HEADLINES

The Newsletter of the Neuroscience Institute of Schizophrenia and Allied Disorders. June 2003. **SPECIAL NSW and QLD EDITION**

How Rats and Mice Are Helping Schizophrenia Research

The Sylvia and Charles Viertel Charitable Foundation awards $240K to NISAD and the Queensland Centre for Schizophrenia Research to develop animal models of schizophrenia

The use of animal models in medical research has recently played a key role in the development of new understanding and treatments of such human diseases as diabetes, Alzheimers and MS, and is now also producing useful results for mental disorders.

How can rats and mice help schizophrenia research? Mainly because any animal with a backbone uses the same neurotransmitter systems in the brain. By studying the interplay of excitatory and inhibitory substances in simpler nervous systems, we can learn more about the fundamental principles that govern the functions of all brains.

An animal model does not have to reproduce all symptoms of a human disorder. Valuable research results can be obtained from an animal affected by a specific symptom of any illness. In schizophrenia, for example, we know that some patients have difficulty sorting and prioritising sensory information. This deficit can lead to 'negative' symptoms, such as poor concentration and motivation. Mice in a laboratory can be made to have similar problems by giving them drugs such as amphetamine or PCP. Once the symptoms have been produced in a mouse, researchers can measure its altered behaviour by monitoring performance in repeated tasks, and comparing it with that of untreated mice. Then researchers can study how dosing the mouse with other drugs, such as antipsychotics, can reduce the symptoms and normalise performance. In this way, finding therapies that work in the animal model may lead to more effective treatments for humans.

Because the DNA of mice is 98 per cent identical with human DNA, animal models can also be used to track down the genes responsible for the predisposition to mental illness. For example, researchers can create genetically altered mice (e.g. mice with a foreign gene added to their genetic makeup) and use them to examine the influence of specific genes on behavior. Recent advances in genetic engineering also allow investigators to activate or inactivate specific genes in specific regions of the brain. By switching genes on and off, and observing the chemical and behavioral effects caused, researchers can narrow down the list of suspect genes.

These are among the many research techniques to be applied in a collaborative research initiative funded by the Sylvia and Charles Viertel Charitable Foundation, and shared by NISAD and the Queensland Centre for Schizophrenia Research (QCSR).

Joining Forces and Sharing Resources

The new trans-state project will enable two of the major schizophrenia research groups in Australia to build a shared resource of skills, research instruments and animal models, thereby creating a critical mass capable of significant breakthroughs to new knowledge.

The NSW-QLD collaboration will initially focus on developing two current lines of research. First, the vitamin D deficiency hypothesis presented by Prof. John McGrath of QCSR in 1999*. This theory suggested that a lack of sunlight during winter months pregnancies can lead to a vitamin D deficiency affecting the baby's developing brain. Second, the current NISAD research using mice with genetically reduced numbers of NMDA neuroreceptors. Earlier research has indicated that blocking these receptors in the brains of human and animal subjects produces schizophrenia-like symptoms. Therefore investigating how the action of anti-psychotic drugs reduces symptoms in the NMDA depleted mice may provide new clues to how such drugs work, and to the genetic origins of schizophrenia symptoms.

**McGrath J (1999) Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophrenia Research, 40: 173-177.*

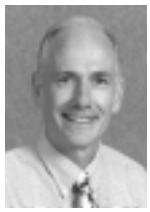
New Name and Director for QCSR

QCSR *Old Logo*

QCMHR *New Logo*

After directing QCSR since 1990, Prof. John McGrath is handing the reins to Genetics Research Director A/Prof. Bryan Mowry.

Prof. John McGrath



A/Prof. Bryan Mowry

"We have a depth of talented researchers in our Centre", says McGrath, "and now this can be reflected in our management structure. I am delighted that Bryan Mowry will be the next head of QCSR."

As well as changing Director, QCSR is also changing its name to the Queensland Centre for Mental Health Research (QCMHR). This is to encompass the broader mental health research portfolio of its Policy and Economics research stream, a group formed since 2000 and headed by Prof. Harvey Whiteford.

Ian Harrison SC

Peter Dempsey

NISAD has also made management and Board changes with the departure of Executive Director Jackie Crossman to initiate her own PR Company; the change of Chairman from Ian Harrison to Peter Dempsey; the election of Dr. Christine Bennett as Deputy Chair, and the departure of Pru Goward from the Board.

At the NISAD Board Meeting of 30 April, the Directors thanked Pru Goward and Jackie Crossman for their contributions, and expressed their appreciation for Ian Harrison's services as Chairman since February 2000. Mr Harrison remains a Board Member.

THE BUILDING INDUSTRY DIGS DEEP

CFMEU, Westfield and Bovis Lend Lease lay solid foundations for more NISAD research

Inspired by the efforts of NISAD's Don McDonald, construction industry unions and management continued their support for schizophrenia research at two major Sydney sites.

On 29 May, NSW Minister for Health Morris Iemma addressed a mass meeting jointly organised by Westfield and the Construction, Forestry, Mining, Energy Union (CFMEU) at the Westfield site in Bondi Junction. He emphasised that schizophrenia has a higher death toll in Australia than AIDS, SIDS and MS combined, but the other illnesses get more publicity and support. Other speakers included Mrs Judy Whitehead who spoke movingly of the schizophrenia-related suicide of her son.

...Continued overleaf

NSW Minister for Health Maurice Iemma takes the stand at the Westfield Bondi Junction site, supported by fellow speakers (L-R) Philip Ward, Dick and Judy Whitehead, and DonMcDonald.

Westfield Director of Construction Tony Sulsters presents a $25,000 cheque to NISAD's Philip Ward .

...Continued from Page 1:

Westfield Director of Construction Tony Sulsters presented a $25,000 cheque to NISAD Scientific Director Prof. Philip Ward. Together with donations from contractors and on-site CFMEU members, the money is to go towards a campaign target of $75,000 to fund a 3-year PhD research scholarship investigating the link between schizophrenia, and 'street' drugs such as cannabis.

Jackson's Landing Workers Dig Deep

(L-R) Darren Power of Bovis Lend Lease, Brian Parker and Ante Zdrilic of CFMEU present to NISAD's Daren Draganic and Don McDonald.

The second construction site fundraising venue was the Bovis Lend Lease project at Jackson's Landing in Pyrmont. On 23 May, speakers from Bovis Lend Lease, CFMEU and NISAD addressed the 350 strong audience at an on-site lunchtime BBQ. A donation cheque of $15,000 was presented on behalf of on-site workers - the first of many expected from the site.

Tony Bleasdale Renews Support

Another strong arm of support from the construction industry came from Tony Bleasdale & Associates who became the first NISAD 3-Year Sponsor to renew support for another 3-year term. As a Silver Sponsor, Tony Bleasdale & Associates donates $10,000 per year. He also appears on the NISAD video presentation 'The Quest for a Cure' speaking compellingly about his parental family's experience with schizophrenia.

Teachers show care for young people

NISAD's Don McDonald and 'Gift of Hope' tissue donor program Patron Marilyn Mitchell addressed a meeting of the NSW Retired Teachers Association, in May. The Members were so impressed by the work of NISAD, wrote Hon. Sec. May Steilberg, that they agreed to make an unusually large donation of $1,000.

Fundraiser Required

NISAD's champion advocate and fundraiser Don McDonald is looking for a person to help inspire and organise support for schizophrenia research. He/she should have drive and a genuine commitment to raising public awareness and donations for schizophrenia research. To apply for this full-time position, please mail your CV to Annette Carter at: NISAD, 384 Victoria Street, Darlinghurst, NSW 2010.

Wollongong is Finishing the Job!

NISAD's $200,000 brain camera is ready to go - thanks to the whole South Coast community.

Wollongong Mayor Alex Darling (L) enjoyed the fight between City Coast Credit Union CEO Stephen Mayers and Steelers Chairman Peter Newell (R) over Anna Kournikova pictures auctioned at the Celebrity Dinner NISAD fundraiser held at Novotel North Beach. Thanks to Ken Robertson - Illawarra Mercury for the photos.

Just a year ago, NISAD's Don McDonald started recruiting South Coast support for purchasing a Beta Imager for the schizophrenia research group at the University of Wollongong. The campaign kicked off with a $50,000 donation from the Mining Division of the Construction, Forestry, Mining and Energy Union, and was quickly reinforced with support from the union's Construction Division, Joy Mining, the Australian Manufacturing Workers Union, the South Coast Labor Council, and Rotary Clubs. Then Wollongong City Council and the City Coast Credit Union stepped in to push the campaign towards the $200,000 goal - strongly supported by feature stories in the Illawarra Mercury and Shellharbour Kiama Advertiser.

Lord Mayor Alex Darling's team recently organised a Celebrity Dinner fundraiser at the Novotel North Beach, where such auction items as St George Illawarra Dragon's skipper Trent Barrett, and a Silverchair guitar helped raise the campaign total to $171,000.

Uni Contributes First Schizophrenia Research Fellowship

In expectation of the campaign's successful conclusion, the Beta Imager has been installed at the University of Wollongong ready for the opening ceremony expected soon.

Acknowledging the sustained community effort of the campaign, the University will initiate a new Postdoctorate Fellowship in schizophrenia research - the first such position to be funded by any NSW university. When switched on, the Beta Imager will be the only one of its kind operating in the Southern Hemisphere.

Research Register Appeal Goes National

The Schizophrenia Research Register is receiving a boost in numbers of volunteers following re-screening of its TV appeal on all NSW channels.

Designed and produced by NISAD Communications Director Alan Tunbridge, the 30 second animated clip focusses attention on the 31,000 unidentified Australian children now under 12 who will certainly develop schizophrenia after age 15 - unless better early detection and treatment methods are found.

This year, the appeal was also broadcast nationally on SBS TV, attracting responses from schizophrenia patients and family members outside NSW. Such volunteers are being referred to schizophrenia research groups in their home State.

Last year, the TV appeal helped to add 300 names to the Register, which

A frame from the 30 sec. TV appeal for volunteers to join NISAD's Schizophrenia Research Register.

now totals more than 900 volunteers. To date, 350 have participated in a research study.

DNA Bank Wins Ethics Committee Approval

The plan for the DNA Bank for Schizophrenia and Allied Disorders has been approved by the Hunter Area Research Ethics Committee and University of Newcastle Human Research Ethics Committee. Helped by a grant from the Baxter Charitable Foundation, NISAD has started contacting Research Register members in the Hunter region to request their participation by providing blood samples from which DNA will be extracted. Such DNA samples from patients and close relatives will be especially valuable because Register members have already provided clinical details of their case histories, and many have participated in MRI studies from which brain scans have been obtained. Register members in other NSW areas will be contacted as local ethics committees approve the program. For more information about the DNA Bank or the Register, please **Freecall 1800 639 295.**

Rebecca: A Letter from Queensland.....

When I visited her parents they showed me a picture of their daughter at age 11. She looked like an angel: stunningly beautiful, blond, apple cheeked. She was the kind of child that everyone loved - intelligent and with a love of nature, animals and art. Up until her mid teens Becky aspired to becoming a marine scientist.

Sadly, there are no pictures of Becky at 22. At age 21 she committed suicide, the tragic result of a four year struggle with schizophrenia in its most severe form. Her story is only too familiar to the families and carers of people with this illness. There were puzzling signs of withdrawal and self-neglect in her mid-teens. These quickly progressed to the body, mind and soul destroying symptoms of the type that shatters the lives of not only the sufferer but every family member. Becky was one of the 30% of people with schizophrenia whom current treatments did not help.

Many families would have hidden the facts of Becky's life and death, a sad result of the stigma still surrounding mental illness. Becky's parents chose instead to celebrate her life by raising awareness of the illness, and the need for research that will result in more effective treatment. At her memorial service her parents asked that donations be made to schizophrenia research, and they found their way to us at QCSR. Later they held a fundraising filmnight in their small country town screening 'A Beautiful Mind'. Again, QCSR was the recipient.

Her parents gave their reasons. "We wanted to make something positive out of something so negative, and address in some way one of our daughter's pleas – 'why don't they do more to find out how to help people like us?'" Our daughter's experience taught us that there is still a lot to be learned about how to manage and treat schizophrenia. There needs to be much more public education about the illness to get rid of the stigma. There has to be more research to find what causes the illness so there are treatments that work for young people like our daughter. We also need services that will provide greater continuity of care for the patient, and more support and involvement for families and carers."

"What is currently available was not sufficient to keep our daughter alive. We want to help change that."

Trish Nolan - Research Manager QCSR

QCSR EPIDEMIOLOGY GROUP

Worldwide schizophrenia research involves so many symptoms, possible causes, and scientific disciplines that the field is in danger of being overwhelmed by the volume and variety of information it generates. Consequently, the task of the QCSR Epidemiology Group is not only to conduct studies into the incidence and prevalence of the illness, but also to collect and synthesise scientific papers from many different sources about specific aspects of the schizophrenia problem. One such project now underway at QCSR is a systematic review of incidence and prevalence data. To date, over 1,000 scientific papers have been collected for critical analysis.

A similar QCSR epidemiological study helped establish that babies born in winter months had a higher risk of schizophrenia in later life.

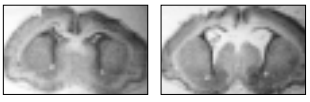
The Risk of Winter Births

Except for infectious diseases such as congenital rubella, few other diseases have such clearly established seasonal birth risk factors as schizophrenia and bipolar disorder. Over 200 studies have indicated that babies born in winter months have a 5-8 per cent higher chance of developing these disorders.

In the largest southern hemisphere epidemiology study, babies born in July-September were shown to have an 8 per cent greater risk. Those who had been born in the northern hemisphere in Jan-March and who had later moved to the southern hemisphere were shown to have a 9 per cent greater risk. Clearly, something is happening to winter pregnancies that makes the baby more susceptible to schizophrenia in later life.

QCSR DEVELOPMENTAL NEUROBIOLOGY GROUP

The Developmental Neurobiology Research Group is investigating whether this winter birth risk is due to a lack of vitamin D (partly obtained by skin exposure to sunlight) during foetal development. Other factors supporting this idea are that schizophrenia is more prevalent among people born in cities than those born in the countryside, and that offspring of dark-skinned immigrants to northern countries are three times more likely to develop schizophrenia than the pale-skinned population.



Post mortem rat brains showing (left) normal development, and (right) enlarged ventricals in vitamin D depleted rats. Ventricular enlargement is a typical abnormality of human schizophrenia affected brains.

This vitamin D hypothesis was first suggested in 1999 by QCSR's Director John McGrath. The Queensland team, with Alan Mackay-Sim of Griffith University, later demonstrated that pregnant rats deprived of vitamin D produced offspring with anatomical and other brain abnormalities similar to those shown in people with schizophrenia. This ongoing research program is also investigating the role of vitamin D in the normal development of brain cells.

How to get brain samples from live patients

Another breakthrough being pioneered by the Developmental Neurobiology Group may solve some of the problems of using postmortem brain tissue for research. The rapid deterioration of brain tissue after death usually gives researchers poor material to work with. It would be much better if we could use samples from live brains, but it's impossible to get them in a non-invasive way. Or is it?

The QCSR team have developed a technique for collecting an easily accessible nervous tissue in living individuals: the olfactory mucosa located at the back of the nasal cavity. Furthermore, the olfactory neuroepithelium exhibits characteristics of great interest to neuroscience. As this tissue is permanently renewed (even in adult humans), it can serve as a model to study the factors involved in nerve growth. The olfactory mucosa is a reservoir of glial and neural stem cells that is readily accessible via biopsy. Thus, the olfactory neuroepithelium can be considered as a "window" that allows the examination of factors involved in brain development. Using this technique, significant differences in cell proliferation, apoptosis (rate of cell death) and response to dopamine have already been found between samples from schizophrenia patients and controls.

QCSR GENETICS RESEARCH PROGRAM

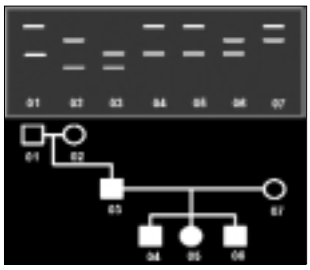
The Global Search for Schizophrenia Genes

Although the great majority of cases arise in families with no recorded history of the illness, schizophrenia is known to carry an ascending scale of risk in relatives of patients. This risk ranges from 2 per cent in Uncles, through 36 per cent if both parents are affected, to 57 percent in identical twins of patients. To search for the genes responsible for this susceptibility, QCSR has established one of Australia's leading gene array facilities and is collaborating with many other research groups at home and overseas on a variety of long-term projects.

Family, twin and adoption studies show that genetic factors are responsible for around 80% of the predisposition to schizophrenia; environmental factors such as pregnancy and birth complications may also play a causative role. The genetics program, directed by Dr Bryan Mowry, recruits different types of families from both ethnically diverse (Australia) and genetically isolated populations (Fiji, Sarawak, India) to account for different gene patterns across the world.

For example, the Brahmin people of Tamil Nadu, a south-eastern state of India, migrated into southern India 2000 years ago. Traditionally, their marriages have been prearranged, with a preference for first-cousin partners. In this project, genetic material (DNA) is collected from Brahmin patients with schizophrenia and their family members. Diagnostic data, detailed family data, and blood samples will be gathered from 90 - 100 extended families, each containing two or more members with schizophrenia. Analysis of their genetic code will enable a search for possible schizophrenia susceptibility genes.

QCSR's genetics laboratory, at the Queensland Institute of Medical Research, has processed over 3000 blood samples from around Australia and from overseas, as a DNA resource for genetic analyses. The genetics group has published a whole genome screen for schizophrenia and contributes to international collaborative analyses of the most prominent hot spot chromosomal regions. In line with the need to recruit large samples in order to detect schizophrenia genes the group is collaborating with eight US groups to recruit over 500 schizophrenia sibling-pair families, and have been recently funded to collect a very large sample of individuals both with and without schizophrenia. To complement family studies in the search for potential causative factors for psychosis, both genetic and non-genetic, the genetics group, in collaboration with state and national colleagues, has commenced a study of Australian twins with psychosis to be recruited for a series of clinical, neurobiological and genetic investigations.



A Family Tree of Schizophrenia

In the laboratory, all families are screened using a set of DNA markers to identify which particular markers are inherited with the illness from one generation to the next. In this sample diagram, 01-07 indicate individual family members. Squares and circles show male and female, with white shapes indicating schizophrenia. The four rows of white dashes in the top section indicate the presence of the markers being tested. Therefore the diagram shows that subjects 01 and 02 had a son (03) who developed schizophrenia. His wife (07) did not have the illness, but they produced two sons (04 and 06) and one daughter (05) all of whom developed schizophrenia. All four schizophrenia subjects (03-06) have inherited one particular gene (third row down) from 01.

DNA Microarray studies are also underway in the genetics laboratory, in collaboration with the Developmental Neurobiology Group and the Centre of Molecular Neurobiology, Griffith University. Olfactory and skin biopsies from four groups (schizophrenia, bipolar disorder, unaffected family members of affected cases, and healthy controls) have been arrayed and preliminary data from the skin fibroblast cultures show that several DNA transcripts are expressed at significantly higher levels in the patient group compared with controls. Encouragingly, these findings overlap with those from brain expression profiling studies in schizophrenia.

QCSR POLICY AND ECONOMICS RESEARCH PROGRAM

Towards a Better Life for Patients

Mental health treatment and rehabilitation require not just effective psychiatric and medical care, but a wide range of social, educational, vocational and housing services. This makes mental health service coordination very complex. The QCSR Policy and Economics Research Group brings together researchers from many disciplines to increase understanding in this complex field.

Sue Caleo (health economist) and Siobhan Coulter (Doctoral student), members of the QCSR Policy and Economics research stream.

The many projects underway include an enquiry into loss of employment opportunity for people with schizophrenia and other serious mental illnesses.

Unemployment rates among Australians with schizophrenia, for example, are over 80 per cent. However, evidence is accumulating that employment is both feasible and beneficial for many people seeking vocational recovery from the consequences of mental illness. The project aims to facilitate more effective employment outcomes, improve social functioning, enhance illness recovery and improve the career development of patients.

Another project addresses the urgent problem of patients moving from the medical system to the prison system. Since the national closure of psychiatric institutions, so many people with mental illnesses find their way into gaol that such correctional facilities may now be providing the largest long-term mental health service in Australia.

There is currently no information on the incidence and prevalence of mental disorders in our prisons. The QCSR research team is now investigating this, and also the development of a valid and reliable screening instrument to identify cases.

Gavin Cooper

Bob MacDonald

Aiding schizophrenia research in Sydney and Newcastle

Reinforcing NISAD's Newcastle team, Gavin Cooper is bringing his valuable expertise in Computer Programming and Data Management to schizophrenia research initiatives based at James Fletcher Hospital and University of Newcastle. He will support the cognitive neuroscience research programs at these centres.

Supported by NISAD, Bob MacDonald's role with the NSW Tissue Resource Centre is to liaise with the Department of Forensic Medicine to obtain suitable brain tissue donations for schizophrenia research. After gaining permission from next-of-kin, it is essential that tissue is collected rapidly, and that details of all donors' medical history and clinical background are investigated to determine research suitability.

Onset of schizophrenia is usually between the ages of 15 and 25. Whether you are reading this in NSW or Queensland, please consider making a tax deductible donation to your research institute.
QCSR Tel: (07) 3271 8694 Web: www.qcsr.uq.edu.au
NISAD Tel: (02) 9295 8407 Web: www.nisad.org.au

NISAD RESEARCH

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

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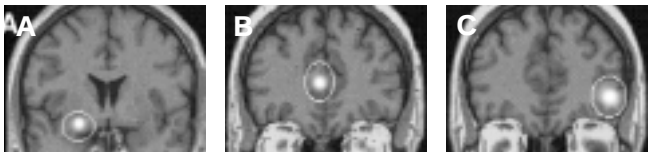

WITH AROUSAL **WITH AROUSAL** **WITHOUT AROUSAL**

Compiled from all fMRI images recorded in this study, images A and B show where emotion processing brain activity is dramatically reduced in schizophrenia subjects compared to healthy control subjects. Image C shows where reduced activity occurs in schizophrenia subjects when no emotional arousal is present.

Charting the Circuits of Emotional Response

For carers and family members, one of the most distressing symptoms of schizophrenia is the loss of empathy or 'emotional understanding'. It sometimes seems that the affected person is being deliberately indifferent to the feelings and affections of others. All too often, the result is a steadily increasing alienation from the family.

Supervised by Prof. Leanne Williams and Dr. Anthony Harris at Westmead Hospital's Brain Dynamics Centre, NISAD's Dr Pritha Das is using a novel combination of two research technologies to investigate differences in how schizophrenia affected brains and normal brains process emotion.

This study involves Functional Magnetic Resonance Imaging (fMRI) in conjunction with Skin Conductance Response (SCR). fMRI records the brain activity of research subjects while they view a series of alternating emotionally arousing and emotionally neutral facial images. Simultaneously, a specially designed SCR sensor attached to a finger records levels of emotional arousal by measuring minute increases in sweat rate. The combined fMRI and SCR recordings not only show which brain areas are being used to process emotional arousal, but also which brain areas are active when arousal is absent.

Early results from this small pilot study show that emotional arousal in normal control subjects is marked by strong activity in the amygdala of the limbic centre, whereas schizophrenia subjects showed very little activity here (fig. A above). Similar activity differences were recorded for the medial prefrontal area (fig. B above). Interestingly, schizophrenia subjects with a history of positive symptoms showed the greatest differences in these areas.

Dr Pritha Das with two of the images she is using to generate and record emotional responses.

Similarly reduced activity in schizophrenia affected brains was recorded when subjects viewed stimulating facial images but recorded no emotional arousal (fig. C above). Here, subjects with a history of predominantly negative symptoms recorded the lowest activity in the lateral prefrontal area compared to normal controls.

Overall, the study confirms that schizophrenia causes radical changes to the way the brain processes emotion, and also pinpoints the areas of greatest change. This study is now being extended to a larger sample of subjects.

Telstra does it with Trivia!

With a national network of more than 4,000 members, Telstra Friends is Australia's largest corporate volunteer program. On 5 June, Sydney members enjoyed a Trivia Night at the Metropolitan Hotel, George Street, raising over $2,000 for NISAD schizophrenia research.

Telstra Corporate Affairs Manager Tim Scott, with Telstra Friends Coordinator Emma Reid, managed to fill all 100 seats for the event. Telstra Sponsorships also came to the party, donating a framed Rabbitohs' shirt which was raffled on the night.

Established in 1993, Telstra Friends are celebrating ten years of community service activities.

"Our volunteers are community minded, and were happy to lend their support to such a worthy cause as NISAD," said Emma Reid, who coordinates Friends activities in New South Wales and Queensland. The evening was such a success that Telstra Friends are looking at making the NISAD Trivia Night a regular date on their annual calendar of events.

Top: Don McDonald thanks Trivia Night attendees for the support. Below: A Trivia team gets one right.

NISAD's Don McDonald attended and thanked all participants.

Visit the Websites at www.nisad.org.au and www.qcsr.uq.edu.au

HeadLines is written, designed and produced by NISAD Communications Director Alan Tunbridge.
The opinions expressed in HeadLines do not necessarily represent the views of all NISAD's participating scientists.

NISAD Schizophrenia Research
SPARE A THOUGHT. FIND A CURE.