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The Brain Research Institute was established at Austin Health, Melbourne, Australia in 1996. It supports collaboration between specialties in order to develop a better understanding of how a healthy or diseased brain functions.

The Brain Research Institute (BRI) performs internationally competitive research to help understand the structure and function of the human brain with studies including both healthy people and people affected by injury and disease. Ownership of Australia’s first 3 Tesla (3T) Magnetic Resonance Imaging (MRI) machines and the addition of a second 3T are a mainstay of BRI’s research capability, opening up new and challenging areas of neuroscientific and biotechnical research.

BRI is proud to offer the use of this technology platform to scientists for whom MRI can answer some of the most interesting biological questions. The power of this platform is extraordinary, and the exciting potential will be increasingly realised as new research programs and collaborations develop.

BRI has a vision that advanced MR technology in conjunction with world-class skills is a foundation for many areas of Australian biotechnology. We believe that a long term outcome of our research is a paradigm shift in health care delivery in the context of an aging population and unsustainable costs in the current hospital system. The cost efficiency that results from improved diagnostic methods developed in such a research environment will have profound effects on hospital based health care costs. This will allow many hospital-based activities to be conducted cheaply in an outpatient setting.

To understand the function of the human brain in health and disease, through engagement of our own and collaborating scientists in research of the highest scientific and ethical standards. Our success will be measured by improved understanding of brain function, earlier and more accurate diagnosis of human brain diseases and by the development of new treatments.

Brain Research Institute is:

→ An Affiliated Institute of The University of Melbourne
→ An Administering Institute of the National Health & Medical Research Council
→ Accredited Independent Medical Research Institute

MISSION STATEMENT
Chris Blake  
Chairman, Brain Research Institute  
Regional General Manager, People & Organisational Development  
National Australia Bank  

Chris Blake joined National Australia Bank in September 2006 as the Regional General Manager, People & Organisational Development.

In the role, Chris is responsible for leading and implementing people initiatives across the business, and developing both individual and organisational capability to help transform the culture and bring the NAB brand to life through its people.

Prior to joining NAB, Chris spent 20 years with PricewaterhouseCoopers, the last ten of these as a Partner. His most recent role was the National Leader of its People, Culture and Performance practice, where he worked with Boards, CEOs and executive teams to help develop the organisational capability and align their ‘people’ strategies with their broader business strategy.

Some of the key clients that Chris worked with at PwC were Qantas, ANZ, CSL, NAB, Telstra and Tattersalls.

Professional Memberships: Member, Institute of Chartered Accountants; Fellow, Taxation Institute of Australia; Member, Australian Human Resource Institute; Australian Institute of Company Directors.

Tom Buchan  
Managing Director, Buchan Consulting  

Tom Buchan is a previous Chairman of the Brain Imaging Research Foundation and is currently Managing Director of Buchan, a national consultancy specialising in business strategy, communication and public policy. He has over 25 years experience in corporate and financial communication and is responsible for constructing strategies at chief executive and board levels, frequently acting as policy adviser to global corporations and large private and publicly listed companies. Before establishing Buchan in 1985, Tom was a senior adviser to the Federal Government and to the Premier of Victoria.

Professional Qualifications: Bachelor of Commerce (University of Melbourne).  
Other Current Appointments: Director Foundation 49; Member Novell Advisory Board.

Mark Jones  
Partner, KPMG  

Mark Jones is a Partner in KPMG’s Risk and Advisory Services (‘RAS’) practice. Mark specialises in the provision of internal audit, risk management and governance services to major Australian organisations in the finance, insurance, retail, manufacturing and entertainment industries. Mark leads KPMG’s Corporate Governance practice and has national responsibility for risk management of KPMG’s RAS practice.

Qualifications and Memberships: Bachelor of Arts (Honours) in Economics (University of Sheffield UK); MBA (Melbourne Business School); Fellow, Institute of Chartered Accountants in England and Wales; Associate, Institute of Chartered Accountants (Australia); Member, CPA Australia; Member, Institute of Internal Auditors Australia; Member, Australian Institute of Company Directors and Registered Company Auditor.

Thomas J Schneider  
Chairman, Schneider (Australia)  

Dr. Thomas J. Schneider is the Chairman and CEO of Schneider (Australia) Consulting and President, CEO and Founder of Restructuring Associates Inc., a consulting firm based in Washington, D.C. He is Of-Counsel to the law firm of O’Connor & Hannan in Washington, D.C. Dr. Schneider is also a member of the Board of Trustees of the Institute for Genomic Research (TIGR), and the Venter Institute.

Over the past 30 years, Dr. Schneider has advised companies of all sizes, including numerous Fortune 200 companies, on corporate strategic planning, union-management partnerships, and the design of high performance organisations. He has published and lectured around the world on high performance organisations, union-management partnerships, and biotechnology.

Dr. Schneider received his A.B., magna cum laude with highest honours from Harvard University, and his J.D. from Harvard Law School. He obtained a Doctor of Philosophy Degree from Oxford University in industrial and organizational sociology. In 1999 he was awarded an Honorary Doctor of Laws degree from Deakin University in Australia “for the leadership in the restructuring of industrial relations in the United States of America.”
Anne Ward
General Counsel, Australia
National Australia Bank Limited
After a successful career of more than 20 years in private legal practice, Anne joined the National Australia Bank as General Counsel Australia in December 2005.

Anne chairs the Board of Qantas Superannuation Limited, Trustee of the Qantas Superannuation Plan which is one of the largest corporate superannuation funds in Australia.

Anne’s past directorships include Epworth Hospital, widely regarded as one of Australia’s premier private hospitals, and Transport Accident Commission of Victoria.

Until December 2005, Anne was a senior Corporate Partner at Minter Ellison Lawyers in Melbourne. During her years in private practice, as well as having extensive transactional experience, Anne regularly advised on corporate governance and regulatory issues including directors’ duties and liability, takeovers and business re structuring. She is known for her strategic, commercial approach which combines technical, legal expertise with significant practical experience in the boardroom.

Margaret Jackson, AC
Chairman, Qantas Airways Limited
Margaret Jackson was appointed Chairman of Qantas on 1 August 2000. She was first appointed to the Qantas Board of Directors on 1 July 1992. She is also a Director of Australia and New Zealand Banking Group Limited and a Director of Billabong International Limited.

Margaret is also Chairman of the Asia Pacific Business Coalition on HIV/AIDS, is a Fellow of the Australian Institute of Company Directors; a Member of the Foreign Affairs Council; a Member of the Melbourne University Business School Association; an Executive Committee member of the Australia Japan Business Co-operation Committee; and Chairmen’s Panel Member, Business Council of Australia.

Margaret holds a Bachelor of Economics Degree from Monash University and completed an MBA with distinction at Melbourne University. She received an Honorary Doctorate of Laws from Monash University in December 2002 and a Companion of the Order of Australia in the General Division (AC) in June 2003 Ms Jackson is also a Fellow of the Institute of Chartered Accountants in Australia.

Before beginning her career as a full time company director in 1992, she was a Partner of KPMG Peat Marwick’s Management Consulting Division.

She has formerly served as Chairman of the Transport Accident Commission and Methodist Ladies’ College and as Deputy Chairman of Southcorp Limited, a Director of the Howard Florey Institute of Experimental Physiology and Medicine, Co-Chair of the Australia New Zealand Leadership Forum, a Director of John Fairfax Holdings Limited, the Brain Research Institute, The Broken Hill Proprietary Company Limited, Pacific Dunlop Limited, Australian Telecommunications Corporation [Telecom] and the Australian Wool Corporation.

Graeme Jackson
Director, Brain Research Institute
Professor Graeme Jackson is the founder and Director of the Brain Research Institute and a Neurologist at the Austin Hospital, Melbourne.

He is internationally recognised as an expert and authority in new MR technologies, particularly in the field of animal and human studies of epilepsy. Graeme also holds an honours degree in Psychology and a doctorate in Medicine. From 1990–1995 he was a Paediatric Neurologist at Great Ormond Street Hospital for Sick Children, London.

Graeme holds a number of other positions, both clinical and academic. He is a Professorial Fellow of the Department of Medicine Austin Health/ Northern Health at The University of Melbourne. He is an Adjunct Professor in the Department of Radiology at The University of Melbourne which recognises his ability to integrate imaging technology with biological questions. He is also an Honorary Neurologist at the Royal Children’s Hospital in Melbourne and a board member of Neurosciences Victoria.

His group is at the forefront of unraveling the structural and functional abnormalities in the human brain that are associated with epilepsy.

The new MRI system, and the relocation of the Connelly biophysics group from London to BRI, gives Australia world-leading science capabilities in bioimaging.

This year we are celebrating the 10th anniversary of the Brain Research Institute. Our early aim was to support the vision of advanced bioimaging in an environment that is closely linked to clinical and health outcomes.

Today BRI has developed as a leading scientific independent research institute with strong corporate and philanthropic support. Realisation of the success of this model came in 1999 when funding was obtained to install the first high field 3Tesla MRI system. This was the seventh GE system installed in the world and the first such system in the southern hemisphere. This system has remained 100% dedicated to the research environment, where the funding for the system comes from the users and research grants.

BRI has been robustly supported by the strong research culture and ongoing commitment of Austin Health. The integration of research and health services at Austin Health is delivering improved health outcomes for patients, through new and improved treatments, procedures and processes.

In the Australian and particularly the Victorian context, BRI has also become a leader in the development and implementation of such very powerful technology, and its application to the understanding of clinical disease of the brain. We have also proudly contributed to a sense within the University, hospital and research communities, that large new infrastructure initiatives like that undertaken by BRI, can be supported if led by committed people. The rich scientific collaborations and interactions within Victoria, Australia and internationally are testaments to this success.
People

BRI recently welcomed Professor Alan Connelly and his world class team of physicists and neuroscientists from the prestigious University College London. This, in my opinion, represents a highly significant development for science in Australia.

Professor Alan Connelly is the Deputy Director of BRI and he has greatly enhanced our capabilities and international reach. He has strong links as a development scientist with Siemens in Germany, and has overseen the installation of our new 3T project.

Professor Sam Berkovic, the Director of the Epilepsy Research Centre (ERC) is the scientific director of BRI and gives focus and international standing to the wide range of work done at the Austin in Epilepsy. The focus of BRI is epilepsy imaging and the links with genetics are becoming ever more important. This is an area in which we are undoubtedly world leaders.

The staff of BRI work with passion and commitment to ensure that the focus and quality of the science is world class. All are great to work with and we are very proud of the culture we have at BRI for the pursuit of scientific excellence. The integration of the London sourced team with BRI has been a tremendous success and all can feel how this lifts the science possibilities and standards.

Development and Growth of Platform Technology

BRI sees its role in science in two ways: firstly, support and development of cutting edge platform technologies in MRI that support a wide range of users throughout Australia, New Zealand and a broad range of the research community; secondly, using these technologies, with deep understanding of the strength and limitations of the techniques, to answer critical problems in understanding brain function and disease.

Professor Connelly, and the MRI Development Group are responsible for driving the expansion of the MRI platform capability based on advanced MRI information acquisition and analysis.

The MRI Development Group brings a new understanding of MRI, new skills in development, linkages with the international community and a world-class reputation both in development and in teaching. This will be the seed for an ongoing skill base in bioimaging in Australia that will be seen as increasingly significant in future years.

I personally see the development of the concentrated human resources of talented and knowledgeable people in MRI to be the hardest part of scientific development and the most important for the future of biosciences in Australia. Keeping this talent coupled to well posed clinical problems and cutting edge technology is a primary strategy of BRI.

The development of advanced imaging technologies at BRI will provide local opportunity for world leading science developments that have immediate health care benefits. BRI and other neuroscience research groups, with important questions to address, can work in conjunction with experienced MRI development scientists to apply the new techniques to clinical areas of epilepsy, stroke, brain trauma and mental health.

BRI now has its second high field 3 Tesla MRI. This has been funded by the Victorian State Government STI program and federal Grants combined with corporate support. This second 3T MRI system realises the vision of an integrated MRI and neuroscience facility, where basic problems in biology (from large animal models through to human studies) can be fully investigated with advanced MRI methods.
The MRI Development group and the upgrade of the MRI capabilities, will facilitate expansion of the neuroscience programs of BRI researchers, and of our extensive range of collaborators. The technical development work will both be driven by important neuroscientific goals, and will in turn feed back into the neuroscience directions as technical advances influence the questions that can be addressed. Such a synergistic relationship will enable neuroscience research in Victoria to stay at the forefront of what is possible worldwide. There is no doubt that neuroimaging, in all its forms is becoming more central to experiments in biology and understanding of disease, and is an essential platform for biotechnology and health delivery.

Science Highlights
In parallel with the support and development of platform technologies has been the development of research programs.

The renewal of the NHMRC Epilepsy Program Grant in 2006 for a further 5 years is recognition that BRI and the broader Neuroscience group at Austin Health are internationally recognised as leading the thinking and applications of imaging technologies and genetics to the problems associated with epilepsy. Austin Neurosciences is generally perceived by most in the international community as one of the lead epilepsy research centres in the world with pre-eminence in imaging and genetics.

In the first Program Grant one of the six investigators was from BRI. In the Program Grant renewal, three of the nine investigators come from BRI and are associated with imaging. This grant was obtained with Professor Sam Berkovic and Professor Ingrid Scheffer, from the Epilepsy Research Centre, Professor David Reutens from Monash University, Associate Professor John Mulley and Dr Jozef Gecz from The University of Adelaide and Dr Steve Petrou from the Howard Florey Institute. This comprehensive, multidisciplinary program reflects the strength of our scientific collaborations, as well as the increasingly important contribution of the imaging sciences to such major neuroscientific undertakings.

A question of fundamental importance being addressed through BRI’s Epilepsy Imaging Program is an understanding of the mechanisms of seizure generation. One of the keys helping us unlock these secrets is functional magnetic resonance imaging (fMRI) combined with simultaneously acquired electroencephalography (EEG). We have developed a world-leading method to overcome technical limitations, allowing us to simultaneously acquire EEG and MRI. The device is now in routine use at BRI, to investigate the mechanisms of seizure generation.

We are also using a multitude of neuroimaging approaches, including functional, structural and physiological measures, to characterise seizure types. These are then married with other data such as genetic profiles, clinical symptoms and neuropsychological measures to help understand the disease.
Research Grant Funding
BRI has achieved a steady increase in Peer Reviewed Grant Funding over the last ten years. It has been a tight environment for researchers in an enormously competitive field, so our sustained success in obtaining research funding through traditional peer reviewed sources such as the NHMRC has been very pleasing.

Publications
Given that the primary purpose of BRI is scientific research, it is worth reflecting on the scientific output of BRI and broader epilepsy groups at the Austin. Our publications, and particularly the high rate of citation by other researchers of our published research, continues to be impressive and a source of pride that our science has influenced thinking in our field.

BRI has strong collaborative links with Professor Sam Berkovic and colleagues at the ERC, and over the last 10 years our epilepsy work has produced over 20 publications that have been cited more than 100 times. Citation rate does reflect the impact of papers on the thinking of researchers internationally, and over 100 citations represents what would be thought of as a classic paper in the field.

New Neuroscience Institute
Our strong scientific output, the success of our model of private and government partnership, and the international reputation BRI has developed, has led to support from Government for us to join with other neuroscience institutes in Melbourne to form a world class, critical mass federation of neuroscience institutes. The Howard Florey Institute, the National Stroke Research Institute and BRI will create a neuroscience centre in Melbourne that can compete as a leading neuroscience institute on the world stage. New facilities will be built at Parkville and at Austin Health.

While this presents many challenges to the highly focused model of science that BRI has been very adept at, it does create opportunities for integration of our core platforms and programs into a much larger neuroscience institute.

Institute Board
The BRI Board welcomed new member Dr Thomas Schneider. Tom is the Chairman and CEO of Schneider (Australia) Consulting and is also a member of the Board of Trustees of the Institute for Genomic Research (TIGR), and the Venter Institute. He brings over 30 years of valuable experience from high performance biotechnology organisations.

The vision and support of the current BRI board has brought BRI to the status of a world class neuroscience facility. My heartfelt thanks to the academic and administrative teams that have made all this possible through dedication and talent, and to the BRI Board who do an outstanding job of supporting the research and making it all possible. We do indeed have a special opportunity to change the way the bioscience world thinks of biology and how hospitals will operate in the future.

Challenges
In the past 10 years BRI has grown from a clear vision and a few key individuals to a powerful group of scientists with complementary abilities, clear focus, international reputations and in an environment that provides uncompromising scientific opportunity with cutting edge and world class equipment and platform.

As a scientific group we can look to the future with great confidence and excitement. We are privileged to be able to address fundamental questions of biology with new technological approaches in the context of clinically relevant issues.

Graeme Jackson
Director
White matter abnormalities have been implicated in many disease states, including multiple sclerosis, stroke, epilepsy, tumours, dementia, and in a range of mental health disorders (e.g. schizophrenia). The pathophysiologic basis of many of these disorders is thought to be related to abnormalities in the structural connections between different areas of the brain. Furthermore, knowledge of white matter organisation is essential for neurosurgery, to ensure the preservation of the patient’s most important functions. There is therefore enormous interest from neuroscientists, psychiatrists and neurosurgeons in using this technique. Despite important recent developments, there is currently no reliable method to properly characterise the structural connectivity. One important aspect of the research at the BRI is the development of improved acquisition and processing methods for Diffusion MRI, with especial emphasis in its role to study brain connectivity.

Inferring white matter connectivity using diffusion-weighted imaging. Diffusion-weighted MRI is sensitive to the microscopic motion or diffusion of water molecules in the brain along a given direction. In the white matter, which consists of tightly packed bundles of neuronal axons, the regular arrangement of fibres introduces a directional dependence of the image intensity (i.e. anisotropy). This information can be used by the so-called ‘fibre-tracking’ algorithms, to track the path of the fibres and to infer the structural connectivity. However, the model currently used (known as the diffusion tensor model) is invalid in regions containing multiple white matter tracts that cross or pass very close to each other. This can lead to the fibre-tracking algorithm to venture into an adjacent tract with very different end points, and connections may be inferred that do not exist in reality.

To address this important problem, we have developed an alternative model that does not suffer from this limitation, using a concept known as spherical deconvolution. Our method produces an estimate of the distribution of fibre orientations directly from the Diffusion MRI data, regardless of how many fibre bundles may be present. The accurate characterisation of the distribution of fibre populations present in each pixel can be used to improve fibre-tracking algorithms, avoiding the errors introduced by the tensor model.
Perfusion MRI: How can we measure vascular networks? (images 4a & 4b)

Perfusion MRI is a non-invasive imaging technique for measuring cerebral perfusion [blood delivery to brain tissue per unit time]. Blood delivers oxygen and nutrients to the tissue, which are necessary for cellular metabolism. The survival of the brain is dependent on a continuous and adequate supply of blood, and failure of the cerebral circulation can result in cell death. Similarly, some clinical conditions are associated with a hyperperfusion status [such as epilepsy and tumours] due to their increased energy demand. For these reasons, the ability to measure perfusion accurately, non-invasively, and with good spatial resolution would offer the chance to identify and characterise abnormal tissue in many clinical conditions.

A significant expansion in the availability of MRI scanners has taken place in the last decade, and Perfusion MRI has become an important diagnostic technique. Every major MRI scanner manufacturer provides imaging sequences for Perfusion MRI, but their product analytical software is still somewhat rudimentary. Improved methods to quantify perfusion and characterise the vascular networks in the brain is an important aspect of research at the BRI.

Bolus delay and dispersion effects in perfusion quantification.

Bolus-tracking MRI is the most commonly used Perfusion MRI technique in clinical studies. It involves injection of a bolus of contrast agent. Perfusion quantification requires measurement of the arterial input function (AIF), which describes the input of contrast agent to the tissue. Although this function can vary throughout the brain, a single function is commonly used in practice. However, the presence of vascular abnormalities [e.g. arterial stenosis, occlusion, or collateral supply] may cause distortions in the bolus [delay and dispersion], which we showed can lead to severe local underestimations in perfusion quantification.

One solution to this delay and dispersion problem involves estimation of a local AIF from a small vessel closer to the tissue of interest. However, this is problematic due to partial volume effects [i.e. contamination with the surrounding tissue]. We have recently developed a method to define a local AIF using independent component analysis, a technique designed to identify temporal/spatial independent patterns. Using this methodology, the underestimation in perfusion quantification is minimised.

Accurate perfusion imaging will help guide therapy in patients with stroke.

1 Limitations of diffusion tensor fibre-tracking. The connections established from the corpus callosum to the spinal cord (x symbols) are anatomically incorrect. Moreover, many real connections to lateral cortical regions (* symbols) have not been identified. This is due to crossing fibres in the regions shown by the arrows; in that area there are three fibre bundles present.

2 Fibre-tracking using spherical deconvolution. The erroneous connections were not identified. Moreover, the connections to lateral cortical regions have been identified.

3 Fibre orientations for the region highlighted on the left. The diffusion tensor model gives only one direction for each pixel (middle). However, each pixel may contain several directions, which can be identified correctly using the spherical deconvolution method (right).

4 (a) Local AIF in a patient with vascular abnormalities in the major R cerebral arteries. (b) Perfusion maps calculated using the local AIF (left) and the traditional method (right). Both methods show areas of reduced perfusion. However, perfusion is underestimated with the latter (arrows) due to the unaccounted effects of bolus delay and dispersion.
As part of a collaboration with Dr. J.R. Cebral (USA), we have developed a novel method to create a subject-specific vascular model, which is based on combining high-resolution MR images and MR angiography with computer generated 3D arterial tree structures. These vascular models can provide detailed anatomical knowledge of the various intracerebral vascular territories, which is crucial for the differential diagnosis of thromboembolic and border zone ischemia. A natural extension of this methodology is to combine it with work we have done previously on calculating the transport of blood along major arteries. In this way, the transport throughout the arterial tree could be determined, including the distribution of blood at the microvascular level, therefore providing an alternative MR method to estimate cerebral perfusion. This will also allow the calculation of flow redistribution during arterial occlusions and estimation of the affected area of the brain. Furthermore, by incorporating a model of autoregulation, the effect on perfusion of vascular abnormalities such as stenosis and occlusion could be estimated.

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MRI development

What is the arterial origin for the regional blood supply within the brain?

Another important aspect of understanding cerebral perfusion is to determine the arterial origin for the blood supplied to the different regions of the brain, i.e. the vascular network. This information, known as the cerebral arterial territories, can play a key role for the management of stroke patients in the differential diagnosis of haemodynamic border zone infarction and thromboembolic ischemia. This differentiation is largely based on the location of the visualized infarct relative to the arterial territories and so-called ‘border zone’ regions.

However, individual arterial territories are difficult to identify in vivo, and a large variability between different patients has been shown. Therefore, interpretation of acute stroke subtype and underlying pathogenesis, based on the topographic patterns alone, is often inaccurate.

There is a need for the development of new techniques for the mapping of arterial territories. The currently limited understanding of the collateral circulation in the human brain can be greatly enhanced through the development of vascular models, providing the basis for future therapeutic and prognostic applications. It should be emphasised that realistic vascular models play an important role complementing experimental methods, and often enable the determination of haemodynamic characteristics that are difficult to obtain in vivo non-invasively.

A natural extension of this methodology is to combine it with work we have done previously on calculating the transport of blood along major arteries. In this way, the transport throughout the arterial tree could be determined, including the distribution of blood at the microvascular level, therefore providing an alternative MR method to estimate cerebral perfusion. This will also allow the calculation of flow redistribution during arterial occlusions and estimation of the affected area of the brain. Furthermore, by incorporating a model of autoregulation, the effect on perfusion of vascular abnormalities such as stenosis and occlusion could be estimated.

Realistic models of brain vasculature will improve diagnosis in patients with stroke.
Can we diagnose disease by imaging brain physiology?
Magnetic Resonance Imaging (MRI) scanners are extremely flexible imaging machines, capable of non-invasively detecting tissue characteristics and even determining the chemical makeup of internal organs in the body. Current research at BRI includes the development of improved imaging sequences and automated analytical methods to detect subtle changes in brain tissue characteristics in patients with various diseases.

T2-relaxometry: An indicator of the health of brain tissue.
The measurement of T2 relaxation time [“T2 relaxometry”], has been established as a reliable tool for the quantitative measure of tissue abnormalities in temporal lobe epilepsy. At BRI the measurement of the T2 is achieved using an optimized pulse sequence that has been developed in our Institute. We have also developed a novel analysis method that we call voxel based relaxometry (VBR) which provides an automated objective description of areas of T2 abnormality in groups of patients with epilepsy compared to control patients. Results of volume and T2 abnormalities in a group of subjects with unilateral left hippocampal sclerosis (HS) are shown in Figure 6.

Sodium Imaging with MRI can be used to determine the viability of damaged brain tissue.
Conventional MRI is based on the signal derived from proton nuclei of water. Most other MRI sensitive nuclei are difficult to detect because they are present at low concentration or have low sensitivity to the MR signal. We are now able to generate images based on sodium, the second most common nucleus in tissue. The physical properties of sodium result in the signal being very short-lived. To detect this small signal, a new pulse sequence called twisted-projection-imaging (TPI) is necessary. This pulse sequence allows the collection of images such as those shown in Figure 7. Such images have potential use in a number of diseases such as epilepsy and stroke. The TPI sequence will be used at the BRI to assess changes in tissue sodium distribution after seizures.

Advanced imaging techniques can identify abnormal brain regions that can’t be seen any other way.
Measuring activity in brain networks allows better understanding of complex functions such as language.

**Normal brain networks**
Functional magnetic resonance imaging, or fMRI, is a method that uses changes in blood oxygen levels during brain activity to map the anatomical location of different brain functions. First demonstrated in humans in the early 1990’s, it has been exploited to study cognitive function in groups of healthy controls and patients. Traditionally, fMRI has been used to identify a focal region associated with a particular cognitive function. We know however that this is not a realistic model of brain function. Studies performed at BRI have helped demonstrate that the brain operates instead as an extended network, where information is sent back and forth between different regions, with each region performing some small element of the actual processing task.

Functional connectivity is a method being explored at BRI that is designed to measure this network of cooperation with the aid of fMRI. We are interested both in technical aspects of the method, together with application of the method to cognitive science, and the study of epilepsy.

**Can we measure the brain’s functional networks?**
Functional connectivity measures brain networks by detecting correlations in the fluctuations in voxel signal timecourses during a continuous cognitive state (typically rest). It has the great advantage (compared to conventional fMRI) that it doesn’t require a subject perform a specific cognitive task during the scan. It is thus sensitive to detecting regions that are working in concert to perform specific time-locked functions, rather than looking for regions that behave in an externally imposed state. This means we make no assumptions about what the brain is doing.

Although functional connectivity has been used to investigate networks associated with language, memory, motor function, and disease-induced changes, little work has been done to validate and optimise the method. A particular concern is the sensitivity of functional connectivity results to physiological noise, such as cardiac and respiratory motion. Current work at BRI seeks to optimise and validate connectivity, minimising the confounding effects of physiological noise, and ensuring that clinical use of the technique will lead to meaningful results.
Probing the fine functional structure of the language network.

Cognitive functions such as language involve a network of focal brain regions, together with the connections between them. Understanding cognition requires the understanding of both the focal cortical processing and the co-ordination of the whole network. Disorders of brain function can be considered as primarily disruptions of local cortical function (such as stroke), miscommunication between focal regions (as has been suggested for schizophrenia), or both (possibly in epilepsy).

Work conducted at BRI has demonstrated that functional regions traditionally associated with a single cognitive function show functional specialization (see figure 8), when studied using functional connectivity. This continues to be investigated, both in the healthy brain and in disease. We wish to understand the cognitive basis for such functional specialization, as well as how it changes in disease.

Can we measure language function in young children?

The determination of language lateralisation prior to neurosurgery aids in surgical planning, and can improve the preservation of language function in epilepsy patients. Language fMRI can be used to non-invasively measure language laterality index (LI), which correlates well with invasive clinical language testing. Unfortunately there are cases where it is difficult to perform, such as for very young children and for patients with cognitive impairment.

At BRI we are using functional connectivity to measure the laterality of language networks, without the need for active performance of a language task. Connectivity can detect language networks largely similar to those seen in an activation study and detect subtle changes in these networks in patients with epilepsy. This approach promises assessment of language laterality in patients with severe epilepsy, as well as in infants and young children with language impairment, none of whom cannot be assessed with current approaches, which require the performance of an active language task.

We seek to understand how the brain can recover important functions after injury.
How can we “see” into the brain?
The detection of changes in brain activity using EEG has been a mainstay of the clinical diagnosis of epilepsy for decades. EEG informs us on the existence and timing of events (including electrical events that occur without any clinical symptoms); however EEG is unable to reveal the precise location of the brain activity. Functional MRI allows the exploration of the brain's blood flow response to events, and is very good at revealing the spatial location of brain activity. Compared to EEG however it has rather poor time resolution. Marrying the two techniques is technically very challenging, for the MRI environment consists of very high static and changing magnetic fields that usually swamp the microvolt signals from the scalp EEG.

We have developed a world-leading method to overcome the technical limitations allowing us to simultaneously acquire EEG and MRI. The device is now in routine use at BRI, to investigate the mechanisms of seizure generation. There is still much work to be done to understand the information that we are now able to acquire, such as determining how the location of brain activity associated with sub-clinical abnormal electrical events in the brain may relate to seizure generation itself. We hope that this work will eventually lead to a robust method for the all-important localisation of the seizure focus in individuals with severe epilepsy, thus dramatically improving the chances of being able to surgically intervene to cure their condition.

What is the sequence of events that lead to a clinical seizure?
Another promising approach is to investigate neurophysiological changes immediately before the onset of a seizure. It is known that changes in brain activity can occur minutes or even hours prior to clinical symptoms. We have successfully used functional MRI to demonstrate areas of increased and decreased activity many minutes prior to seizure onset. Importantly, our results indicate that there are changes in the lead up to a seizure in areas that include, but are not limited to, the presumed seizure focus. The relationship of these signal changes to seizure generation, and how these data might help to localise the epileptic network and ‘seizure focus’ for surgical treatment, is a complex question that we are actively pursuing.

Epilepsy is a major interest of BRI scientists: we are dedicated to linking our research to the cure of our patients with seizures.

Seizure origins
There is a relatively high prevalence of epilepsy in the general population (it has been estimated that about 1 in every 140 people suffer from epilepsy). Despite this, the mechanisms of seizure generation remain unclear. A significant proportion of people with continuing seizures are resistant to anti-epileptic drugs; no viable treatment options exist for some patients.

Using combinations of neuroimaging techniques at the BRI, we have made significant breakthroughs to help us understand the mechanisms of seizure generation. One of the keys helping us unlock these secrets is functional magnetic resonance imaging (fMRI) and simultaneously acquired electroencephalography (EEG). The method that allows this technology to be used simultaneously has been developed at the BRI, and is the subject of a current patent application. Structural and physiological MRI methods are also being developed and applied at BRI to investigate changes in brain networks that occur in epilepsy.
Brain Function

One example of the endophenotyping studies being undertaken at BRI is that of the specific epilepsy syndrome Benign Epilepsy with Centro-Temporal Spikes (BECTS). BECTS is a common cause of epilepsy in primary school children. BECTS is characterised by focal epileptic discharges (spikes) without frequent seizures or apparent brain pathology. Children with BECTS also experience cognitive difficulties but the relationship between the cognitive problems and the ‘spikes’ is unknown. Participants complete a battery of neuropsychological tests assessing intelligence, receptive and expressive language, primary memory, new learning, academic attainment, and executive function. In addition, neuroimaging measures including structural, functional (including simultaneous EEG/fMRI) and physiological (T2 relaxometry) are acquired. We will determine if BECTS is associated with a specific or a diffuse cognitive impairment, and if any revealing features can be found in the neuroimaging measures that can help explain the mechanisms of the condition.

In brain markers of epilepsy

A phenotype is a physical characteristic, for example the colour of your eyes. Some phenotypes are associated with a disease, such as the short stature and flattened facial profile of those suffering Down’s syndrome. An endophenotype is in internal characteristic, such as the shape of your brain. At the BRI, we using a multitude of neuroimaging sequences including functional, structural and physiological measures, to determine the endophenotypes associated with particular types of Epilepsy. These are then combined with other data such as genetic profiles, clinical symptoms and neuropsychological measures to help understand the disease. Particular features associated with a condition may be causative of seizures, a consequence of seizures, neither or both. Researchers at BRI are helping determine the significance of identified features. Ultimately this will lead to improved diagnosis and treatment of the disease.

The use of many different imaging techniques helps us understand brain disease.
Brain Structure
How does disease affect the structure of the brain?
Structural neuroimaging using magnetic resonance imaging (MRI) is an important diagnostic and research tool, non-invasively providing a three dimensional view of the internal structure of the living human brain. In some brain diseases there are obvious structural abnormalities that can be seen using MRI. In many other diseases however we are discovering that there are subtle changes in brain structure that cannot be seen by eye.

MRI scanners allow us to “see” into the living brain.

Researchers at the brain research institute are using MRI to investigate how the shape of brain structures may be subtly altered in people with conditions such as obstructive sleep apnoea and epilepsy, to assist in the understanding and better treatment of these conditions.

The measurement of shape changes is accomplished by analysing the MRI scans of large numbers of patients, and comparing these using to the MRI scans of people with no neurological disorders. Our research has indicated that specific regions of the brains of people with epilepsy have a smaller volume than normal subjects (Figure 13). These specific brain regions coincide with regions identified in separate functional experiments in which we have demonstrated decreased blood flow during epileptic seizure activity.

The outcomes of our structural imaging research will enable the scientific community to map patterns of structural change in brain tissue and determine the relationship between these structural changes and altered function of pathological tissue.

How does disease affect brain chemistry?
Magnetic resonance spectroscopy (MRS) gives information about metabolites containing a particular nucleus in regions of the brain. The technique provides a metabolite profile that can act as a disease ‘finger-print’. We use MRS at the BRI to measure metabolites that contain either proton or phosphorus nuclei. Metabolite profiles have the potential to show a ‘metabolic phenotype’ associated with different forms of epilepsy — such as the effect of genetic changes that result in increased susceptibility to epilepsy. Metabolite information is also useful in cases that do not show abnormalities with standard imaging methods. The technique also provides information on the short-term and long-term changes associated with seizures.

MRS is performed at the BRI to examine how proton-containing metabolites change with epilepsy. This information is helping unravel the mysteries of the mechanisms and long term effects of epilepsy.

13 Regions of gray matter volume reduction in subjects with Childhood Absence Epilepsy syndrome.

14 Phosphorus-31 MR spectrum recorded from the temporal lobe of a patient with epilepsy in the normal state (left) and from the same temporal lobe immediately after a seizure (right). Note the large decrease in phosphocreatine (peak 4).
Other brain disorders
The BRI supports collaborations with other research organizations. The following are some examples:

**Stroke**

**Schizophrenia**
Identification of markers for disease in patients at risk of developing full-blown schizophrenia. These markers will allow for earlier administration and improved drug treatments.

**Cerebral Palsy**
Central and peripheral effects of Botulinum toxin [Botox] A on upper limb function in children with cerebral palsy.

**Sleep apnoea**
MR investigation of obstructive sleep apnoea syndrome.

**Parkinson’s disease**
MR characterisation of abnormalities in the substantia nigra in patients with Parkinson’s disease.

**Huntington’s Disease**
Effects pre- and post-therapy on cognition in Huntington’s disease.

**Anorexia Nervosa**
Examining brain response to treatments of Anorexia Nervosa in young people.

**Diabetes**
Central nervous system changes in young people with type 1 diabetes.

Collaborations
- Austin Health
- Baker Heart Research Institute
- Brain Foundation
- Epilepsy Foundation
- Epilepsy Society of Australia
- Flinders Medical Centre (S.A.)
- Howard Florey Institute
- Institute for Breathing & Sleep
- Mental Health Research Institute
- Monash University
- Murdoch Children’s Research Institute
- National Stroke Research Institute
- Royal Children’s Hospital
- Royal Hobart Hospital
- Royal Melbourne Hospital
- Swinburne University
- University of Melbourne
- University of Queensland

International
- Århus University Hospital (Denmark)
- Foothills Hospital (Calgary Canada)
- George Mason University (USA)
- Harvard University (USA)
- Institute of Neurological Science (Mangone Italy)
- International League Against Epilepsy
- Leiden University Medical Centre (The Netherlands)
- Lund University (Sweden)
- New York University (USA)
- Northern Illinois University (USA)
- The Institute for Genomic Research (USA)
- University College London (UK)
- University of Auckland (NZ)
- University of West Virginia (USA)
Income – Source of Funds 2005/06

NHMRC Grants 44%
Commonwealth Infrastructure 2%
MRI Income 18%
Neuroscience Victoria 16%
State Infrastructure 10%
Other Grants 3%
Other Income 7%

Expenses – Application of Expenses 2005/06

Travel & Conference Expenses 3%
Salary & Associated Expenses 56%
Research Expenses 15%
Depreciation Expenses 13%
Administrative Expenses 2%
Insurance / Professional 3%
MR Maintenance 8%
**Competitive grants used to access and conduct research at BRI**

<table>
<thead>
<tr>
<th>Grant Program</th>
<th>Grant Title &amp; Researcher</th>
<th>Total Grant ($)</th>
<th>Year Awarded</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC Program</td>
<td>Epilepsy: Molecular basis and mechanisms in the era of functional genomics. Berkovic, Jackson, Connelly, Mulley, Scheffer, Reuters, Petrou, Getz, Waites</td>
<td>11,361</td>
<td>2006</td>
<td>5</td>
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<tr>
<td>NHMRC Project</td>
<td>Validating and optimising the analysis of magnetic resonance physiology data. Waites, Abbott, Pell</td>
<td>92</td>
<td>2006</td>
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<tr>
<td>NHMRC Project</td>
<td>Do Spikes affect Language in BECTS? Archer, Harvey, Saling</td>
<td>215</td>
<td>2005</td>
<td>3</td>
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<tr>
<td>NHMRC Project</td>
<td>The role of the posterior cingulate cortex in verbal associative learning. Lillywhite, Waites, Pell</td>
<td>145</td>
<td>2005</td>
<td>3</td>
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<tr>
<td>NHMRC Project</td>
<td>Brain adaptation and recovery of touch sensation after stroke. Carey, Abbott</td>
<td>335</td>
<td>2004</td>
<td>3</td>
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<tr>
<td>NHMRC Project</td>
<td>Practitioners Fellowship. Jackson</td>
<td>391</td>
<td>2004</td>
<td>5</td>
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<tr>
<td>NHMRC Project</td>
<td>An event related fMRI study of cognitive deficits in Huntington’s Disease. Georgiou – Karistianis, Egan, Churchyard, Stritharan</td>
<td>255</td>
<td>2004</td>
<td>3</td>
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<tr>
<td>NHMRC Project</td>
<td>High Field Magnetic Resonance Evaluation of Cerebral &amp; Brainstem Dysfunction in Obstructive Sleep Apnoea. Pierce, Briellmann, O’Donoghue</td>
<td>335</td>
<td>2003</td>
<td>3</td>
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<tr>
<td>NHMRC Project</td>
<td>Reorganisation of the language system in epilepsy. Abbott, Saling, Briellmann</td>
<td>186</td>
<td>2003</td>
<td>3</td>
</tr>
<tr>
<td>NHMRC Project</td>
<td>Structural and diffusion tensor neuroimaging in twins discordant for psychosis. Mowry, Hannah, Pantelis, Chalk, Rose, Wood</td>
<td>457</td>
<td>2003</td>
<td>3</td>
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<td>Juvenile Diabetes</td>
<td>CNS outcomes in young people with type 1 diabetes – a 12 year follow up. Northam, Wellard, Werther</td>
<td>300</td>
<td>2003</td>
<td>3</td>
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<tr>
<td>Research Foundation</td>
<td>Epilepsy: A collaborative research program from genome to patient. Berkovic, Jackson, Scheffer, Reuters, Williams, Petrou</td>
<td>8,225</td>
<td>2002</td>
<td>3</td>
</tr>
<tr>
<td>Neurosciences</td>
<td>MRI/EEG in the investigation of seizure focus. Jackson, Briellmann</td>
<td>140</td>
<td>2002</td>
<td>3</td>
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<td>Victoria (NSV)</td>
<td>Neurodegeneration/Neuroprotection. Briellmann, Pelli, Jackson</td>
<td>60</td>
<td>2002</td>
<td>3</td>
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<tr>
<td>NSV Project</td>
<td>Seizure associated, short term MRS changes. Jackson, Berkovic, Wellard, Briellmann</td>
<td>130</td>
<td>2002</td>
<td>3</td>
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<tr>
<td>NSV Project</td>
<td>Whole brain T2 relaxometry, a new tool for localisation of brain pathology. Cook, Jackson</td>
<td>160</td>
<td>2002</td>
<td>3</td>
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In Press 2006

• Labate A, Briellmann RS, Scheffer IE, Abbott DF, Jackson GD. Thalamic atrophy in childhood absence epilepsy. Epilepsia 2006;47:399-405.

Published 2006


Published 2005

Published 2005 continued


Published 2004

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In Press 2006

• Derry CP, Duncan J, Berkovic SF. Paroxysmal motor disorders of sleep: the clinical spectrum and differentiation from epilepsy. Epilepsia 2006 [in press, accepted 31/03/04].

• Grinton BE, Scheffer IE, Berkovic SF. Ethical, legal and social dimensions of epilepsy genetics. Epilepsia [in press, accepted 30 June 2006].


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• Berkovic SF, Petrou S. Febrile seizures: traffic slows in the heat. Trends in Molecular Medicine 2006 [Invited editorial commentary, epub ahead of print].


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Published 2004

• Mulley JC, Heron SE, Scheffer IE, Berkovic SF. Seizure phenotype and the neuronal nicotinic acetylcholine receptor a4 subunit. Epilepsia 2004;45:561.
• Mulley JC, Heron SE, Scheffer IE, Berkovic SF. Seizure phenotype and the neuronal nicotinic acetylcholine receptor a4 subunit. Epilepsia 2004;45:561.