

FROM THE PRESIDENT



Professor Philip Thompson

There have been considerable developments to report with respect to the strategic positioning of the Brain Foundation since the last edition.

I am pleased to report that the restructure implemented earlier this year is producing results and the financial position of the Brain Foundation has been strengthened. There have also been developments with respect to the strategic positioning of the Brain Foundation since the last edition.

Active consideration is now being given to the nature and structure of joint operations with the Australian Association of Neurologists and an affirmative policy is being launched to increase membership by neurologists, neurosurgeons and neuroscientists. Once in place, these moves will be a positive fillip for all our activities. Please phone the office on 1300 886 660 if you are

interested in finding out more about membership of the Brain Foundation or subscribing to Headache Australia. Please note that you do not need medical qualifications to be a member.

A further step in our restructuring will be to raise awareness of the national focus of our Scientific Committee. This year, 17 research projects, some from each state, were funded from a pool of applications that topped \$1 million dollars. While grants are awarded on an order of merit basis, the history of the awards shows representation from all states and major regional areas. As a result, we will continue to pursue jointly funded projects with other organisations that are aligned to a specific neurological condition wherever and whenever possible.

Our profile in the community has been building, helped by newspaper articles and by a National Headache Awareness Week at the end of September sponsored by Boots using its Nurofen Brand. 300,000 of the new pocket-sized headache brochures were distributed to Pharmacies around Australia. Information from a national survey was included in the new brochures and there were a number of prime-time radio interviews and live appearances on Channel 9 and Sky Channel.

The campaign succeeded in generating greater awareness of our websites with the usage statistics showing a jump of nearly ten times the usual rate of inquiry and there was a resultant increase in memberships. That burst of activity lifted website usage figures for the last twelve months to nearly two million hits.

Mission

The Brain Foundation was established in 1970 by members of the Australian Association of Neurologists and the Neurosurgical Society of Australasia to reduce the incidence and impact of brain, spinal cord and nervous system disorders, diseases and injuries through the provision of support, community education and research

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Please consider the Biannual Appeal sheet enclosed with this newsletter. Your past generosity has enabled us to continue our carer, community and research grants programmes and your continuing support is greatly appreciated. The directors, staff and I join in wishing you and your loved ones very best wishes for Christmas and a rewarding New Year.

SIGNIFICANT ADVANCES SINCE THE LAST ISSUE

Genetic link found between hormones and migraines

Director of the Genomics Research Centre Professor Lyn Griffiths and her team of researchers at Griffith University have identified a genetic link between hormones and migraines.

Professor Griffiths said it was the first time a hormone receptor gene had been strongly associated with migraine. "We always knew that hormones were involved, now we know there's a genetic basis," Professor Griffiths said.

"It seems so obvious now, but it's a whole new area of discovery.

"This is the initial finding, now we need to

look at the mutations to see how a change in the DNA sequence affects the gene. There is more than one gene involved in migraines and different variations affect people differently."

Professor Griffith said women were three times more likely than men to suffer from migraines and they often experienced their first migraine at puberty.

"Pregnancy and menopause can also play havoc with migraines, which shows further evidence that hormones such as oestrogen and progesterone are implicated," she said.

"There is also what we call a 'menstrual migraine' whereby migraines become more prevalent during menstruation."



Professor Lyn Griffiths



While an effective treatment for the condition has not yet been identified, an awareness of the genetic link in hormones could help migraine management, particularly during hormonal changes.

She said Hormone Replacement Therapy and the Pill in some cases could worsen migraines, while in other cases lessen the burden.

"If women find their migraines worsen after going on the Pill, they may want to rethink their birth control options, because it's more than likely not psychosomatic."

Migraine facts

- Migraines affect the nervous system of the body, causing nausea, vomiting and debilitating headaches
- As many of 12 per cent of Australians suffer from migraine
- About 90 per cent of migraine sufferers turn to painkillers to ease their pain, sometimes in excessive amounts
- At present, the accurate diagnosis of migraine is difficult and current drug treatments only seem to be effective in some patients
- Migraines tend to worsen in the 20s, but begin to ease in the 30s and 40s before almost dropping off completely in the 50s
- With 10 years of migraine research behind them, Professor Griffiths and her team at the Genomics Research Centre are the world leaders in the field.

The Genomics Research Centre is always seeking volunteer migraine sufferers to provide blood samples at its Southport clinic (opposite the Gold Coast Hospital). Please contact Sharon Quinlan on 07 5509 7300 to find out how you can help the centre and its quest to find a cure for migraines.

Special Book Offer

A limited number of the latest edition of Professor Jim Lance's book about headache and migraine are available at a special price to readers of Brainwaves. The full title is:

"Migraine and Other Headaches. A practical guide to understanding, preventing and treating headaches."

In his review, Oliver Sacks, Professor of Neurology, Albert Einstein College of Medicine, New York stated:

"What is delightful, and unexpected, is that Professor Lance is no remote specialist or scholar as one might suppose from his formidable reputation, but a down-to-earth physician. There is no other book on this subject that can compare with Migraine and Other Headaches."

If you would like one please use the Biannual Appeal form as an order form and fax it in with your card details or post the form in the reply paid envelope with your payment. The cost is just \$10 plus \$2 postage.

NATIONAL OFFICE



Gerald Edmunds

Aspire Workshop

In August, the Consumer Relations team of Pfizer conducted a two-day workshop for around 50 Health Consumer Organisation (HCO) representatives. Gerald Edmunds, the Brain foundation's National CEO presented a segment about cost effective ways for 'Not-for-profit' organizations to develop and maintain websites and minimise the cost of hosting.

Called ASPIRE: An Exchange of Best Practice Initiatives Across Health Consumer Organisations, the workshop was designed as a showcase of projects undertaken by Australian HCOs using grants awarded under the Pfizer Foundation's 'Strengthening Patient Organizations Around the World' scheme.

Awarded to Australian HCOs over a four-year period (which ended in 2003), these grants were aimed at providing opportunities to develop projects that would enhance the capacity of these organisations.

The resulting projects presented at the workshop were:

- **Patient, family, carer and community websites (Brain Foundation, presented by Gerald Edmunds)**
- A national call centre (The Australian Lung Foundation)
- Capacity building project (Chronic Illness Alliance of NSW)
- No breaks breakfast (Osteoporosis Australia)
- A national market research study and awareness campaign (Alzheimer's Australia VIC)
- Young adult education seminars (Diabetes Australia)
- Education program for schools and professions in contact with people with mental illness (Schizophrenia Fellowship of NSW)

- Partnerships in Health Promotion: An awareness campaign of the links between stress, anxiety and depression (Mental Health Foundation of Australia)
- Education program for Indigenous Australians (Epilepsy ACT)
- Organisational sustainability and diversification strategy (Palliative Care Australia)
- Skills training program for health professionals (The Cancer Council)

A Steering Committee of nine of the grant recipient organisations worked with Pfizer Australia's Consumer Relations team to develop the format, agenda and invitation list for the event.

The workshop also provided an opportunity for networking and the exchange of ideas and expertise in the Health Consumer environment.

NATIONAL HEADACHE SURVEY

A national survey about headaches was conducted in the lead up to the National Headache Awareness Week. The initiative, launched last September, was sponsored by Boots Healthcare under their brand Neurofen and communications with the community were managed by the International Public Relations firm, Edelman.

The results were quite alarming, showing that headache is the most commonly suffered pain in Australia, with 82% having experienced a headache severe enough for them to have sought at least non-prescription pain treatment in the last 12 months! Despite this, there is a general lack of public and professional awareness of headache and its impact on individual sufferers and society.

The survey also found that that only 22% of Australians consider headache to be a major health condition and seek medical advice and treatment. That is why the Brain Foundation, through Headache Australia, will continue to raise awareness about the importance of seeking the right advice and treatment for headaches, especially if there is a sudden and unexplainable onset of severe headaches that could be a warning of something very serious.

During the last Headache Awareness Week, Boots arranged the distribution of 300,000 of a new headache brochure to all Pharmacies in Australia. The brochure contains a 'tick' test of five questions. If one or more of the statements is true for the person taking the test, then it indicates that they should be seeking medical advice for their headache.

Some other facts to emerge from the survey projected to national level were:



- 78% of Australians have suffered from headache;
- 1 in 20 Australians say that they get a headache everyday or most days;
- More than 1 in 10 Australians get a headache at least once a week;
- Just over 80% of women suffer from headache compared to just over 70% for men;
- 83 % of married people reported ever having headaches while the figure for single people is 72%! (no comment from the married Editor);
- 43% of Australians reported that headache affects their ability to work effectively either often or occasionally;
- 12% of Australians reported that their attendance at work or TAFE College / University is affected by headache either often or occasionally.

Surveys like this are very valuable as they reinforce that there is much yet to be achieved in raising awareness about the seriousness of headache. There is also a need for an employer awareness campaign so that the reasons why the World Health Organization has classified Headache as a disability are known and understood. There are clearly many implications for the workplace. The Brain Foundation is grateful to Boots Healthcare for underwriting the survey. The survey data was promulgated nationally during the National Headache Awareness Week described by the President and achieved very large audiences on radio and television as well wide readership in the press. Planning is now underway for a national programme for Brain Awareness Week next March.

New South Wales

A number of articles have been prepared for newspapers and journals. The most striking result was for an article on Migraine in the Health Supplement of the Sydney Morning Herald written by Professor Allesandro Zagami. Such a large number of readers were attracted to our website that the inquiry rate was five times normal.

There is growing interest from people in regional areas wanting to establish neurological support groups. Albury is in the early stages while Broken Hill has advanced to the stage where a visit is planned to formalise arrangements. At the time of writing, the Tamworth Golden Bowl was about to run a Christmas Market at the Tamworth Racecourse. The results will be in the next Brainwaves.

New CEO appointed in Victoria

Sharon Strugnell has just taken up the position of CEO Victoria for the Brain Foundation and she is kindly sharing her first impressions with us.

Five weeks has flown by since my appointment as CEO of Brain Foundation Victoria (BFV). It has been non-stop learning and knowledge building in the area of Neurological Disorders, Acquired Brain Injuries (ABI) and Headache and Migraine coupled with meeting key people and really getting to know the sector.

It has been important building a rapport with the board and staff to understand the direction and way forward for BFV and for staff there is an air of excitement and enthusiasm in the planning for our future within the national body.

Attendance at the final Carer's Education Programme and Lunches has been timely and has shown me just how exclusive this work is to BFV and has highlighted the need to do more for a carer looking after a loved one with an ABI or neurological condition.

My background is education and training and community development and I believe this programme is unique to BFV in its delivery and information provided. I believe very strongly that everyone has the basic right to all the information in a specific situation so that they may make informed decisions.

Having had extensive experience in fundraising, along with successfully gaining government support and funding as well as corporate sponsorship, I fully understand the conundrum of reliability on government and external partnerships to sustain a not-for-profit organisation.

Therefore, I look forward to meeting the varied players in the sector and am extremely keen to cultivate strategic partnerships and to strengthen beneficial alliances which will provide new opportunities for Brain Foundation Victoria, and not least a healthy relationship with the National office. While our main focus is upon carer seminars and programmes, our major research project for this year is to establish a Registrar position with the Howard Florey Institute to investigate movement disorder.

South Australia

Research Grants

Brain Foundation(SA) provides for grants in aid of research projects concerning the causes, diagnosis, prevention and treatment of diseases of the nervous system. This year there were 3 successful candidates approved by the Scientific Advisory Committee. A summary of their work follows.

Philip C. Burcham, BSc (Hons) PhD

MRACI CChem

Molecular Toxicology Research Group

Dept. Clinical & Experimental

Pharmacology, The University of Adelaide

"Aldehyde adduct-trapping agents as potential anti-Alzheimer's therapies"

The research project by Drs Phil Burcham and Ian Musgrave (both Senior Lecturers in the Department of Clinical & Experimental Pharmacology at the University of Adelaide) will explore a novel drug mechanism for blocking the death of nerve cells in the Alzheimer's brain. The project builds upon a considerable body of world wide data that shows a vital role for a process known as oxidative stress in Alzheimer brain degeneration. This process involves overproduction of reactive substances known as free radicals, which attack vital components within brain cells including DNA, protein and fatty acids. The latter are especially prone to free radical damage, and undergo rapid decomposition to form many toxic substances that further amplify damage to brain structures. This research project will explore the biochemical events underlying the toxicity of acrolein - the most toxic substance formed during the oxidation of fatty acids. Acrolein forms in increased amounts in the Alzheimer brain, which is a worrying feature of the disease since work in Dr Burcham's laboratory has found that acrolein is a highly efficient protein aggregating agent. Since formation of amyloid aggregates is a key feature of Alzheimer's disease, it could be that acrolein exacerbates this process. Dr Burcham and colleagues have recently identified a class of "cross-link blocker" drugs that prevent protein aggregation by acrolein, and this project will explore the value of these drugs at blocking the toxicity of aggregated amyloid molecules to cultured cells.

A/Professor James A Temlett;

"Organotypic Mesencephalic Dopamine (DA) cell cultures: Studies of cell death relevant to Parkinson's disease"

Parkinson's disease is a progressive neurodegeneration caused by DA cell death within the midbrain substantia nigra, affecting 2% of elderly Australians. Genetic predisposition to oxidative stress and abnormal protein handling in cells of the nigra compacta are associated with accumulation of toxic proteins, including α -synuclein. This research will examine the role of growth factors, along with oxidative stress mechanisms, relevant in cellular apoptosis in an in vitro cell culture method.

Organotypic mesencephalic dopamine(DA) cell cultures will be used to determine the effect of growth factors and selective neurotoxins, on dopamine cell survival and dopamine liberation in the presence of their natural target striatal neurons. Using this novel technique of DA cell growth, we hypothesise that growth factors will increase the yield in number of DA cells cultured and expression of dopamine over a fixed development period. We will count dopamine cells in each culture, correlating



weekly HPLC measured dopamine and other catecholamine expression.

Using a novel organotypic DA cell culture system we are able to delineate DA cell morphology, numbers and DA expression. We seek to prevent DA cellular apoptosis, inhibit oxidative stress and encourage DA cell growth with functional neurotransmitter release. Real time HPLC-DA assays may provide a means of testing DA cell viability without contaminating the cultures, or interfering with their growth. If practical this advance will enhance the possibility of DA cell transplantation directly relevant to the management of Parkinson's disease.

Robert Vink, PhD, Head, Department of Pathology, University of Adelaide
"Neuropeptide release inhibitors as a novel therapeutic intervention after brain injury".



The Hanson Institute Centre for Neurological Diseases has had a long-term interest in developing therapies to combat the development of neurologic impairments after traumatic brain injury. One factor that is recognised as being critical to outcome after traumatic brain injury is oedema, or brain swelling. Recent evidence from our laboratory has established that neurotransmitter chemicals known as neuropeptides are integrally involved in the development of brain oedema after traumatic brain injury, and that preventing their involvement in the brain injury process significantly reduces brain swelling and results in a profound improvement in neurological outcome. This series of studies will develop a pharmacotherapy that can be administered after traumatic brain injury and that will inhibit the release of neuropeptides and consequently attenuate brain swelling and improve neurological outcome.

Any success will potentially reduce the degree of neurological deficits that are caused by traumatic brain injury, as well as profoundly reducing the time of hospitalization of brain trauma patients.

Western Australia

Headache and Migraine WA Inc, formally known as the Migraine Support Group of WA, has recently become an incorporated group, thereby gaining it's new title. As the former title suggests, the role of the group is to offer support to sufferers of headache and migraine. The group is run completely by volunteers; we do not have medical knowledge.

All volunteers are either past or present headache or migraine sufferers or who know of others in this situation. We have an enquiry line which is checked daily and all calls are returned. For further details you are looking for support, please call (08) 9346-3350, extension 67541. Please feel free to leave a message and a contact number so we can return your call.

Lannab Sawers-Diggins'

A record number of grants were awarded in 2003 and a selection of the progress and concluding reports follow.

Cigarette smoking, genetic risk factors and the aetiology of Parkinson's disease: An examination of gene-environment interactions.

Chief Investigator GD Mellick, University of Queensland, School of Medicine, Princess Alexandra Hospital, Brisbane



Background. Parkinson's disease (PD) is a common neurodegenerative disease that affects between 0.2 and 0.4% of Australians. Sufferers experience a range of movement disabilities (tremor, rigidity and slowness) often accompanied by non-motor symptoms like depression, anxiety and panic attacks. The disease primarily results from the degeneration of certain brain cells called dopaminergic neurons, although the underlying triggers for this degeneration remain unclear. Current opinion contends that both environmental and genetic factors play a role, with complex interactions between genetic susceptibility and

environmental exposure responsible for initiating nigral degeneration (Le Couteur et al., 2002).

Cigarette smoking is one of very few confirmed risk-altering factors for PD, demonstrating an inverse association (Hernan et al., 2001). The reasons for this are poorly understood but suggest that either: (1) cigarette smoke contains neuroprotective chemicals; or (2) that an individual's genetic predisposition to avoid smoking may share similarities with predisposition for the development of PD. Considerable evidence argues that unidentified chemicals in cigarette smoke have direct or indirect neuroprotective properties. The efficacy of these chemicals depends on metabolic processes influenced by genetic make-up. Conversely, cigarette smoke contains a multitude of toxic molecules, many of which have the potential to enhance free-radical production promoting neurodegeneration. Genetic predilections which enhance the amount of these chemicals in the brain may actually increase an individuals risk for neurodegenerative disease. Therefore, genetic factors influencing the metabolism of cigarette smoke may modulate this apparently protective effect with respect to PD. Our project specifically examines the interactions between genetic risk factors, smoking and the risk for PD.

Our project is using an epidemiological approach, called case-only design to study these gene-smoking interactions. The approach, which is novel in PD research, searches for genetic factors over-represented in smoking-exposed or non-exposed cases. This can identify interactive effects with increased statistical power and fewer potential sources of bias compared to conventional case-control approaches. The case-only approach is only valid if the genetic trait does not directly influence smoking generally, something which can be tested in subjects who do not have PD. However, identifying genetic factors that directly influence smoking exposure is also extremely interesting and was a secondary aim of our project. If such a dependency is observed, the case-only approach makes way for the more conventional case-control analysis.

Progress. We recruited 400 neurologist-diagnosed PD cases from Neurology clinics in Queensland and collected extensive data about their smoking history using a structured questionnaire. In addition 400 healthy aged subjects were also recruited and interviewed. Blood samples were taken enabling DNA collection from each study subject.

We then identified genes which code for proteins suspected to play a role in either the



metabolisms of cigarette smoke, the production of free radicals or the metabolism of toxins (good candidates for gene-smoking interactions in the aetiology of PD). Some of these genes had already been studied as candidate risk factors for the disease. So far we have investigated polymorphisms (commonly occurring genetic forms) of six genes that code for various isoforms of glutathione-S-transferase (GST). We showed that none of these genetic traits influenced smoking status in our unaffected subjects (so case-only analysis was valid).

However, when PD cases were studied, we revealed a potential interactive effect between smoking and one particular version of the GSTP1 gene (called the 114Val variant). People who carried this variant and who smoked were more likely to develop PD. The effect increased with increasing cigarette smoking dose. This is particularly interesting given that smoking itself is less common in PD cases (43% had ever smoked compared with 56% in unaffected subjects of similar age and gender). Furthermore, in non-smokers, we found that people carrying 114Val were also less likely to be PD cases. This suggests that in combination these two risk factors may render individuals more susceptible to PD. This data has now been reviewed and is provisionally accepted into the journal *Neuroscience Letters* (Deng et al., 2004).

Our work is currently investigating a second series of candidate gene variants in the cytochrome P450 family. Initial analyses have shown that some of these variants alter smoking status in unaffected subjects. Interestingly, some may also influence other environmental exposures (such as exposure to herbicides and pesticides). This also has important implications for our PD research.

As part of the current project, we were able to replicate very interesting research suggesting that CYP2D6 "poor metabolisers" are at significantly increased risk of developing PD if they are also exposed to herbicides and pesticides (Deng et al., 2004). For many years, there have been conflicting data about the effect of CYP2D6 status on PD risk. We found that "poor metabolisers" who were not exposed to toxins were not at risk for PD. Discrepancies in past studies may be explained by addressing gene-environment interactions, which were not previously considered. This work is described in our article recently accepted for publication in the journal *Annals of Neurology* (Deng et al., 2004). We are currently exploring the way smoking status fits in to the CYP2D6-PD story.

We thank the Brain Foundation for their support of this important work.

References:

1. Deng Y, Newman B, Dunne M P, Silburn P A, Mellick G D (2004) *Case-only study of interactions between genetic polymorphisms of GSTM1, P1, T1 and Z1 and smoking in Parkinson's disease. Neuroscience Letters Provisional Acceptance (May 4): MS#NSL-04-352*
2. Deng Y, Newman B, Dunne M P, Silburn P A, Mellick G D (2004) *Further evidence that interactions between CYP2D6 and pesticide exposure increase risk for Parkinson's disease. Ann Neurol IN PRESS: MS#20143*
3. Hernan MA, Zhang S M, Rueda-deCastro A M, Colditz G A, Speizer F E, Ascherio A (2001) *Cigarette smoking and the incidence of Parkinson's disease in two prospective studies. Ann Neurol 50(6): 780-6.*
4. Le Couteur D G, Muller M, Yang M C, Mellick G D, McLean A J (2002) *Age-environment and gene-environment interactions in the pathogenesis of Parkinson's disease. Rev Environ Health 17(1): 51-64.*

Brain Foundation Research Grant - Interim Progress Report

Project: Cortical Neuroprosthesis to Restore Visual Perception to Blind Patients.

Investigators: Professor Minas T. Coroneo¹, Professor John W. Morley², Dr Vivek Chowdhury¹.

¹ Department of Ophthalmology, Prince of Wales Hospital. ² School of Medical Sciences, UNSW.



Dr Vivek Chowdhury, Professor Minas T. Coroneo, Professor John W. Morley.

Background: The aim of this research project is to develop a medical device to restore basic visual sensations to patients who suffer from end-stage blindness and currently have no light perception. This device, a "visual prosthesis" or "bionic eye", will hopefully help affected patients with simple mobility tasks, and act as a sensory aid for the rehabilitation of blind patients. This project is at the forefront of neuroprosthetic research and is still in its infancy. However research in this area has been greatly influenced by the success of the cochlear implant in restoring hearing to deaf patients.

The device consists of an array of multiple electrodes which are placed over the "occipital lobe" of the brain – this is the area of the brain which processes visual sensations. Electrical stimulation of this part

of the brain in blind patients evokes the perception of simple visual sensations referred to as "phosphenes", which are usually described as small spots of light in the patient's visual field. By correlating these electrically induced phosphene sensations with images of the environment obtained by a digital camera worn by the patient, they will obtain a very simple visual appreciation of the structure of their environment.

Progress/Outlook: We have developed an in-vivo animal model to investigate visual cortex stimulation in the cat, and have used this model to assess electrode arrays and stimulation parameters for a cortical neuroprosthesis. We have performed a very successful series of experiments, the results of which have been communicated in the following paper and abstract publications. We have also been awarded an NH&MRC Development Grant to continue our research in 2004.

Papers: 1. Chowdhury V, Morley JM, Coroneo MT. An in-vivo paradigm for the evaluation of stimulating electrodes for use with a visual prosthesis. *A NZ Journal of Surgery* 2004;74(5):372-378.

2. Chowdhury V, Morley JM, Coroneo MT. Surface Stimulation of the Brain with a Prototype Array for a Visual Cortex Prosthesis. *Journal of Clinical Neuroscience*. 2004;(In Press).

Abstracts: 1. Chowdhury V, Morley J, Coroneo MT. Electrical stimulation of the visual cortex in the cat with a prototype visual prosthesis for blind patients. *Proceedings of the Surgical Research Society of Australasia Annual Scientific Meeting*. 2003.

2. Chowdhury V, Morley JW, Coroneo MT. Parameters for electrical stimulation of the retina and cerebral cortex in an in-vivo cat model to evaluate a bionic eye prosthesis. *Proceedings of the Royal Australian and New Zealand College of Ophthalmologists 35th Annual Scientific Congress*. 2003.

In 2004 we will be continuing our animal experiments in order to further define the electrode and stimulus characteristics which would be most suitable for electrical stimulation of the visual cortex. We will also be preparing for a potential clinical trial of a visual cortex prosthesis in a blind patient. Progress to clinical studies of this device will depend on the demonstration of the safety and feasibility of the device in animal models.

Brain Foundation Research Grant in 2003

Parkinson's Disease Research Grant. Progress Report: 19th May, 2004

Dr Wayne Reid, Dept of Neuropathology, POWMRI.



Neuropsychological changes in Parkinson's disease (PD): A longitudinal study.

Co-Investigators:

Prof. Glenda Halliday, Prince of Wales Medical Research Institute; Dr Mariese Hely, Department of Neurology Westmead Hospital; Prof. John Morris, Department of Neurology Westmead Hospital

Background: Much has been written on the subject of dementia and neurocognitive impairment in idiopathic Parkinson's disease (PD) over the last fifty years. Despite the research effort, opinion about dementia and cognitive dysfunction in PD remain subjects of controversy. Cross-sectional studies have identified two factors associated with cognitive status in PD; age of onset of disease and disease duration. In particular, age of PD onset is an important predictor of early cognitive impairment in PD, with increased prevalence of dementia in patients with an older age of onset. In younger PD patients, dementia is related to a longer duration of disease. However there are few prospective longitudinal studies that have examined the changes in neuropsychological functioning in the same cohort of patients from the early untreated stages of the disease, to death and autopsy confirmation of disease.

Through the Brain Foundation the present study has been able to continue a longitudinal study of de novo cases of PD in Sydney examining the changes in neuropsychological functioning and dementia in this PD population over 18 to 20 years. This provides the most comprehensive longitudinal study of cognition in PD to date. In addition we have obtained tissue from those patients consenting to autopsy over this time and have been able to combine the prospective clinical profiles with neuropathological changes, providing some insight into the varying clinical features of different neurodegenerative disorders associated with PD.

Progress: Over the last few months the longitudinal data base has been developed to include the 15 and 20 year follow-up data. Analyses on the outcome of the 15 year follow-up study has been done and a paper is in the final draft.

This work is to be presented at the International Movement Disorders Conference in Rome in June and Dr Reid will be giving a lecture and having meetings in Stavanger, Norway with Dr Dag Aarsland and his group to discuss the setting up of a large collaborative research project on dementia in Parkinson's disease.

Preliminary results:

- Over a 15 year period the greatest changes in neuropsychological functioning in PD occurs in Reaction Time, Executive

Function, Vocabulary, Verbal Fluency, & Memory that are consistent with disruption of subcortical, frontal and medial temporal lobe systems.

- Patients with disease onset before 50 years do not dement over 15 years whereas for those with disease onset between 50 and 59 years the prevalence increases from 7% at baseline to 80% at 15 years, for onset between 60-69 the prevalence increases from 14% to 88% and 70-70 year onset from 45% to 100% over the same time period.
- Baseline predictor variables for dementia were poor scores on the Ravens Progressive Matrices Test Verbal Fluency (FAS), Animal Category Fluency, error score on the Benton Visual Retention Test, Choice Reaction Time and lower education.
- The death rate in PD significantly increase after 3 years compared with the general Australian population and is significantly greater in PD. PD with dementia > non-dementia.
- Clinicopathological correlations suggest a number of coexistent pathologies are likely to be responsible for the dementia in PD and that the greatest impact of these pathologies, for most typical PD patients is in the later stages of the disease.

Imaging the Ischaemic Penumbra with Perfusion CT

Chief Investigator:

Dr MW Parsons, B Med, Ph D, FRACP. Department of Neurology, John Hunter Hospital. Co-investigator: Dr C Levi, Department of Neurology, John Hunter Hospital

Background: Extension of the therapeutic window for stroke thrombolysis beyond the currently proven 3 hour window could substantially increase the number of patients able to receive thrombolysis. However, for this to occur, it is likely better selection criteria based on cerebral pathophysiology (the 'tissue clock'), rather than a rigid time clock are necessary. In particular, improved imaging techniques are required to visualise the ischaemic penumbra (brain tissue with reduced blood flow that is still viable), as many patients still have such salvageable tissue well beyond 3 hours. Diffusion and perfusion MRI can identify acute stroke patients with an ischaemic penumbra. However, hyperacute stroke MRI will always have its critics. Valid criticisms include its cost, limited availability, and the increased time of scanning compared to CT.

Newer generation CT scanners (helical, multi-slice) are capable of evaluating brain

perfusion, allowing accurate quantitation of cerebral blood flow (CBF) and volume (CBV). In the next few years, most stroke centres should be able to complete this form of imaging within minutes of the patient presenting to the emergency department. Perfusion CT is well tolerated and not time-consuming, and can be integrated into the cerebral survey undergone by all stroke patients.

This project aims to validate the use of perfusion CT in imaging the ischaemic penumbra with delayed MR to measure outcome infarct size. Can perfusion CT predict which brain tissue will be salvaged with reperfusion, and die without it?

Progress: To date, 20 patients have been studied. Full data analysis has not yet been undertaken but some preliminary results have been presented at the recent Australian Association of Neurologists Annual Scientific Meeting. The abstract is below. Patient recruitment is ongoing. With this John Hunter pilot data, we hope to obtain funding for a multi-centre Australian trial of 100 patients to further validate this new CT technique. Ultimately, if this unique study validates CTP imaging of the ischaemic penumbra this would have a major impact on the management of acute stroke worldwide, and would finally enable translation of an exciting scientific concept into routine clinical practice. It is anticipated that CTP would be widely used to improve patient selection for stroke thrombolysis, particularly to extend the time window so that a greater number of patients can be safely offered this therapy.

CT perfusion source images markedly improve the appreciation of early ischaemic change

Elizabeth Pepper, Mark Parsons, Christopher Levi.

Department of Neurology John Hunter Hospital. Newcastle, Australia.

Background: If stroke thrombolysis is going to become a widely used therapy, doctors in the emergency department (ED) will need to become more proficient in the interpretation of early ischaemic change on CT, but these changes are often very subtle on non-contrast CT (NCCT). CT perfusion imaging relies on the rapid speed of modern helical scanners to trace the passage of a bolus of intravenous contrast. Colour maps of cerebral perfusion have great potential, but additional training in image post-processing is needed to generate these maps. However, contrast-enhanced grayscale CTP source images (CTPSI) are automatically presented on the CT console.

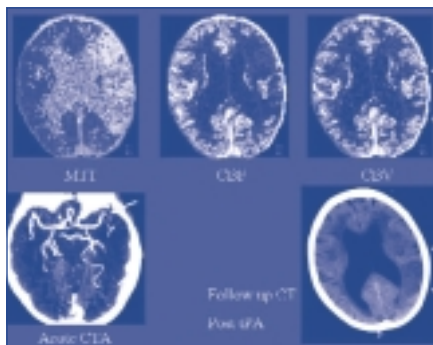
Methods: We tested the accuracy of three ED physicians and three medical registrars



in assessing presence and extent of early ischaemic change on NCCT and CTP source images. Fifteen acute stroke patients' CT scans were presented. Two stroke neurologists' assessments of the scans were considered the gold standard.

Results: On NCCT, sensitivity for any ischaemic change was 53%, specificity 42%, and agreement with gold standard very poor ($\kappa=0.18$). On CTPSI, for any ischaemic change, sensitivity (93%) and specificity (83%) improved, with markedly better agreement with the gold standard ($\kappa=0.85$). On NCCT, sensitivity for $>1/3$ MCA ischaemic change was 41%, specificity 90%, and agreement with gold standard again poor ($\kappa=0.22$). On CTPSI, sensitivity for $>1/3$ MCA ischaemic change again improved to 94%, with specificity 83%, and excellent agreement ($\kappa=0.77$). The proportion of correct decisions for any ischaemic change was significantly better ($\chi^2=28.5$, $p<0.001$) on CTPSI (83/90) than NCCT (52/90). Importantly, the proportion of correct decisions for $>1/3$ MCA ischaemic change was also significantly better ($\chi^2=17.3$, $p<0.001$) on CTPSI (61/66) than NCCT (17/30).

Conclusions: CTP source images substantially improve the diagnostic accuracy of identification of early ischaemic change in stroke.



Example of perfusion CT from recent patient at John Hunter Hospital below. The patient was imaged at 2 hours with a large left middle cerebral artery (MCA) infarct. CTP shows a large cerebral blood flow (CBF) and mean contrast transit time (MTT) lesion with smaller cerebral blood volume lesion (CBV) lesion. This is consistent with the CTP defined 'tissue at risk' hypothesis. CT angiography shows distal MCA stem occlusion (arrow). Patient was given open label t-PA, and ultrasound demonstrated recanalisation in the MCA during t-PA infusion, with improvement in National Institutes of Health Stroke Scale score (NIHSS) from 21 at baseline to 13 post t-PA. Follow-up CT shows that the final infarct is very similar in size to the acute CBV lesion (arrows).

Analogues of MDMA ('ecstasy') as potential therapeutic agents for the treatment of Parkinson's disease.

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Collaborators: Dr Jonathan Brotchie, Dr Tom Johnston, University Health Network, Toronto, Canada.



Dr Matthew Piggott and Honours Student Ben Van Doorn

Background: Levodopa is the mainstay of treatment for Parkinson's disease (PD) and is extremely effective in the short term. Unfortunately, however, long term use leads to reduced and fluctuating efficacy and is accompanied by the manifestation of involuntary movements (levodopa induced dyskinesia, LID) which often become so disabling as to negate the benefits of levodopa therapy.

A few years ago, a young Parkinson's patient with severe LID made a serendipitous discovery when taking the illicit drug 'ecstasy'. He found that 'ecstasy' markedly extended the duration of action of levodopa (on-time) and dramatically reduced the dyskinesia which usually accompanied its use. A similar result has since been observed in a PD-LID primate model.

'Ecstasy' is not a valid (therapeutic) drug candidate because it is neurotoxic and psychoactive. However, if these side effects can be dissociated from the ability to extend on-time and alleviate dyskinesia, a novel adjunctive therapy for the treatment of PD might be realised.

Adverse side-effects are a common impediment to drug discovery. Medicinal chemists seek to overcome this problem by modifying the chemical structure of their drug lead. In this case, the lead compound is methylenedioxyamphetamine (MDMA), the chemical synonym for 'ecstasy'. Our research involves synthesising a series of analogues which vary slightly in structure to that of MDMA. The analogues are then tested in a rat model that has previously been used to identify drugs with therapeutic potential for PD, by our collaborators.

Progress-Outlook: So far we have identified several compounds which seem to enhance the effects of levodopa (increase movement), one which appears to extend on-time and another that reduces movements which are analogous to dyskinesia in human sufferers. The results are very preliminary but they have been promising enough to elevate some of the compounds to the next level of testing, in a primate model which more closely mimics the human condition. We are currently working to extend the series of MDMA analogues and to further modify those that have already shown promising activity.

Our results have been presented at the Movement Disorders meeting (Rome, June), the Royal Australian Chemical Institute Organic Chemistry Conference (Cairns, July) and will be presented at the meeting of the Society for Neuroscience (San Diego, Oct-Nov). Publication of the work is also in preparation.

Thanks go to the Honours students who have worked on this project, to our collaborators for their enthusiastic contributions and of course to the Brain Foundation for making this work possible.

Brain organisation in epilepsy patients with benign developmental tumours.

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In most healthy people the left hemisphere is in charge of the language function. However, some persons use the right or both hemispheres for language. This is called atypical language lateralization. Atypical language lateralisation is more frequent in patients with early brain lesions, particularly when affecting the left hemisphere. It is generally thought that the language system can shift to the unaffected contralateral hemisphere. Benign developmental tumors, such as dysembryoblastic neuroepithelial tumour (DNET) and ganglioglioma (GG) are an important cause of refractory epilepsy. In our study, we assessed language lateralisation in patients with DNET or GG in the temporal lobe, and expected a higher frequency of atypical lateralisation than found in healthy people.

We recruited 10 consecutive epilepsy patients with developmental tumors. The diagnosis was made based on magnetic resonance imaging (MRI) and tissue histology. We assessed language lateralisation with functional MR imaging at a 3-tesla scanner. We continuously acquired images, whilst the subjects performed a language task inside the scanner. The subjects read nouns projected on a screen



(such as 'frog'), and had to silently generate a corresponding verb (such as 'jump'). Afterwards, we analysed the images to obtain language maps (figure), and calculated the number of activated image-points (voxels) in the right and left hemisphere. The results were expressed as a laterality-index, indicating the degree of left or right-hemispheric lateralisation.

Atypical language was found in three of the 10 subjects, and was more frequently present than in healthy controls. However, the clinical and tumor characteristics of the subjects with atypical language were not different from the patients with typical language. In particular there was no relationship with the side of the tumor, or the age at the beginning of the seizures.

These results confirm that the frequency atypical language lateralisation is increased in patients with refractory epilepsy. However, atypical language is not found in all subjects, the majority of the patients show typical, left-hemispheric dominance. This indicates that a benign developmental tumour in the temporal lobe does not generally induce atypical language lateralization. These preliminary findings are interesting, we now plan to increase the number of subjects included in this project, and further analyse additional scans performed in these 10 subjects. We are grateful for the support of the Brain Foundation for this project.

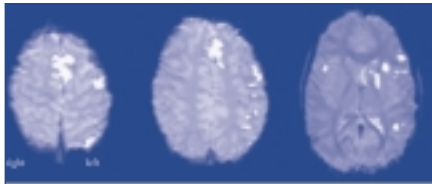


Figure shows the language activation maps in a patient with a left temporal DNET. Representative axial slices were chosen. Activation is displayed in warm colours, overlaid onto the EPI images. Note that there is predominantly left hemispheric activation, in typical language areas.

There are still a number of reports yet to be published from the record number funded in 2003 and there were a total of 17 fully or part funded projects awarded in 2004. The president and directors are grateful to all who take the trouble to prepare and submit applications and it is never easy for the Scientific Committee to set priorities for funding. However, the Brain Foundation does fund about the same proportion of applications received as does the National Health and Medical Research Council and it is hoped that there will be a larger amount to disburse next year. In fact, the chairman of the Scientific Committee, Professor Michael Halmagyi remarked that Australia offers the world very cost effective medical research

because of government funded institutions and the international status of research projects.

Biannual Appeal

The president and directors are very grateful for the very generous support given to our June Appeal that raised thousands of dollars for our programmes. It is their hope that every Brainwaves reader will make a donation, of whatever amount that they can, so that the Brain Foundation can continue and extend its carer, community education and research programmes. It is particularly helpful if you would kindly consider joining either the Brain Foundation or Headache Australia as the more members that we have, the stronger our case for corporate and government funding. There are some more details below and there is a form for your receipt details enclosed with a pre-paid return envelope, thank you.

Major Sponsors

The Brain Foundation is grateful to everyone who is generous enough to donate and space would not permit us to individually recognise everyone who has contributed. However, we would like to make special mention of those who have made large donations. Some who have made large donations, prefer to remain anonymous, those who are listed hope that will encourage others to join them as major donors. They are:

Rochford International; Sir Ron Brierly; Lady Sonia McMahon; JB Were Foundation; Mr & Mrs J P & D P English; Alison Hayward; Fiona Brownlee; Pamela Thomas; David Burns; Marilyn Jessop; Dr Francis Hooper.

Membership

Please note that membership of the Brain Foundation is open to all Brainwaves readers. For those of you who suffer migraines or severe headache, membership of Headache Australia will put you in touch with others through the forums where discussion about the effects of new and alternative treatments occurs. You can arrange payment of your first annual fee on the enclosed Biannual appeal form. For more information call 1300 886 660.

Up To Date Records

If you still have the envelope in which Brainwaves was delivered, you will see that at the top there is a code that starts with BW0402 / XXXX where XXXX is your number in our records. Please let us know if there are any changes on the enclosed Biannual Appeal form and add your E – address if you would like to receive notices and Brainwaves by E – mail.

That is a good time to **consider making a donation**. In particular, a regular monthly amount is less drain on your funds and would probably give us a larger donation over a year. Our database will provide records for tax purposes as total amounts over \$2 are deductible.

In Memoriam

The President and directors pass their condolences and gratefully acknowledge gifts in memory of the following:

Fernando Martinez; Vera Lena Kennon; Cameron Urquhart; Warren Joseph Heapy; John Perdikaris; K Drinam; Pam East; Annie MacCallum; Sharon Lee Kennedy; Giovanna Virga; Kleanthis (Clem) Tsakalides; Steve Simic.

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