BRAINwaves

The Newsletter of the Brain Foundation incorporating the Migraine Newsletter. **Winter 2005**

FROM THE PRESIDENT

Professor Philip Thompson

Thanks to all of you who kindly responded to our biannual appeal. Distribution in January meant that that we were after the Tsunami Appeals but that seems to have focussed everyone's generosity and our appeal was well supported. This time Brainwaves is being distributed so that your donations can be lodged for a tax deduction straight away.

I am happy to report that the Board plans to further develop its service to the community by identifying and developing plans to achieve the potential benefits that can be achieved by a unified national organization of the Brain Foundation. The Brain Foundation has an important part to play in providing information to the community about diseases and injuries to the nervous system, in parallel with the rapid increase in awareness about these diseases and brain function in general. Our reach is also to those who support and care for those afflicted, as well as continuing our drive to raise funds to enable new research.

It is with pleasure that I announce the Board is taking positive steps to demonstrate a national perspective on research by making new appointments to the scientific committee. I have accepted the role of Chairman of the restructured committee and I am glad to welcome Professor Elsdon Storey as a new member. Professor Storey is the Professor of Neurology at the Alfred Hospital Annex of Monash University. When the committee meets in July to determine the order of merit of the applications. For the first time, Parkinson's NSW has announced that they will pool their research funds to be added to the amounts that the Brain Foundation will allocate to Parkinson's research. As the success of this approach is proved, I anticipate that other organizations will see the merit of joining funds for transparent and unbiased support of the most meritorious projects in their area.

Traffic to the web site continues to increase as a result of our promotions and its content will be monitored and reviewed by strengthening our links with the Australian Association of Neurologists (AAN) that will lead to specialist sub-committees regularly updating the information in each of the sixty five diagnosed disorders now covered and adding others not already included. This is extremely valuable work as it is an accepted adjunct to the information provided by GPs and specialists. One example of a number of the reactions we receive is the very kind message from a person who wrote:

"Thank you for your wonderful web site. I have just been diagnosed with a brain tumour and have been advised to undergo surgery with follow-up radiotherapy and possible chemotherapy (depending on pathology results). Although I had already asked my neurosurgeon lots of questions, I found your website very helpful and informative. There is still much that is unknown, of course, and more will be revealed as my treatment progresses, but I feel now that I am more prepared for what is to come and better able to understand what is going to happen. I think also that your information has prepared me to interpret the news and plans the neurosurgeon may have for me along this journey to recovery."

We need your help to maintain this level of support and to continue our national research programme. I urge you to consider our appeal and be as generous as you can thinking about someone you know and care for who has a neurological problem or injury or who suffers severe headaches or migraine.

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

In this issue

Special Book Offer

A limited number of the latest edition (2000) 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.

ANNUAL RESEARCH AWARDS

The Annual Awards Presentation was held in late November at Darling Park, Darling Harbour courtesy of Bruce Morgan, a senior partner of PricewaterhouseCoopers. Most of the awardees were able to attend with a number coming from interstate. We were also pleased to be able to invite the new CEO of the Prince of Wales Medical Research Institute, Professor Peter Schofield and the presidents and CEOs of Alzheimer's and Parkinson's NSW. The scientific committee had a difficult time selecting the 17 successful projects from 48 applications totalling just over $1 million. The projects selected are described in the research section of our web site. The awards will be completed earlier this year because we have now regrouped after the first year of moving to fiscal from a calendar financial year.

Professor Michael Halmagyi was the MC and Professor Jim Lance AO CBE gave a very illuminating description of each project before they were formally awarded by Carol Ettleson, a former President of the Golden Bowl.

Professor Annie Bye from Sydney Children's Hospital was among those receiving an award for her proposal to: *Complete a longitudinal study that will provide guidelines regarding the ideal neurophysiological and cognitive assessment in BRE.*

Professor Annie Bye receiving her award.

A brochure of the award night presentations is available from the office, just call 1300 886 660

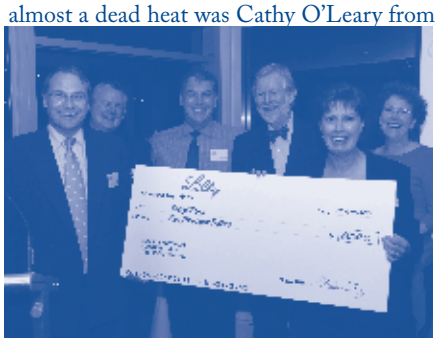
Brain Awareness Week: 14th - 20th March

There was a joint venture initiative for Brain Awareness Week in March this year. I combined with Professor George Paxinos, President of the Australian Neuroscience Society (ANS) and Bronwyn Dilley of the National Neuroscience Facility (NNF) to set up a new web site www.brainaware.org.au to allow participating organizations to list events that they were planning. The site is also intended to be a place where advances in neuroscience will be posted in future and it will be the focus for all Brain Awareness Week activities from next year on.

ACE Journalist Awards

The Eli Lilly – European School of Oncology ACE Awards (Awarding Cancer Enlightenment) for journalists were finalised in April. This year there was a new section for television journalists so the other judges and I had a broader job to do. The standards were very high and the TV winner, Sheryl Taylor from Channel 9 is pictured below with A/Prof Robyn Stuart-Harris who is the European School of Oncology Representative. In the background are Bernie Banton of the Asbestos Diseases Foundation of Australia, a well known person from his struggles and successes for those affected by asbestos, Wiliam Darbyshire from the Australian Lung Foundation in Brisbane, myself and Anne Jackson from the Australian Medical Writers' Association.

The winner of the press section in what was almost a dead heat was Cathy O'Leary from



Sheryl Taylor from Channel 9

Cathy O'Leary receiving her prize.

The Brain Foundation was represented at the ACE Journalist Awards by Board members Lady Sonia McMahon and Prof Nick Dorsch pictured chatting after the presentations.

Prof Nick Doesch, Lady Sonia McMahon and Gerald Edmunds

Finance

It is now just over a year since I came on board and I am happy to report that we have "trimmed the sails", reduced costs by over 50% and gained a modest increase in funding. However, we do rely upon the generosity of individuals such as you, our readers, who kindly donate and some who also make bequests and upon philanthropic trusts and corporations. The way we are now set up, any additional donations will go directly to community education programmes, broadening carer programmes and research.

My programme to attract workplace donations has been launched. There are immediate benefits to those who use this system to support a charity. First, the Tax Office allows their tax deduction to be refunded each pay period so a $10

Professor Lance addressing the audience at the Awards Presentation

donationonly reduces a person's pay by $7.00 if the person is paying 30% on their top dollars, $5.80 if the person is paying 42% on their top dollars, or by $5.30 if the person is on the top 47% rate. The other benefit is that amount such as $5.30 to $7.00 per pay does not affect the budget much while a once only, annual donation of $520 probably won't happen. Please consider if you would like to support us in this way.

NEW SOUTH WALES

The first Christmas Market run by the North West Golden Bowl at Tamworth Racecourse was very well attended and succeeded in raising over $5,000. Even though there had to be a great deal of forward planning, all the committee members were there on the day to ensure that everything went according to plan. The success has led the committee to commit to another market in November this year with stalls ranging from Flea Market to Up Market.

Some of the crowd are shown in the undercover area.

Good Health and Beauty Show: Darling Harbour, Friday the 17th to Sunday the 19th June

The Pharmacy Guild has kindly sponsored the Brain Foundation to a stall at the Good Health and Beauty Expo that will be held at Darling Harbour from the 17th to the 19th June this year. It is a significant gesture as the stalls are $5,000 for the small ones. This will give us an opportunity to meet as many of the visitors as possible to explain how we aim to help. I will be piloting some merchandise and if it proves useful to people I will make it more widely available. I will also be reaching out to headache and migraine sufferers to explain that by joining Headache Australia they will be helping us to help them. The more members that we have in Headache Australia, the more leverage we will have to raise funds for research

There is more about the Show on www.goodhealthandbeauty.com.au

Broken Hill

The Neurological Support Group at Broken Hill was started up by Jamie Mitchell earlier in 2004. He has been successful in gradually gaining support and was able to make a formal launch at a Fund Raising Dinner in November. The Brain Foundation is giving every possible support to this group. Jamie has lost two brothers to Motor Neurone Disease however, he can see that there are common needs for all affected by neurological problems and has aimed to be a forum and support for all. I was able to visit Broken Hill to meet the Federal and State Members and Scott Howe, the CEO of Outback Development to help put the case for resources to set up and furnish an office for the large number of people who will benefit from the Support Group in Broken Hill.

The picture below shows committee members from left Gordon Lanbine, the BF CEO, Federal Member, John Cobb, Holly Lines –Treasurer, and George and Wendy Diamentios at the Fundraising Dinner to launch the Group. The dinner raised over $3,000.

The Broken Hill Group now have a regular stall one day a week at the Hospital that allows them to disseminate material and organise meetings.

VICTORIA

From the CEO

It has been six months into my tenure but as new CEO of Brain Foundation Victoria (BFV) I feel quite at home. I was attracted to this organisation on many levels and am ready to tackle the challenges that come with the position of Chief Executive Officer.

One of the many attractions was the 'on the ground' work we do within the community, providing education, support and information on acquired brain injury (ABI) to people and their families.

Our service delivery, in particular to carers – the unrecognised people who, often not through choice, give up much of their lives to take care of a loved one struck down with some kind of brain disorder - has proved to be a valuable necessity delivered by the knowledgeable and experienced staff that make up the BFV team. Our carer services are unique in their focus on ABI and its life altering and permanent impact on the family.

Possibly some of the more recognisable faces to join our team are our Brain Foundation Victoria Ambassadors; performer Michael Cormick and triathlete Chris Legh. A BFV ambassador is a person who has been directly affected by acquired brain injury or headache & migraine and who would like to promote our mission. We would like to thank our ambassadors for their acknowledgment of our work and volunteering to lend their time and support to our cause.

In six months it has been a busy time but exciting too and you will read further on about our activities, everything from the programs we have delivered to our sponsorship of the BFV inaugural research fellow looking at movement disorders such as Parkinson's disease and much, much more in between.

New Staff Member

Penni Stodel is the newest staff member shown second from the left in the back row. She joined the Brain Foundation in December, 2004, as the ABI Slow to Recover (STR) Case Manager. Her role involves working with clients and their families, in conjunction with therapists and attendant care agencies to implement rehabilitation programs for those clients who are eligible for and accepted onto the Slow to Recover Program.

Staff of BFV photo, L-R Jacob, Penni, Greta, Rachael; seated, Sharon and Helene.

Penni said "One of the most exciting opportunities since I started as Case Manager has been the ability to apply for 'One Off' Funding through the Slow to Recover program for items which would not normally be funded. For example, I was able to get funding for a digital camera for a client who has difficulty with memory. The camera will be used throughout the day to take photos of different people and activities, and the photos to be used as a prompt to stimulate memory and encourage orientation to time and place. Funding was also obtained for a huge variety of goods and services from massage therapy for less mobile clients in order to provide am opportunity for positive touch and stimulation, to purchasing an exercise bike for home use to provide an accessible opportunity for strength and stamina training for more physically able clients. I look forward to more successes over the coming year with clients and their families but always recognise that there will be challenges."

Sufferers Gather for Headache and Migraine Seminar

Chronic Headache and Migraine is such a huge problem for many people and yet it is still a largely unaddressed area, despite the costs involved to government and workplaces. We held a seminar on how to use the GP and specialists effectively and talk about practical tips on pain management and complimentary therapies. Our speakers were Dr John O'Sullivan, a GP actively involved in training other GPs about Migraine; Dr John Heywood, a neurologist at the Migraine Clinic of St Vincent's; and Dr Victor Wilk, a musculoskeletal medicine practitioner at the Brighton Spinal & Sports Medicine Clinic.

Feedback for the Headache & Migraine Seminar was overwhelmingly positive. BFV had between 40 and 65 attendants, certainly enough to fill our seminar room! Attendees were certainly interested in a longer follow up, with emphasis placed on improving quality of life, community understanding, managing aura symptoms, complimentary therapies and diet.

Anyone interested in being contacted about future seminars or in setting up support/self-help groups for migraine, contact Rachael through email (admin@brainfoundation.org.au) or 03 9845 2950

Brain Awareness Week Colouring Competition - champs visit St Mary's Primary School

The inaugural colouring competition was held as part of the International Brain Awareness Week activities run by the Howard Florey Institute, Australia's largest neuroscience institute, during March. Brain Foundation Victoria sponsored the competition's prizes. About 400 students from seven metropolitan primary schools entered the competition, which involved them colouring-in a picture of a scientist pointing to a brain. (Howard Florey Institute).Students from three Catholic primary schools in the South-Eastern suburbs received prizes honouring their colouring-in skills.

Fellowship Presentation. Katya is shown with CEO, BFV Sharon, Professor Mal Horne and BFV President, Philip Thomas.

BFV Movement Disorder Research Fellowship

Melbourne's Howard Florey Institute and the Brain Foundation Victoria have combined forces to launch the inaugural Brain Foundation Victoria Fellow as Dr Katya Kotschet. BFV hosted a cocktail party on the 16th March at the Howard Florey Institute to launch the fellowship and welcome Dr Kotschet into the fold!

The Fellowship was created to encourage the growth of clinical care and research projects in movement disorders, and develop treatments that slow or halt the progression of these illnesses such as Parkinson's disease. Brain Foundation Victoria provided the financial base that gave confidence to the Howard Florey Institute and St Vincent's Hospital to support the Fellow position. Appreciation also to Ipsen, Novartis and Allergen for providing financial support. (Howard Florey Institute).

RESEARCH REPORTS

The role of dysferlin in muscular dystrophy

Dr Sandra Cooper, Westmead Children's Hospital

Many forms of muscular dystrophy are associated with a structural fragility of the muscle membrane, whereby membrane damage exceeds the ability of muscle to repair itself, resulting in the progressive degeneration of muscle fibres. This funding from the Brain foundation contributes to a new research initiative in our laboratory studying a new form of muscular dystrophy, caused by mutations in the gene dysferlin. Rather than having a structural role, dysferlin has recently been shown to play a role in repairing the small sites of membrane damage caused through normal physical activity. In dysferlin patients, the structure of the membrane is normal, but membrane repair is impaired.

Our project seeks to more clearly define the role of dysferlin in skeletal muscle, and to study other proteins that interact with dysferlin and/or contribute to the muscle repair pathway. There are many patients with muscular dystrophy, in whom the genetic cause is unknown. We believe that some of these patients may have defects in other proteins that are also involved in the muscle repair process.

We have a group of patients with dysferlin muscular dystrophy, and a group of forty patients who may be defective in other components of the membrane repair pathway. This Brain foundation funding has been used to generate a new dysferlin antibody for our studies, providing a powerful analytical tool. We will use muscle samples and muscle cell lines to firstly define more about the normal biology of dysferlin, and then use our patient samples to examine what happens to the muscle membrane repair process when there is a mutation in dysferlin.

Project Name: Role of Tau in Parkinson's Disease

Chief Investigator : Dr John BJ Kwok

Background :

A genetic locus that may be important in idiopathic Parkinson's Disease (PD) is the Microtubule Associated Protein Tau (MAPT) gene on chromosome 17q. We have shown that increased Tau protein levels are an important factor in the aetiology of idiopathic PD. This result has recently been published in the journal Annals of Neurology (Kwok JBJ et al, 2004, Annals Neurol; vol 55, p329-334).

Progress:

We predicted that other molecules that impinge in the activity of Tau may also be important genetic factors in idiopathic late-onset PD. Glycogen synthase kinase-3? (GSK-3?) is serine/threonine specific kinase that phosphorylates Tau, thus modifying its activity. We demonstrated that a genetic variant within GSK3B is significantly associated with an increased risk of Parkinson's disease in two ethnically diverse cohorts of patients, derived from Caucasians (Australian) and Chinese (Hong Kong) populations.

Outlook:

We plan to examine the role of GSK3B in additional cohorts of PD patients, as well as performing a series of molecular and biochemical studies to elucidate the underlying pathogenic mechanism. The knowledge that GSK3B may be involved in PD is particularly important as there are many therapeutic agents, such as Lithium, that acts on this molecule and may represent novel forms of treatment for the neurodegenerative disease.

Title Project: The role of the pre-supplementary motor area in age related gait slowing: a functional MRI study (a pilot study)

Chief Investigator:
Gerald Anthony (Tony) Broe
Senior Scientist, Prince of Wales Medical Research Institute, Barker Street, Randwick NSW 2031

Introduction:

Many neurological impairments, prevalent in the older population, have been attributed to the "normal" ageing process. Alternatively we regard common syndromes such as mild cognitive impairment and extrapyramidal gait slowing, as due to selective vulnerability of specific neuronal populations. We have recently shown that

gait slowing predicts dementia (Waite et al. 2001). We have previously shown a major loss (80%) of pre-SMA pyramidal neurons in Parkinson's disease. Planning of both motor and cognitive tasks, one of the key functions of the pre-SMA, is a process which is slowed in some older people. We hypothesised that the pre-SMA is involved in age related extrapyramidal gait slowing and in PD.

Methods:

The first stage of this study was to recruit healthy, non gait slowed young and older subjects, and subjects with Parkinson's disease (PD) with POWH Ethics Approval. After clinical and neuropsychological assessment, 10 subjects had a functional MRI scan at the Mayne Clinical Research Imaging Centre, Prince of Wales Medical Research Institute. The fMRI paradigm used involved the execution and imagination of a motor task. The motor task was the flexion and extension of either the right or left hand, or both hands. It was hypothesised that all the subjects would activate their primary motor cortex (M1) during the execution of the motor task. During the imagination of the motor task, it was hypothesised that the young and older non-gait slowed subjects would activate their pre-SMA, whereas the PD subjects would not.

Results:

As hypothesised, all the subjects activated their M1 during the execution of the motor task, and some activated the SMA proper. During the imagination of the motor task the young and older non-gait slowed subjects activated the pre-SMA as hypothesised; PD subjects did not activate their pre-SMA, as hypothesised; however the older normal subjects showed a decreased volume of fMRI activation (see Figure).

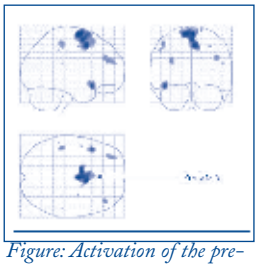


Figure: Activation of the pre-SMA in a young adult.

Discussion:

The pilot studies were consistent with our hypotheses, however an additional finding was a smaller volume of pre-SMA activation in older non-gait slowed subjects, who had minor extrapyramidal signs. We have tentatively attributed this pilot finding to the same neurodegenerative process in the pre-SMA, i.e. functional impairment of its pyramidal non-dopaminergic neurons, which has not yet progressed to the stage of gait slowing. The further progression of this study will include the recruitment of larger populations of each study group (n=20), including older gait slowed subjects. This will enable us to determine whether the pre-SMA is a brain region contributing to extrapyramidal gait slowing in older people who do not reach clinical criteria for a diagnosis of PD, as well as in subjects with PD.

Waite, L M, Broe, G A, Grayson, D A, Creasey, H 2001, 'Preclinical syndromes predict dementia: the Sydney older persons study', Journal of Neurology, Neurosurgery & Psychiatry, vol. 71, pp. 296-302.

Vitamin E analogs as inducers of apoptosis and anti-cancer agents.

Dr Jiri Nuezil, School of Health Sciences, Griffith University

Vitamin E (VE) analogs, epitomized by a-tocopheryl succinate (a-TOS), are potent inducers of apoptosis and anti-cancer agents. In this project, we tested their effect on the highly malignant N-type neuroblastoma (Nb) cells and their differentiated, neuron-like counterparts. Nb cells were highly susceptible to several VE analogs, while differentiated Nb cells were relatively resistant to a-TOS. The importance of caspase-9 rather than caspase-8, as judged by specific siRNAs studies, together with the loss of the inner mitochondrial potential suggest that a-TOS triggers apoptosis in Nb cells via the mitochondrial pathway. Cultured Nb cells were sensitized to a-TOS by pre-treatment with Bcl-2, Bcl-xL or Mcl-1 siRNAs, while the malignant cell line was more resistant to the vitamin E analog when Bax was knocked down. In contrast, over-expression of Bcl-2 in Nb cells rendered them more resistant to a-TOS-induced apoptosis. The resistance of differentiated Nb cells to a-TOS-mediated apoptosis occurred via two modes; first, by up-regulation of the anti-apoptotic Bcl-2 family proteins, and second by accumulation of decreased levels of reactive oxygen species when challenged with a-TOS. We conclude that a-TOS is highly selective in killing malignant brain cancer cells while relatively inert toward differentiated neuronal cells, and that vitamin E analogs may be novel therapeutics for the treatment of tumors such as neuroblastomas.

Swettenham E, Witting PK, Salvatore BA, Neuzil J (2005) a-Tocopheryl succinate selectively induces apoptosis in neuroblastoma cells: Potential therapy of malignancies of the nervous system? J Neurochem (in press).

Reader's Concern about anti-oxidant supplements impact on smokers

This is a departure from our professionally based research to note a concern that was expressed about the use of anti-oxidants for a positive effect on brains that we recommend as part of the Healthy Brain Programme. It seems that smokers face some additional health risks to the well-known and publicised ones that come from smoking. So, for their benefit I have included the following extract from the material that 'Sue' asked me to include.

"I'm aware of some clinical trials published in the 1990's that have returned some horrifying results on the effects of the anti-oxidant betacarotene (a vitamin A precursor) on smokers. These studies, the ATBC (1) and CARET (2) studies, found an increased lung cancer risk for those smokers taking beta-carotene supplements. In fact, the results of the ATBC study, carried out on 29,133 Finnish smokers, were so alarming that the study was stopped early. In short, the trial showed that male smokers who took the anti-oxidant had an 18% increased risk of contracting lung cancer and an 8% increased risk of death (3). The American Medical Association (AMA) then followed the progress of the participants after the trial had been wound up, and found that within 4 - 6 years of the trial finishing there was a a 7% higher mortality rate in those men who had taken the beta-carotene supplements. Thereafter, mortality rates were the same for placebo and supplement takers. (3) The results of this study were then backed up by the Beta-Carotene and Retinol Efficacy Trial (CARET) study that finished in 1996.

In 2003 the AMA finally concluded that "smokers should avoid beta-carotene supplementation". (4)

In the meantime, the American Heart Association has been having it's own say proclaiming in August 2004 that various studies have shown that popping vitamins has virtually no cardiovascular benefit. In fact, there is "little reason to advise that individuals take antioxidant supplements to reduce their risk of cardiovascular disease". (5)

Obviously there is a lot that is unknown in this area. In the meantime, everyone would be wise to tell their physicians and proactively research any supplement you're taking. After all, of what use is a healthy mind if you're dying of cancer?

"Sue"

Nicotine and Schizophrenia

Dr Richard Loiacono and Ms Nicola Ingram, Department of Pharmacology, Monash University

Schizophrenia is a debilitating disorder that affects about 1% of the population. Schizophrenic patients have a diminished capacity to filter out unimportant features of their environment; their attention is drawn capriciously to details a normal person would ignore. This preoccupation with details can lead to misperception of their environment and contributes to the delusional characteristics of their illness. There are some interesting relationships between schizophrenia and smoking; in schizophrenia there is a loss of specific receptors for nicotine as the disease progresses

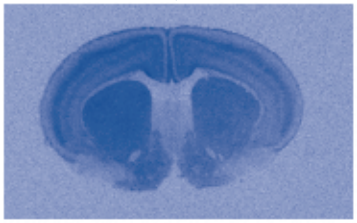
(Court et al., 1999) while other studies have shown a mutation in these receptors in patients suffering schizophrenia (Leonard et al., 2000). Interestingly schizophrenic patients show a high use of tobacco smoking (greater than 90% of all schizophrenics are heavy smokers); and it has been suggested that schizophrenic patients may be "self-medicating" with nicotine in order to counteract some of the behavioural problems associated with schizophrenia.

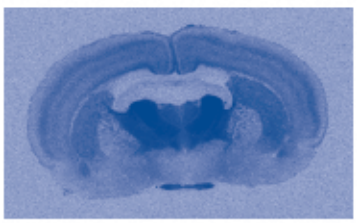
Using a behavioural test that examines sensory filtering and techniques that measure the population of receptors in the brain that respond to nicotine, we examined the role that nicotine, and hence smoking, may play in schizophrenia. Our main questions were, given the prevalent use of nicotine amongst schizophrenic patients, (i) does nicotine have any effects on some of the aberrant behaviours seen in schizophrenia? (ii) what happens when we combine nicotine with current antipsychotic drugs, as would be occurring in the clinical setting.

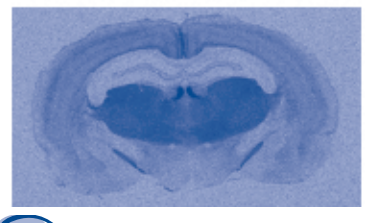
In collaboration with Dr M van den Buuse of the Mental Health Research Institute, Victoria, we found that nicotine does appear to have a mild beneficial effect in some of the behaviours that may be relevant to filtering and misperception that is common to schizophrenics1. More interestingly, this effect wanes and negatively impacts on the effects of some antipsychotic agents. We have also shown that long term administration of antipsychotic agents (and combinations of nicotine with various antipsychotic agents) induce long term changes in populations of receptors for nicotine in brain2.

1 Ingram I, Van Den Buuse M, Loiacono R (2004). Effect of nicotine and antipsychotic drugs on prepulse inhibition. Int J Neuropsychopharmacol, 7 Suppl 1 S266

2 Ingram I, Loiacono R (2005). Nicotine and antipsychotic drugs regulate nicotinic receptors.. Proc Aust Neurosci Soc, 16 126.







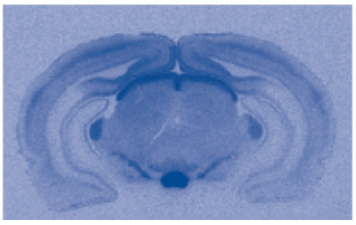


Fig. Distribution of 125I-epibatidine binding in consecutive coronal sections of untreated brain. Darker regions indicate areas with the greatest abundance of nicotinic receptors. 125I-epibatidine binding is used to mark out and measure levels of the _4_2 subtype of nicotinic receptor in specific regions of brain. Using this technique changes to this population of receptors in response to various drug treatments and combinations can be defined.

A population-based study of the relation between sub-clinical cerebovascular disease and brain function in older Tasmanians.

Dr Velandai Srikanth, University of Tasmania

There is great uncertainty surrounding the effect of subclinical cerebrovascular disease on brain function in older people. Our primary aim was to evaluate the effect of age-related brain changes on gait, balance and cognition in a population-based sample of older Tasmanians using high resolution MRI scans and sensitive measures of gait, balance and cognition. The funding received from the Brain Foundatuion was to assist in the commencement of this unique project and demonstrate feasibility. We were able to employ a research nurse and commence recruitment for this pilot study.

So far, the protocols have been developed and tested on an initial sample of 10 and a further 30 participants have now been recruited. Therefore, the seeding funds received from the Brain Foundation have been critical to the successful commencement of this large scale study, which is intended to answer several key questions regarding vascular brain dysfunction.

A Study of Cortical Activation by Sensory Stimulation using Functional Magnetic Resonance Imaging.

Professor James Colebatch, Prince of Wales Hospital and Medical Research Institute (with Professor Sgandevia and Dr D Wardman)

This project was designed to investigate the differences between a selective cutaneous and a selective muscle afferent stimulus using fMRI on a 3T machine. We made an fMRI-compatible stimulus setup and have recorded from eight normal volunteers. We have used the software package SPM2 for analysis and this has not been completed. We were able to establish that activations in motor and sensory areas of the brain could be seen in some single subjects. Within a given subject, repetition of the stimulus usually gave somewhat different results, possibly due to habituation. We are presently combining corresponding trials within and between subjects to determine whether this strengthens our activations. We expect to be able to show clear differences between the two forms of stimulation. A more powerful stimulus is required to be certain of activations within all individual subjects.

Variability in isoform expression patterns of tyrosine hydroxylase in Parkinson's disease

Investigators:: L. Lee and K. L. Double

The two aims of this current project are to compare expression of a polymorphism in intron 1 of the gene for tyrosine hydroxylase (TH), the rate limiting enzyme in dopamine production in persons with Parkinson's disease compared with controls and to determine if the expression of TH in the vulnerable pigmented cells in Parkinson's disease differs to that in controls. Preliminary analysis of the genetic data indicates that difference in TH genes does not affect susceptibility to Parkinson's disease but that a particular polymorphism of TH is associated with the age of onset of this disorder. Preliminary results using specific antibodies for each of the 4 different human isoforms of TH have demonstrated that TH isoforms 1 and 2 (present in all species) are present in lightly pigmented neurons while isoforms 3 and 4, the 2 isoforms specific to the human brain, are found only within the most densely pigmented neurons, suggesting that TH isoform expression may influence the degree of cellular pigmentation. The work on both aspects of this project is continuing.

A potential new test for diagnosing early dopamine cell loss: An initial screening analysis with risk factor assessment

Investigators: K.L. Double, G.M. Halliday, D. Rowe, R. Joffe, J. Blackie, H. Brodaty, P. Sachdev, D. Chan, W. Reid, A. Corbett, M. Hayes, D. Le Couteur, J. Morris, V. Fung, M. Hely, M. Jones and V. Gebski

The project aimed to assess the potential for a new blood test to diagnose Parkinson's disease in an objective manner. Over 200 subjects were recruited and assessed for this study. We found that the blood test response is significantly enhanced in patients with a clinical diagnosis of Parkinson's disease

compared with normal controls and patients with depression. These results, and those of a parallel project in Germany, enabled us to submit a patent for this technology and to attract research support from Roche Diagnostics in Germany. The data on the blood test are currently being prepared for publication in the scientific literature, while data on changes in the ability to smell as a possible test for Parkinson's disease also gathered during the project are now published. Based on the results of the project, Drs. Double and Rowe successfully applied for a NHMRC Development Grant 2004-2006 to further this work and further collaboration with industry is being sought. We are extremely grateful to the Australian Brain Foundation for their support of this project during its initial phase. This support has allowed us to demonstrate the potential of this test to the point where we are now attracting interest to develop this test from other sources.

Publications: Double, L.L., Rowe, D.B., Hayes, M., Chan, D.K.Y., Blackie, J., Corbett, A., Joffe, R. Fung, V.S., Morris, J., and Halliday, G.M. (2003) Identifying the pattern of olfactory deficits in Parkinson's disease using the Brief Smell Identification Test (B-SIT). Archives Neurol 60, 545-549.

Mechanisms of cell death and neuroprotection strategies in Parkinson's Disease

K. L. Double

The aims of the current project were to compare the functional effects of human and synthetic melanins in in vitro systems and to determine whether neuromelanin could act to protect dopaminergic cells, especially in a highly oxidative environment. The project was unable to be completed in 2000 due to insufficient funds and also as the student working on the project broke of his PhD candidature. The project was completed however during Dr. Double's visit to Germany in 2003. Experiments on neuronal and glial cell lines demonstrated that synthetic dopamine melanin (DAM), widely used as a model of human neuromelanin pigment, stimulated functional toxicity and resulted in cell death by apoptotic mechanisms. In contrast, the native neuromelanin pigment was not toxic to the cells. Further experiments in primary rat mesencephalic cultures confirmed these results, thus demonstrating that DAM is a poor model of human neuromelanin. Further, we demonstrated in the primary cultures that human neuromelanin, but not DAM, attenuated oxidative cell death. This is the first functional data to support the widely held hypothesis that neuromelanin plays a protective role in the cells which contain it.

Publication: Li, J., Scheller, C., Koutsilieri, E., Griffiths, F., Beart, P.M., Mercer, L.D., Halliday, G., Kettle, E., Rowe, D., Riederer, P., Gerlach, M., Rodriguez, M. and Double, K.L. Differential effects of human neuromelanin and synthetic dopamine melanin on neuronal and glial cells. J. Neurochem. (accepted Feb. 8th 2005).

A Study of Cortical Activation by Sensory Stimulation Using Functional Magnetic Resonance Imaging

James Colebatch, Prince of Wales Hospital and POW Medical Research Institute

(with Professor SC Gandevia and Dr. D. Wardman).

This project was designed to investigate the differences in cortical between a selective cutaneous and a selective muscle afferent stimulus using fMRI on a 3T machine. We made an fMRI-compatible stimulus setup and have recorded from 8 normal volunteers. We have used the software package SPM2 for analysis and this has not been completed. We were able to establish that activations in motor and sensory areas of the brain could be seen in some single subjects. Within a given subject, repetition of the stimulus usually gave somewhat different results, possibly due to habituation. We are presently combining corresponding trials within and between subjects to determine whether this strengthens our activations. We expect to be able to show clear differences between the two forms of stimulation. A more powerful stimulus is required to be certain of activations within all individual subjects.

James Colebatch,

Antibodies from patients with Parkinson's Disease to isolated human neuromelanin

D.B. Rowe and K. L. Double

This project was the initial study of Dr. Rowe and Dr. Double that demonstrated a peripheral humoral immune response to isolated human neuromelanin and synthetic melanin. It formed the basis of the work that led to the patenting of a blood test as a potential diagnostic tool in Parkinson's disease. The money also purchased an automatic microplate washer that is still in use in Dr. Double's laboratory in the Prince of Wales Medical Research Institute. The work was presented at the American Academy of Neurology in Philadelphia, USA, in 2001.

Publications: Rowe, D.B., Double, K.L., et al. A specific immune response in Parkinson's disease indicates central dopaminergic cell death. Neurology 2001; 56 (Supplement 3): A342 Australian Patent PCT/AU01/01271. K.L. Double, D.B. Rowe, M. Gerlach. P. Riederer, Detection of neurodegenerative disorders. Filing date: 13/9/2001. International Publication number: WO 02/31499 A1, Filing date: 9/10/2001.

Brain organization in epilepsy patients with benign developmental tumours

Angelo Labate, Regula Briellmann, Graeme Jackson

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 lateralisation. 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 tumours, such as dysembryoblastic neuroepithelial tumour (DNET) and ganglioglioma (GG) are an important cause of refractory epilepsy. In our study, we assessed language lateralization 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 tumours. 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 tumour characteristics of the subjects with atypical language were not different from the patients with typical language. In particular there was no relationship with the size of the tumour 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 lateralisation. 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.

Investigation of genetic variation of the parkin gene in Parkinson's disease

Investigator: Professor Garth Nicholson

Support from the Brain Foundation has been essential to supporting our ongoing research into the genetic causes of parkinsonian syndrome.

We have established that mutations in the known genes causing Parkinson's syndrome are extremely rare. We have tested over 100 Australian families with familiar Parkinson's disease and found only one family of Greek origin with an alpha synuclein mutation. We have tested a larger number of sporadic families for point mutations in the parkin gene and have found no mutations. However, recent reports from the European Parkinson's collaboration have shown deletions and duplications of the parkin gene may be more common. We wish to determine the frequency of these mutations as a cause for sporadic Parkinson's disease in 2001. One paper has been accepted for publication in Annals of Neurology and another paper is being submitted:

Alpha synuclein screening in familial and sporadic Parkinson's disease. 1 Ala 53Thr mutation in a family of Greek origin and one single nucleotide polymorphism.

Garth Nicholson, Gulietta Pupo, Julie Cavanagh, and Jennifer Dawkins.

Parkin gene screening in early and late adult onset Parkinson's disease.

Garth Nicholson and Gulietta Pupo.

Gene Mutation Screening in Parkinson's Disease

Professor Garth Nicholson

Support from the Brain Foundation has been essential to supporting our ongoing research into the genetic causes of parkinsonian syndrome.

Parkinson's disease (PD) is an adult onset degenerative disease that affects the brain pathways concerned with the control of movement. Characteristically it leads to slowing of movements and tremor. Parkinson's disease is usually not inherited but approximately 10% of affected individuals have a family history of the disease. Two genes have been reported with mutations that cause PD. They include alpha synuclein and the parkin gene. Detecting mutations in these candidate genes will eventually allow more accurate diagnosis and treatment of different forms of Parkinson's disease. In particular, patients with mutations can be identified thereby facilitating pathological studies in brain bank material.

The laboratory has developed sequencing techniques suitable for the detection of Parkinson's disease mutations. An *alpha synuclein* mutation (Ala53Thr, the previously described Greek mutation) was identified in one familial Parkinson's family referred to the laboratory. This family has been the subject of a publication describing the clinical and pathological features. We have also found evidence that all reported PD families (except for a unique German mutation), arise from a common founder who lived before 1700, possibly in classical Greek times. This work required the screening of 4 exons in 100 patients. The *parkin* gene screening using present techniques is even more difficult as this gene contains twelve exons. After screening 100 patients for *parkin* point mutations, 6 polymorphisms (normal variations) were identified in the gene. Currently work is continuing to develop rapid screening methods for point mutations in PD candidate genes using denaturing high performance liquid chromatography (DHPLC). In addition, methods are being developed to detect the more common duplication and deletion mutations observed in the *parkin* gene using real time PCR.

IN MEMORIUM

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

Mrs Dell Goodhew,
Mrs Constance Mary Heidenreich,
Mrs Mary Dancuk,
Mrs Mary Egan,
Dr Alice Moyle AM.
Mr Brian O'Dowd

Please contact us for more information about how to make a bequest and the formats necessary to ensure that your wishes are carried out. Would you also kindly nominate a donation to the Brain Foundation as a preferred tribute for loved ones, we do have forms to help with that.

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