinical data must be tested in human tissue where the diagnosis of PD is pathologically validated and the clinical data is extensive and prospectively collected.

We aim to do this in a unique resource of human brain tissue archived from 51 patients with PD who have been prospectively studied and videotaped (The Melbourne Cohort), which in 2008 came under the auspices of the Australian Brain Bank Network (ABBN). In addition, the ABBN also holds the Sydney Cohort, consisting of 29 donors who have also been prospectively studied. With this detailed, prospective and validated clinical data we hope to uncover how this newly identified genetic risk factor can be directly linked to a functional biochemical differences that may cause dyskinesias.

HLA type and temporal lobe epilepsy

Dr Kee Meng Tan

Department of Neurology, Royal Melbourne Hospital

Co-Investigators: Professor Terence O'Brien and Dr Brian Tait

The epilepsies are a heterogeneous group of disorders, some inherited and some acquired. The pathogenesis of acquired epilepsies is likely to involve environmental factors and genetic susceptibility. This study forms part of a cluster of projects examining genetic influences on acquired epilepsies. These projects will test the hypothesis that variations in the immune/inflammatory response determine whether or not a patient will subsequently develop epilepsy following cerebral insult such as head injury or childhood febrile seizures. Variations in human leukocyte antigen (HLA) typing have been shown in a Turkish study to correlate with mesial temporal lobe epilepsy, and the Brain Foundation grant will allow similar testing to be performed on a larger scale in an ethnically different population.

Award Winners and Projects:

Peripheral nerve excitability in neurological ion channel disorders.

Dr Susan Tomlinson

Faculty of Medicine,
University of Sydney

Co-Investigator: Professor David Burke

Ion channels are membrane bound proteins which allow passage of charged particles in and out of neurons. They play a pivotal role in the electrical activity of nerve cell membranes which is essential for normal cell function including neurotransmitter release. Increasingly it is being recognized that ion channel dysfunction, genetic or acquired, can result in neurological symptoms. Such presentations often reflect the location and function of the specific channel affected. Ion channel disorders may manifest symptoms commonly seen in clinical practice, such as epilepsy, migraine, ataxia. Neurological ion channel disorders often pose a diagnostic challenge to the clinician, as symptoms may be intermittent, with the patient recovering in between episodes, resulting in a paucity of clinical findings to direct the diagnosis. Furthermore, investigation (e.g. biopsy or imaging) may reveal structurally normal tissue, despite a functionally abnormal cell membrane.

This research project focuses on genetic neuronal ion channel disorders, particularly those resulting in epilepsy. Although uncommon, genetic neuronal ion channel disorders are ideal disease models in which to study channel dysfunction in detail, as the underlying defect is known. In this way, mechanisms of common neurological diseases (e.g. idiopathic epilepsy or migraine) can be better understood. Peripheral nerve excitability studies will be used in patients with genetic neuronal ion channel disorders that result in epilepsy syndromes to assess how the genetic channel dysfunction affects the nerve. Given that many of the channels expressed in the brain are also expressed in peripheral nerve, the non-invasive excitability testing of peripheral nerve may be able to serve as a surrogate marker to activity in the central nervous system and potentially serve to direct genetic testing or as a diagnostic aid. In situations where a dysfunctional channel is not expressed in peripheral nerve excitability testing can explore compensatory changes in peripheral nerve, as has been seen in other central nervous system conditions.

Dr Raymond Garrick – Representative for Dr Susan Tomlinson

Pathophysiological insights into HIV and antiretroviral drug related neuropathy afforded by axonal excitability testing.

Dr Karl Ng

University of Sydney,
Royal North Shore Hospital
& Royal Prince Alfred Hospital

Co-Investigators: Professor David Burke and Professor Bruce Brew

The human immunodeficiency virus affects approximately 40 million people worldwide, with a large socioeconomic and medical burden. Despite progress in patient longevity, painful peripheral neuropathy is prevalent and an estimated 36% are affected by peripheral neuropathy in those with advanced HIV using sensitive neurophysiological techniques. Most patients suffer a distal sensory polyneuropathy probably related to viral disease burden but there are many cases especially in the developing countries that are attributable to the older antiretroviral agents such as stavudine. Differentiation of these two aetiological groups can be difficult on clinical grounds, or even with laboratory methods. The pathogenesis of HIV neuropathy is felt to be related to inflammatory processes centred on the dorsal root ganglion. Virus is mostly localised in the perivascular inflammatory cells here. The envelope glycoprotein, gp120, as well as inducing apoptosis in rat dorsal root ganglion, lowers the threshold for excitation in-vivo. Proinflammatory cytokines have been found in high concentrations in the dorsal root ganglion, and in animal models have been shown to lead to upregulation of sodium channels and neuronal hyperexcitability there. Prominent mitochondrial abnormalities have been seen in antiretroviral related neuropathy after exposure to offending drugs.

The purpose of this study is to use novel in-vivo techniques capable of studying neuronal voltage-gated ionic function to characterise the neuropathy of HIV polyneuropathy and ARV neuropathy. To our knowledge, this method has not been applied to this disease entity. These techniques provide a sophisticated insight into large fibre nodal and internodal ionic channel function. We intend to not only substantiate or refute in-vitro observations of Na channel up regulation in HIV polyneuropathy, but to see if there are features that distinguish a viral vs drug-induced neuropathic condition.

Muscular dystrophy and protection against heart disease.

Professor Richard Jackson

School of Medicine, Griffith University, Department of Medicine, Logan Hospital & University of Queensland

Myotonic dystrophy type 1 is a genetic disease, which is the commonest muscular dystrophy to affect both adults and children. It affects about 1 in 8000 people worldwide, and the so-called classical form of the disease shows clinical manifestations by the teenage years or early 20s.

Myotonic dystrophy affects skeletal, smooth and cardiac muscle, and begins by affecting the hands, feet and facial muscles, and progresses over time to affect all skeletal muscle groups. The major causes of disability and death are effects on the heart and the lungs, causing abnormal heart rhythms, poor contraction of the heart muscle and, in the lungs, an increased tendency to sleep apnea, aspiration pneumonia and poor respiratory effort. As well as these problems, these patients have a modified form of the "metabolic syndrome": they develop high blood fats, impaired ability to metabolise glucose and, subsequently, develop frank type 2 diabetes, and deposit excess fat inside the abdomen. These are all powerful "risk factors" for coronary heart disease, and most people who develop these problems are prone to early heart attacks and angina. Myotonic patients do not develop early coronary disease.

My research will try to find out why myotonic patients are relatively protected against this very common problem of coronary disease, even though they have classical risk factors. We will do this by comparing the activity of certain genes known to associated with coronary disease in myotonic patients and in other people who have the metabolic abnormalities described above, but do not have myotonic dystrophy. This may inform us of ways to protect against the commonest killer in the general community, coronary heart disease.

Prevalence and incidence study of neuromyelitis optica in Australia and New Zealand with population-based sensitivity and specificity of NMO IgG antibody positivity.

Associate Professor Simon Broadley

School of Medicine, Griffith University

Co-Investigators: Dr John Parratt, Associate Professor Robert Heard, Professor Bruce Brew, Dr Jeannette Lechner Scott, Professor Allan Kermode, Dr Pam McCombe, Dr Helmut Butzkuven, Associate Professor Bruce Taylor, Emeritus Professor John Pollard, Dr Mark Slee and Associate Professor Ernie Willoughby.

Neuromyelitis optica is a rare variant of multiple sclerosis which tends to be more severe and particularly affects vision and walking. Recently an unusual antibody to a water channel molecule (aquaporin-4) has been described in association with this condition supporting the long held clinical view that it may be a separate disease or is at least a distinct variant of multiple sclerosis. However, because of overlap in clinical features and a lack of precision in testing for this antibody considerable doubt remains regarding both the status of neurolmyelitis optica as a separate entity and the role of the aquaporin-4 antibody plays in diagnosis. Through a combination of extensive population-based collection of clinical data and systematic testing with MRI and antibodies this study hopes to clearly define the true spectrum of this disease and the value of aquaporin-4 antibodies play in diagnosis. The study will involve a nationwide survey of neuromyelitis optica in Australia and New Zealand and will provide accurate data on the sensitivity and specificity of various components of the diagnostic criteria including the aquaporin-4 antibody test. It is hoped that this study will advance our knowledge of how to diagnose this condition and shed light upon its cause. It is also hoped that the study will provide a platform for future study including clinical trials to improve the treatment of this condition.

Dr John Parratt - Representative for Associate Professor Simon Broadley

Research Grant Progress Reports:

Hydrocephalus and the role of brain water channels

Associate Professor Brian Owler
The Children's Hospital at Westmead

Hydrocephalus, a condition in which there is an increase in the volume of fluid (CSF) inside the brain, remains a significant cause of neurological dysfunction and even death. Through a Brain Foundation Research Grant, we aimed to study the role of a 'water channel' molecule, aquaporin (AQP1), in the production of CSF and hydrocephalus. The study aimed to investigate the effects of hydrocephalus on AQP1 expression and localisation as well as determine whether mice lacking AQP1 will develop hydrocephalus. The study uses a model of hydrocephalus in the mouse. This model involves injection of kaolin into the cistern magna which obstructs the flow of CSF. This causes CSF to build up and subsequently hydrocephalus.

Normally, AQP1 is located along the surface of cells that produce CSF in a structure called the choroid plexus. We have demonstrated that in hydrocephalic mice, while the overall levels of AQP1 are unaltered, a significant proportion of AQP1 is internalised from the surface membrane to the inner aspect of the cell. In this location it is unable to function and may represent a compensatory mechanism in hydrocephalus. We have demonstrated this using a number of techniques such as immunohistochemistry as well as gold-labelled immune electron microscopy. Although this compensatory mechanism, which has not been demonstrated before, appears to occur, the continued presence of AQP1 on the surface or apical membrane of the choroid plexus cells means that is remains significant therapeutic target.

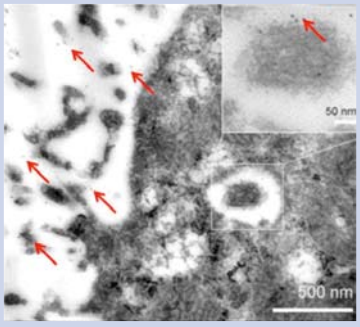


Figure 1: Immuno gold-labelled electron microscopy demonstrating AQP1(arrows) on the microvilli and within a lysosome (inset) of a choroid plexus cell in a hydrocephalic mouse.

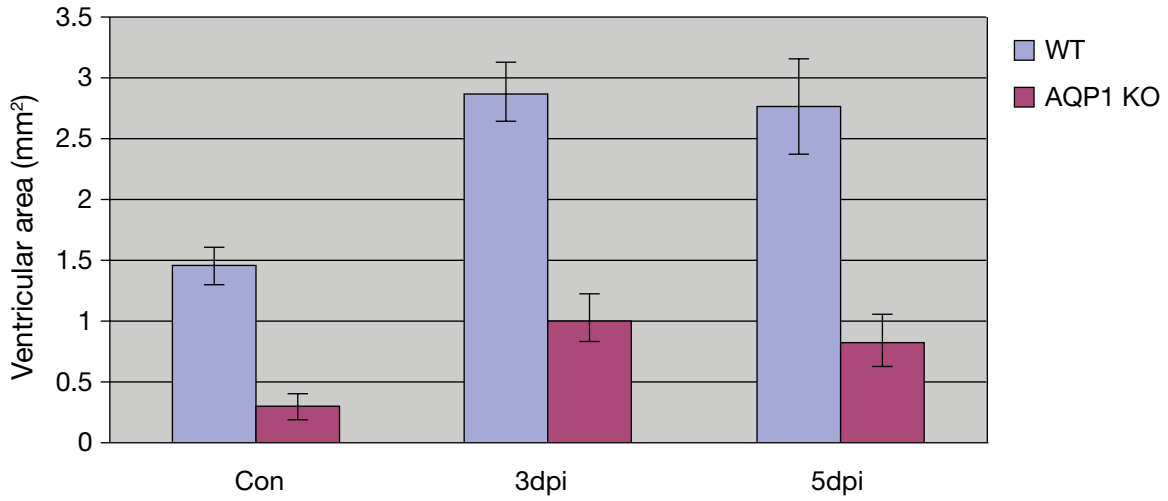


Table 1: Comparison of ventricular area in wild type and AQP1 knockout mice before kaolin injection (Con) and at 3 and 5 days after kaolin injection.

In order to test the importance of AQP1 in the development of hydrocephalus, we performed cisternal kaolin injections in AQP1 knockout mice in order to induce hydrocephalus. Knockout mice are genetically altered mice that lack particular genes that produce certain proteins; in this case AQP1. We found that AQP1 knockout mice had smaller ventricles compared to wild type mice. This is consistent with a reduced rate of CSF production. In mice that underwent cisternal kaolin injection there was a difference between wild type and knockout mice. Knockout mice developed only very mild ventricular dilation compared to wild type mice. This indicates that if we are able to 'block' AQP1, then hydrocephalus could be treated medically or even prevented. Studies are currently examining potential candidates that may be used to block AQP1 and therefore develop an effective medical treatment for hydrocephalus.

As a direct consequence of the research funded by the Brain Foundation, there are likely to be several publications. The laboratory currently has a journal article under review and a second article is preparation. The results were also presented at an international scientific meeting, Hydrocephalus 2009, in Baltimore in September.

This research would not have been possible without the generous support of the Brain Foundation. It has enabled our Laboratory to pursue our research into hydrocephalus which has resulted in a significant contribution this field of research.

Charity Golf Day

Characterisation of a novel neural pathway involved in migraine.

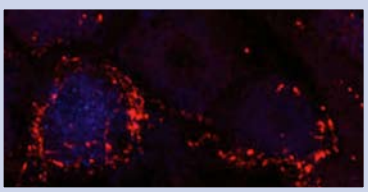
Dr Earnest Jennings

University of Melbourne

People suffering from migraine and cluster headaches often report pain and autonomic symptoms (e.g. nausea, sensitivity to light, crying or runny nose). The latter two symptoms are mediated by a specific group of nerve cells located behind the eye – parasympathetic neurons in the sphenopalatine ganglion. In terms of the project recently funded by the Brain Foundation, we have investigated the connectivity and control of these cells, as they are known to be active in some of the symptoms of migraine. We used histological labels that are specific to headache and precisely visualised the nerve cells using high-resolution confocal microscopy and nerve-tracing methods to determine their connectivity.

We showed, for the first time, that a target of the triptan class of anti-migraine drugs (labelled in red in the figure on the left) is located adjacent to parasympathetic neurons responsible for tear production and runny nose (labelled in blue). In addition, this target is located on sensory nerves, suggesting an interaction between the sensory and autonomic systems.

The data from this study have been presented at an international conference (JJ Ivanusic, V Staikpoloulos & EA Jennings (2008) Society for Neuroscience "Localization of the 5HT-1D receptor in the rat sphenopalatine ganglion"), and is currently being written up for publication. We are grateful to the Brain Foundation for making this study possible.



The spring weather was ideal for the Charity Golf Day at Pymble Golf Club on the 28th of September. NSW Committee member, Val Gibson was the 'driving' force behind the event and was well supported by keen golfer John King the NSW Committee Treasurer.

The day was very successfully managed by Gary Dawson of Bullant Sports, pictured below, starting with breakfast, numerous gifts of golfing equipment and finishing with an auction after lunch. It was such a good day that all participants are looking forward to next year.

Pymble is a very challenging course and the local knowledge of, Ian Haigh, a former Pymble Golf Club Captain and Brain Foundation Treasurer, may have helped him guide his Brain Foundation team to the best score of the day.

Bullant Sports conducts other charity golf days and the winners from each round go into a final on the 10th of December so the Brain Foundation will be well represented.

Pictured above are 3 members of the winning Brain Foundation team, John and Lynne King, Gerald Edmunds and Ian Haigh. Unfortunately, Ian's wife Jenny had to leave straight after the round.

National Headache and Migraine Awareness Week

The main theme for this year's Headache and Migraine Awareness Week was the need for a national register of people suffering chronic headaches and migraine.
In addition, the opportunity was taken to launch a new Headache and Migraine Management diary.

There was strong interest in both these issues and there was Australia-wide coverage through the press and radio interviews. This was reflected in considerably more traffic to the Headache Australia website and inquiries to the office.

The register is important as it represents an attempt by Headache Australia to reach out to the millions who suffer these two distinct neurological conditions, to help us to help them. In the first place, once people who suffer are able to be contacted, they can be kept up to date with advances in treatments. They can also choose to volunteer to be part of research programmes.

Large numbers will also help to build further evidence of the social and economic costs of Chronic Headache and Migraine. All these points can lead to significant increases in funding for research once a large number of people are in the communication cycle.

If you do suffer Migraine or Chronic Headache, you can join the register on the Headache Australia website,

www.headacheaustralia.org.au or by contacting the office on 1300 886 660

Fundraising for the Brain Foundation

Once again the Brain Foundation would like to thank all our wonderful **"Everyday Heroes"** for their fabulous efforts raising funds for us in 2009.

Matt Conroy
Henk Ritman
John Stokes
Bond Leung
Nina Zhou
Susanna Greig
Jaculin Cassell
Angus Macdonald
Elizabeth Bennison
Timothy Grant
Sophia Demetriades
Marisa Spina
Adam Beer
John McCarthy
Nila Oyama
Stephanie Nguyen
Alan Farrell
Anna Thompson
Marissa East
Tennille Sibbritt
Donna Armstrong
Margaret Kidd
Helen Boyd
Laurie Barram

This year our City 2 Surf runners donated a total of $4,360 to Brain Foundation. This is a grand total of $311.43 per kilometre. What a fabulous effort! A very big 'Thank You' to everyone!

Christmas and Celebration E-cards

Brain foundation now offer a number of different types of ecards on our website for you to spread cheers and spirit to your family, friends and colleagues this Christmas and for any other celebrations.

Spend your gift money on something worthy which would benefit even more people for a long time, and support Brain Foundation all year round.

You can send ecards to anyone, anytime and any occasion with a personalised message. Simply choose from one of our selection of ecards or create your own, and the amount you wish to donate and a custom message, your loved ones will receive an ecard with cash donated to Brain Foundation.

Brain Foundation is self funding, so 100% of the generous money we received from you goes directly to funding Australian researchers in their quest to find preventative measure, faster more accurate diagnosis, more efficient and effective treatments and ultimately seeking cures into brain diseases, disorders and injuries as well as spinal injuries.

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:

Linda Woods
David Eury
June Hill
Giovanna Scollo
Matthew Krel
Carolyn McKinlay
Betty Royans
Chiara Tino
Jim Benson
Rod Anderson
Catherine Blair
Donald McIntosh
Meryl Peck
David Affleck
Elsie King
June Kelynack Hill

We gratefully acknowledge other gift received since the last Brainwaves Newsletter:

Professor Denis Halmagyi Memorial Fund – Bequest

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

Name _____

_____

State _____ Postcode _____

Telephone ( ) _____

Mobile _____

Email _____

Please direct our gift to:
❑ Research ❑ Support/information Services

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: _____ / _____

Name on Card _____

Card holders signature _____

Thank you for supporting brain research through the Brain Foundation