

HEADLINES

The Newsletter of the Neuroscience Institute of Schizophrenia and Allied Disorders. March 2003.

Big Federal Support for Major Research Discovery

Distortions in sound processing a clue to schizophrenia risk.

The National Health and Medical Research Council (NHMRC) has awarded a project grant of \$360,000 to expand upon current investigations into an important discovery made in 1991 by members of the scientific group which initiated NISAD.

Awarded to Dr Ulrich Schall and Professors Pat Michie, Philip Ward and Paul Thompson, the grant follows an initial NHMRC award of \$250,000 made in 2001 to develop this line of research.

In 1991, a team including Professors Pat Michie, Stan Catts, Philip Ward, Sally Andrews, Neil McConaghy and Dr. Anne-Marie Shelley found that schizophrenia patients have a reduced brain response to deviant sounds in a repeating sequence of identical sounds.

In the original study*, patients did a computer task involving coloured shapes while being presented via earphones with a repeating pattern of identical sounds, occasionally interrupted by a different sound. In such tests, even though subjects ignore the noise on the earphones, the brain recognises the different sounds, and

produces an electrical response known as mismatch negativity. This response can be recorded via Electrocap sensors placed on the head.

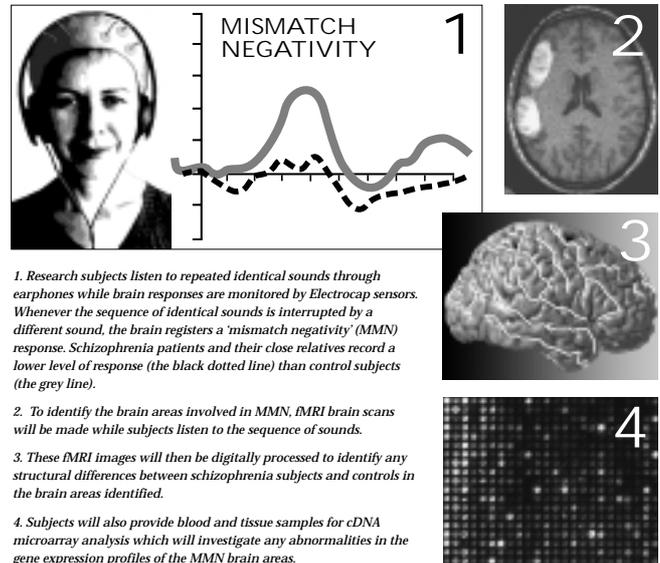
Interestingly, further research by Prof. Michie indicated that first-degree relatives of schizophrenia patients produce similar reduced responses in mismatch negativity tests.

The importance of the original finding was that smaller responses in this auditory test could indicate serious deficits in brain function. For the brain to respond to a deviant sound, it must have a memory of past sounds, so a mismatch negativity test could be used as a measure of memory integrity, and of other high level functions.

Four-Way Coordination to Solve the Puzzle

The potential value of the mismatch negativity discovery warrants the application of four coordinated research methods: Event Related Potentials (ERP monitoring brain activity via Electrocap), fMRI, sMRI, and microarray genetic analysis.

The new NHMRC funded project will use fMRI brain scans to examine patients who have recently developed schizophrenia; those who have suffered from the illness for longer periods of time, and the close relatives of these



1. Research subjects listen to repeated identical sounds through earphones while brain responses are monitored by Electrocap sensors. Whenever the sequence of identical sounds is interrupted by a different sound, the brain registers a 'mismatch negativity' (MMN) response. Schizophrenia patients and their close relatives record a lower level of response (the black dotted line) than control subjects (the grey line).

2. To identify the brain areas involved in MMN, fMRI brain scans will be made while subjects listen to the sequence of sounds.

3. These fMRI images will then be digitally processed to identify any structural differences between schizophrenia subjects and controls in the brain areas identified.

4. Subjects will also provide blood and tissue samples for cDNA microarray analysis which will investigate any abnormalities in the gene expression profiles of the MMN brain areas.

patients. The specific brain regions that are active during auditory information processing will be identified, and linked to the individual brain areas identified via ERP. The new structural sMRI analysis tools used by the NISAD Brain Atlas Initiative will then be applied to identify any differences in brain tissue structure in the areas targeted.

The fourth arm of the investigation, microarray analysis, is funded by NISAD and supervised by Dr Paul Tooney. Blood samples and skin biopsies will be collected from research subjects, and microarrays will be used to compare the levels of expression in genes, and their correlations with the other results of the

collaborative study.

The combined results from this research project have the potential to not only identify genes involved in causing schizophrenia, but also to provide a means whereby individual risk of the illness may be measured.

NISAD's Brain Atlas Initiative and collaborative link with Prof. Paul Thompson's group at the Laboratory of Neuro Imaging, UCLA, was a vital ingredient in the successful award of funding to this research project.

*Shelley, A.M., Ward, P.B., Catts, S.V., Michie, P.T., Andrews, S. & McConaghy, N. Mismatch negativity: An index of preattentive processing deficit in schizophrenia. *Biological Psychiatry*, 1991, 30, 1059-1062.

Stars shine at Year of the Goat fundraiser

Masterminded by Executive Director Jackie Crossman, tickets for NISAD's Chinese New Year of the Goat fundraiser on Sydney Harbour's Goat Island were offered in October, and sold out in a week.

On January 31, 174 guests assembled at Circular Quay to be ferried across to the island's jetty, where a luxury marquee had been erected for the occasion.

Ray Martin once again showed his firm support for NISAD research by undertaking the role of Master of Ceremonies. Keynote speaker was Prof. Allan Fels, the Chairman of the Australian Competition and Consumer Commission who had given schizophrenia awareness such a boost in 2002 by speaking on the ABC's 'Australian Story' series about coping with the

illness in his own family.

Also in attendance were Federal Sex Discrimination Commissioner and NISAD Director Pru Goward, her daughter Kate Fischer, and legendary recording star Helen Reddy. Singer Brooke McLymont gave a stand-out show, and further entertainment was provided by traditional Chinese harpists and dragon dancers.

Live auction items ranged from a 1.14 carat gem from Argyle Diamonds, to a training session in the Australian Army's BlackHawk helicopter simulator. Also offered was a lunch or dinner for three people with Prime Minister John Howard - generously donated by UBS Global Asset Management.

Guests were also tempted to make further donations via silent auction items, and by purchasing 'Lucky



Posed behind the traditional Chinese dragon costume are (L-R) Prof. Allan Fels, Kate Fischer, Ray Martin, Pru Goward, and Helen Reddy.

Envelopes' which might contain a prize voucher for anything from a magnum of Bollinger champagne to a home visit by a chiropractor.

NISAD Chairman Ian Harrison closed the evening with expressions of thanks to the many volunteers who

ensured the event's success, and all attendees went home well satisfied at having raised around \$115,000 for schizophrenia research.

A special thank you list of volunteers and donors is included on the back page.



'Gift of Hope' Tissue Donor Program patron Marilyn Mitchell takes time out in Kyoto.

'Gift of Hope' translates well in Kyoto, Japan

As Patron of NISAD's 'Gift of Hope' Tissue Donor Program, Marilyn Mitchell was invited to speak at the International Schizophrenia Conference held in Kyoto, Japan, in December.

Attended by around 3,000 people from 22 countries, the conference was jointly initiated by IFSAD (International Fellowship of Schizophrenia) and ZENKAREN (National Federation of Families with the Mentally Ill in Japan). The theme was, "The power of the family movement: catalyst for change".

Marilyn was invited by Prof. Niwa of the Fukushima Medical University, a strong advocate of 'brain banking' for schizophrenia research.

During her 30 minute presentation, Marilyn spoke of her own experience with schizophrenia, and also of NISAD's Tissue Donor Program and its value to research. 'Brain banking' is a very new concept in most Asian countries, so Marilyn's session was fully booked out. At the end, several attendees volunteered to become donors on the spot!

In between attending sessions, Marilyn spoke with other delegates from all over the world, and was concerned that all reported similar levels of social stigma attached to schizophrenia. "Overall, I felt the conference was successful in sharing and promoting positive attitudes and policies which may contribute to the improvement of quality of life for the mentally ill and their families," she said.

NISAD Joins Research Australia

Invited by Research Australia's CEO, and NISAD Boardmember Dr. Christine Bennett, the Institute has joined Research Australia, an alliance including many of Australia's leading research institutes, academic institutions, peak industry bodies, consumer groups, small businesses and large Australian corporations.

The new organisation is a national body committed to making health and medical research a higher national priority. What makes Research Australia unique is its broad based membership and extensive network of national and international alliance partners with the common goal of advancing health and medical research.

Further information is available at the website www.researchaustralia.org

How do we direct our attention?

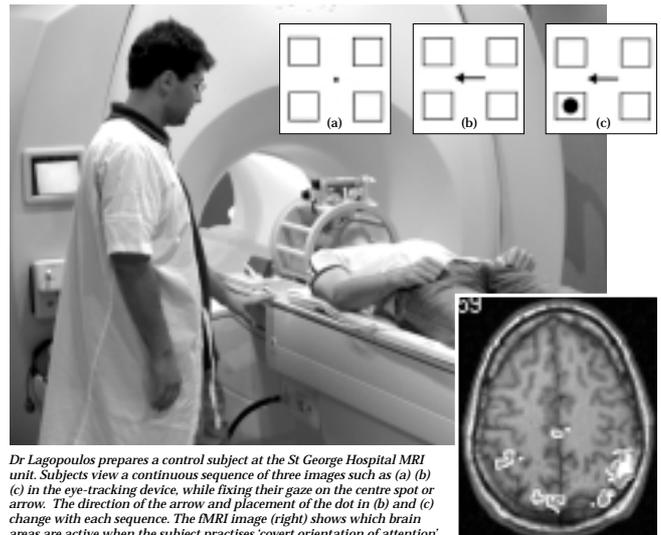
Dr Jim Lagopoulos combines visual scan path techniques and fMRI to investigate how the brain 'pays attention.'

NISAD's Dr Jim Lagopoulos has scored a world first in schizophrenia research by tracking eye movement while simultaneously recording brain activity.

Helped by donations from South Sydney Juniors Rugby League Club, and the Macquarie Bank Foundation, Dr Lagopoulos has used fibre optics and infrared oculography to enable visual scan path tracking of subjects in the magnetic field of MRI brain scanners. He is now applying the technique to investigate whether schizophrenia alters how the brain directs attention.

The September 2002 edition of HeadLines reported significant scan path differences between schizophrenia patients, first degree relatives, and controls. These results immediately begged questions: what was happening in the brain to produce such eye movement differences? Were the three groups of subjects using different parts of the brain to direct attention?

In order to find out, Dr Lagopoulos devised a method of recording only brain activity involved in directing attention, and not activity associated with mechanical eye movements. This



Dr Lagopoulos prepares a control subject at the St George Hospital MRI unit. Subjects view a continuous sequence of three images such as (a) (b) (c) in the eye-tracking device, while fixing their gaze on the centre spot or arrow. The direction of the arrow and placement of the dot in (b) and (c) change with each sequence. The fMRI image (right) shows which brain areas are active when the subject practises 'covert orientation of attention'.

method utilised the ability of the mind known as 'covert orientation of attention' which, for example, enables readers of this paragraph to shift their attention to the images above, without moving their eyes from this word.

Locating the brain areas involved in this attention directing ability could provide valuable clues to the operation of the mental 'executive function', or discriminating faculty, which is so disastrously altered by schizophrenia.

In collaboration with NISAD Scientific Director Prof Philip Ward, Dr Lagopoulos has successfully applied his method to ten healthy volunteer subjects using the St George Hospital MRI unit, and has identified several brain areas involved in covert orientation of attention.

It now remains to apply the same research method to a similar number of schizophrenia subjects, and to compare results.

Understanding Cannabis

Just ten years ago, science discovered that the human brain contains a naturally produced molecule that mimics the active ingredient in marijuana. Since then research has shown that such molecules and their receptors (now known as cannabinoid) are distributed throughout the brain, and seem to play an important role in many brain functions, including those associated with memory formation and motivation.

National surveys indicate that up to 60 per cent of young people aged 17-24 use marijuana, and many parents have good reason to identify the onset of their son's or daughter's schizophrenia symptoms with such drug abuse. But why do some cannabis users develop schizophrenia while the majority do not?

The answer may lie in the numbers and concentrations of cannabinoid receptors in individual brains. While the naturally produced cannabinoid molecules enable certain normal brain functions to occur, it seems that marijuana use introduces an excess which disrupts this system. The degree and duration of disruption may depend upon the number of receptors available.

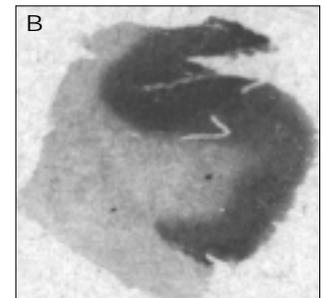
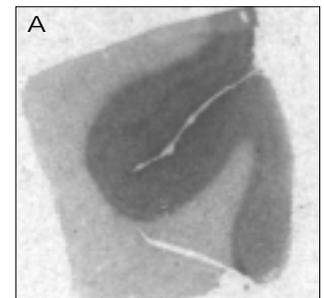
In Australia, around one third of schizophrenia patients are daily users of

cannabis, and such usage is known to exacerbate psychotic symptoms and lead to more frequent relapse episodes.

Research has also shown that long term heavy use of cannabis in people not affected by schizophrenia produces problems in memory, attention and motivation. As these are some of the attributes affected by the 'negative' symptoms of schizophrenia, a direct link is indicated between the effects of the drug and the illness.

Based at the University of Wollongong, NISAD scientist Dr Katerina Zavitsanou is exploring this link by studying the cannabinoid receptors in the anterior cingulate cortex, a brain area known to play an important role in normal cognition, particularly in relation to motivation. Using post-mortem brain tissue from schizophrenia patients and normal controls, Dr Zavitsanou has found significantly more cannabinoid receptors in the schizophrenia group.

Also at Wollongong, affiliated scientist Dr Nadia Solowij was awarded \$30,000 by the Ramaciotti Foundation to investigate the effects of long-term cannabis use on brain function in the general community. This study will include collaboration with NISAD on aspects relating to schizophrenia.



Using post-mortem brain tissue from 9 normal controls (example A) and 10 schizophrenia patients (example B), Dr Zavitsanou used quantitative autoradiography to assess comparative numbers of cannabinoid neuro-receptors in the anterior cingulate cortex - a brain area known to be involved in functions related to 'negative' symptoms of schizophrenia. Overall, the schizophrenia tissue samples were found to have 24%-72% more cannabinoid receptors. This may indicate an inherent special vulnerability to cannabis.



Thanks to Markus Delectite and Clemenger Proximity for the NEW NISAD WEBSITE at www.nisad.org.au



Brainy ladies at the ANS Conference: (L-R) Research Assistant Lisa Azizi, Dr Maria Sarris, and Systems Manager Donna Sheedy.

You're never too old to donate your brain!

Ms Alberta Daniel, aged 102 years, has become the oldest person ever to pledge a brain donation to the NSW Tissue Resource Centre (TRC).

Including the NISAD 'Gift of Hope' donor program, the TRC participated in the Australian Neuroscience Society Conference held in Adelaide in January.

Based at the University of Sydney, the TRC provides an invaluable resource to researchers by making available post-mortem tissue from brains affected by specific mental disorders and conditions, as well as tissue from healthy brains. For information on how to become a donor, please call (02) 9295 8398.



Donna Edye paddles into Townsville to be interviewed by Brisbane TV.

Seaquest hits halfway point

Donna Edye's epic 4,000 km kayak journey down the east coast from Cooktown to Wollongong has reached halfway between Rockhampton and Brisbane.

In an interview on Brisbane TV, Donna drew attention to the plight of families coping with schizophrenia and bipolar disorder, emphasising that these diseases disabled more young people than any other illness.

The beneficiaries of the fundraising and awareness voyage are the Queensland Centre for Schizophrenia Research, Illawarra Health, and NISAD.

Averaging 50 km per day, Donna will continue paddling down the coast, calling in for overnight stops in communities where fundraising events are supported by local media and organisations. Media interest will grow as Donna nears her Wollongong destination. Further details available at: www.deko.org.au

Which Genes Cause Schizophrenia?

Dr Albert Chetcuti uses mice, drugs and gene-chip technology to narrow the list of suspects.

Previous research into the genetic origins of schizophrenia has implicated no less than 13 of the 24 different chromosomes which carry the complete human genome. As each chromosome carries up to 1,400 genes, the list of suspects remains dauntingly long.

Newly appointed NISAD scientist Dr Albert Chetcuti is now working to shorten this list by a novel application of the new 'gene-chip' technology which allows high-speed monitoring of thousands of genes simultaneously.

Which genes are altered by medication?

Every single cell contains a complete set of all the genes necessary to build and maintain the whole body. So how do we get different kinds of cells such as liver cells, skin cells and brain cells? The answer is that while every cell has all the genes, different sets of genes are *switched on* in each cell type, and only the genes necessary to produce each type are allowed to *express* themselves. How the genes express themselves is by creating different types and combinations of proteins to build and govern bodily functions. In the case of brain cells, or neurons, the proteins expressed build the molecular structures which modulate how we think and feel.

The symptoms of schizophrenia indicate that something has gone wrong in the way some neurons operate. Therefore we know that the genes responsible are expressing themselves in an abnormal way.



Dr Albert Chetcuti in the Neurobiology Program Laboratory at the Garvan Institute.

But we also know that current anti-psychotic medications can alleviate symptoms, and often restore the brain to normal functioning. So somehow the medication is correcting the effects of the abnormal gene expression? If so, we can pinpoint the genes responsible for schizophrenia by identifying which gene expressions are altered by medication.

Dr Chetcuti will investigate this hypothesis by dosing a number of mice with antipsychotics such as risperidone or clozapine, and using 'gene-chip' microarray analysis to identify any changes in gene expression. Identical but undosed mice will act as a control comparison group. Although obtained using an animal model, the results from the study will be valuable because the sets of genes in mice and humans are 99% identical.

This study is being conducted under the supervision of Prof. Peter Schofield at the NISAD Centre for Molecular Brain Research in the Garvan Institute, and will include a similarly formulated investigation targeting bipolar disorder.

Bill Grace Picks a Winner for NISAD at Rosehill!



The Bill Grace & Son Charity Race Day on 30 November at Rosehill featured Australia's first horse race dedicated to schizophrenia - the NISAD Schizophrenia Research Handicap.

The announcer appealed to patrons to donate generously, and a 'Punter's Club' in the Member's Enclosure attempted to accumulate winnings on all races for the cause.

Mr Bill Grace visited NISAD's Garvan Institute HQ to present the proceeds of \$15,000.



Top: At Rosehill (L-R) Gabriel Tunbridge, Don McDonald, winning nag and strapper, Brian Parker (CFMEU), Philip Ward, Alan Tunbridge. Above: At NISAD's HQ (L-R) Brian Parker, Mark Childs, Bill Grace, Don McDonald.

WOLLONGONG GOES ONE 'BETA'



The South Coast community continues to drive ahead with the campaign to fund a Beta Imager for NISAD's University of Wollongong research team.

Keeping pace with ever-advancing technology, the original campaign target of a phosphorimager has been replaced with a state-of-the-art Beta Imager that does an even better job of scanning brain tissue. Once installed, the machine will be the only one of its kind in the Southern Hemisphere.

The campaign started off with a \$50,000 donation from the Mining Division of the Construction, Forestry, Mining and Energy Union, and strong support from Joy Mining and the Australian Manufacturing Workers Union. Since then, the South Coast Labor Council, and Rotary Clubs have come on side, edging the total raised towards the \$200,000 goal.

Over the last quarter, the campaign has received a massive boost from articles in the Illawarra Mercury and the Shellharbour Kiama Advertiser.

Lord Mayor, and City Coast Credit Union step in

The Lord Mayor of Wollongong, Councillor Alex Darling has formed a schizophrenia appeal committee, "Light and Hope", to support the BetaImager campaign.

The City Coast Credit Union and its Chief Executive, Mr Stephen Mayor has pledged to match funds raised from the community up to \$35,000.

The Illawarra Mercury is also supporting the campaign by publishing weekly articles to lift public awareness and attract donations.

The Lord Mayor's committee, which is made up of prominent business, community, and union representatives, is planning a wide range of community functions over the coming period and is confident that the remaining funds necessary will be raised. As a result of this development the amount raised has climbed from \$93,000 to \$130,000 in just a few weeks.

Coming activities include a Celebrity Dinner on 27 March at the Novotel North Beach, Sing-A-Long A Sound of Music on 13 April, A Night With a Beautiful Mind on 29 May, and The Lord Mayor's Race Day on 21 June.

Please contact Natasha Mulcahy at City Coast Credit Union for details of the campaign; tickets to functions, and how to donate. Ph. (02) 4252 3588, or email: nmulcahy@cccu.org.au

Reinforcing the Fight Against Schizophrenia

Dr. Bill Budd joins NISAD's Newcastle team to accelerate research into sensory processing dysfunctions as root causes of schizophrenia

Dr Budd took up his new position in January, adding to the Newcastle team his considerable expertise in using Event Related Potentials (ERPs) and functional Magnetic Resonance Imaging (fMRI) to investigate the brain's auditory processing mechanisms.

Commenting on his role, Dr Budd said, "The often dramatic symptoms of schizophrenia, such as auditory hallucinations, thought disorder and delusions, may seem to have little to do with the lines of research which focus on the basic 'nuts and bolts' of the brain's sensory processing mechanisms. But there is increasing evidence that the complex clinical manifestations of psychosis may be the end result of far more subtle dysfunctions in brain systems responsible for lower-level sensory processing."

NISAD's recent research results in mis-match negativity, and visual scan path tracking further support the view that schizophrenia may reflect an initial dysfunction in the basic brainstem and



Dr. Bill Budd.

subcortical structures.

"If we imagine the brain as a multi-storey building, I'll be looking at the foundations rather than the upper floors," said Dr Budd.

Dr Budd completed his PhD studies with NISAD's Prof. Pat Michie in 2000, then worked at the Institute of Hearing Research, UK, before returning to Australia.

Demonstrating the close collaboration between Australian organisations involved in mental health research, Dr. Budd's new position at the Centre for Mental Health Studies at Newcastle's James Fletcher Hospital is jointly supported by the Hunter Medical Research Institute, the University of Newcastle, and NISAD.

Post Graduate Student Numbers Double

Providing opportunities for young scientists to begin careers in schizophrenia research is part of NISAD's mission. In 2003, the number of post graduate students supported by the Institute has doubled to 14 from the 7 supported last year. HeadLines' space limitations allow only two postgraduates to be featured below, with others briefly listed:



■ **Ryan McKay**
Ryan is working with Prof. Max Coltheart at Macquarie University on a study of paranoia and psychosis, aiming to find out if and how lower levels of these mental processes operate in the general community.

"The project I'm working on is designed to investigate paranoia. I'm interested in the processes that underlie clinical paranoia, for example cases where people suffer from delusions of persecution (like Russell Crowe's character in 'A Beautiful Mind'). I'm also interested in what can be called subclinical paranoia: wariness, distrust and suspicion in people who do not qualify as having psychological disorders. One part of the study concerns the extent to which paranoid ideas and beliefs serve a defensive function. To what extent does being paranoid provide a psychological benefit?"



■ **Sonja Schleimer**
With Prof. Graham Johnston and Dr. Jasmine Henderson at University of Sydney, Sonja is investigating the role of GABA transporters, as well as the pharmaceutical effects of medications in schizophrenia.

"My PhD thesis is concerned with the effects of antipsychotic drugs in schizophrenia. I am mainly interested in their interference with GABA, the main inhibitory substance of the brain. With my experiments I will try to understand the longterm effects and changes of these antipsychotic drugs on GABA in certain brain regions. I am also interested in the side effects of these antipsychotic drugs, such as the slowing down of movements, and their relationship to other neurological diseases such as Parkinson disease."

■ **Mark Pearson**
At Concord Hospital, Mark is working with Dr. Hans van der Wall, and Prof. Philip Ward using Gamma camera technology to map neurodevelopmental abnormalities in the brains of young people experiencing their first episodes of schizophrenia. Funding for this scholarship was provided by the Breakfast Point Community Aid Fund.

■ **Matthew Hughes**
Working with Prof. Pat Michie, Dr. Ross Fulham and Dr. Bill Budd at the University of Newcastle, Matthew is studying how the brain controls inhibition of action.

■ **Natasha Matthews**
With Dr. Juanita Todd and Prof. Pat Michie at the University of Newcastle, Natasha is studying sound processing in the brain, aiming to discover if the development of schizophrenia is associated with abnormalities in how language is lateralised in the brain.

■ **Penny Newson**
At University of Newcastle, Penny is working with Prof. Loris Chahl to investigate evidence

that physical sensations are altered by schizophrenia, producing sensory deprivation during development and continuing into adult life.

■ **Amy Richards**
Working with Dr. Juanita Todd and Prof. Pat Michie at the University of Newcastle, Amy is exploring the possibility that individuals with schizophrenia have problems in utilizing the context in which an event occurs to guide their behaviour.

■ **Rebecca Hannan**
At the University of Newcastle, Rebecca is working with Dr. Frini Karayanidis and Prof. Pat Michie to investigate the organisation of cognitive control processes in individuals with and without schizophrenia.

New 2003 Summer Student Scholarships

The following students were awarded NISAD Summer Student Scholarships in 2002-2003. These scholarships provide undergraduates with an introduction to schizophrenia research under the supervision of experienced scientists in NISAD's research centres.

■ **Student:** Jessica Hansen
Centre: Centre for Mental Health Studies, James Fletcher Hospital, Newcastle

■ **Student:** Sharon Monterrubio
Centre: Department of Psychology, University of Wollongong

■ **Student:** Mary-Claire Hanlon
Centre: Centre for Mental Health Studies, James Fletcher Hospital, Newcastle

■ **Student:** Nicholas Kerr
Centre: Neurobiology, The Garvan Institute of Medical Research

■ **Student:** Wan Yi Ng
Centre: Department of Pathology, University of Sydney

■ **Student:** Wayne Anderson
Centre: School of Biomedical Sciences, University of Newcastle

■ **Student:** Renee Granger
Centre: Department of Pharmacology, University of Sydney

■ **Student:** Simon Howell
Centre: Department of Pathology, University of Sydney

For generously supporting the 'Year of the Goat' fundraising dinner, many thanks to:

Ray Martin, Allan Fels, Helen Reddy, Brooke McClymont, Simone Logue Fine Food Company, Pages Equipment Hire, Lion Nathan (Hahn beer), Tyrrell's Wines, Tony Dickin, Matrix Marketing, Champagne Bollinger, Spencer Travel, Orient-Express, The Australian Army, Scuderia Veloce Motors Ferrari, Argyle Diamonds, UBS Global Asset Management, Harley-Davidson, Sydney Morning Herald, Melissa Beowulf, Pepsi, Telstra, Jan Cormack, Manning & Manning, Radisson Treetops Resort, Crown Towers Hotel, Carla Zampatti, Autore South Sea Pearls, Janssen-Cilag, Nest Furniture, Wella, Estee Lauder, Marine Boutique Apartment Hotel, Fisher & Paykel, Guillaume at Bennelong, Otto Ristorante Italiano, King Island Dairy, Random House, 20th Century Fox, Brides of Piccadilly, Chiropractor On The Move, BridgeClimb Sydney, Jets Swimsuits.



Patron: Her Excellency, Professor Marie Bashir AO, Governor of NSW

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Visit the NISAD Website at www.nisad.org.au

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