

HEADLINES

SCHIZOPHRENIA RESEARCH INSTITUTE

JUNE 2007

Schizophrenia research goes nationwide



The elements of the national campaign to recruit the 4,000 volunteers who will help create the Australian Schizophrenia Research Bank.

April 24th saw the launch of the biggest schizophrenia campaign ever seen in Australia: a national media effort mobilising TV, press and radio to recruit 4,000 volunteers who will help create an unprecedented new resource for worldwide schizophrenia research.



The Institute's Chairman Peter Maher faces the Press at the Launch.

The Australian Schizophrenia Research Bank is a 5-year project to recruit 2,000 people with schizophrenia and 2,000 controls, and to obtain brain scans, genetic profiles and detailed individual information - all of which will be cross referenced to become the biggest schizophrenia research database of its type in the world.

Voiceover by Russell Crowe

In producing the TV appeal, the Singleton Ogilvy & Mather team made a special effort in bringing the project to the attention of Russell Crowe, who readily agreed to do the voiceover. Peter Bloomfield of Plush Films applied his special magic to the direction, and the result is a world class attention grabber. To see the finished clip, just visit the Institute's website



Founding Institute Director Judy Gibson with Sam Lipski, CEO of The Pratt Foundation.

Handling the Response

To produce and launch the biggest ever Australian schizophrenia research appeal is a great achievement, and monitoring the hundreds of responses to the 1800 number is another. Australia's leading specialist call centre, McKesson Pacific, has donated its services to ensure that anyone dialling the number will speak to a live operator. 12 Institute volunteers have joined the McKesson team - donated by Institute Board Member Matthew Cullen.

CAN YOU HELP?

View the 30-second TV appeal at: www.schizophreniaresearch.org.au
If you can help recruit people with schizophrenia for the ASRB, call 1800 639 295 for CDs and posters.



Sydney Town Hall glows red for Spark of Genius.

'Spark of Genius' Does it Again

Following the successes of previous years, Spark of Genius '07 attracted 500 guests, 50 volunteers and 40 Australian 'Genii' to Sydney Town Hall on 18 May to help raise \$200,000 for research.

Led by James O'Loghlin, with Mikey Robins and Peter FitzSimons, the entertainment kept coming - with a breathtaking performance by Jane Rutter and 'Aerialize', and later The Latin Kings. Amongst the fun were truly moving moments as Heloise Pratt and Angela Greensill spoke, and scientific insights provided by Profs. Cyndi Shannon Weickert and Vaughan Carr.

Our thanks go to our 'Genii'; our principal sponsor Macquarie Bank; our partners InterContinental Sydney, GE Lighting, RedBalloon Days, ICMI, City of Sydney for the Town Hall, and to all our other sponsors and volunteers.

To view all the event photos, visit www.schizophreniaresearch.org.au



Prof. Ron McCallum arrives by Harley.

TOP SHOTS FROM 'SPARK of GENIUS'



All Spark of Genius images in this publication are by Matthew Duchesne, © Milk & Honey Photography.

And a great night was had by all! See the back page for a list of the 'Genii', Partners, Supporters and Volunteers who made it happen at the Town Hall for 'Spark of Genius' '07 - and for schizophrenia research.

Massive Media Coverage for 'The Bank'

The Australian Schizophrenia Research Bank (ASRB) received an unprecedented 4 minute segment on



Some of the scientists attending the ASRB Launch. Front row L-R: Dr Carmel Loughland, Bridget Soulsby, Prof Cyndi Shannon Weickert, Dr Robyn Langdon, Dr Melissa Green. Back row: Dr Marc Seal, Paul Rasser, Prof Frans Henskens, Prof Ulli Schall, Prof Stan Catts and Prof Bryan Mowry.



Many thanks to Singleton Ogilvy & Mather who delivered the goods for the multi-media appeal: L-R: Matt Andrews, Simon Bloomfield, Lilly Dunne, Stephen Richardson, Leon Beswick. And also a big thank you to Russell Crowe for the voiceover.

ABC TV news on the evening of the 24 April launch, and ASRB Manager Dr Carmel Loughland has since been interviewed on Sky News, Channel 7's 'Sunrise' breakfast show, and the Sydney Morning Herald's online video site. Other coverage of the launch has appeared in national and regional media.

Together with the screening on many channels of the Bank's TV appeal, this media support has resulted in over 1,000 volunteers calling 1800 639 295, or registering via the Institute's website since the April launch.

Dr Carmel Loughland commented, "I've been involved with many campaigns for schizophrenia over the years, but have never experienced such a positive response from the media and the public. It's simply marvellous!"

Gene Researcher Wins \$60K US Grant

Institute scientist Dr Murray Cairns was granted a \$60,000 'Young Investigator Award' by the US-based National Alliance for Research on Schizophrenia and Depression



Dr Murray Cairns

(NARSAD), one of only two awarded this year to Australian researchers.

"Through recent studies of gene profiling, we already know that in cases of schizophrenia hundreds of genes are altered. This begs the questions: why do genes alter and what are the mechanisms that alter genes?" said Dr Cairns.

Based at the University of Newcastle's School of Biomedical Science, Dr Cairns will research the non-coding RNA molecules between genes to try to determine what role they play in switching genes on and off, and how they might contribute to the development of schizophrenia.

Australia's New Schizophrenia Research Laboratory

Institute scientists gather to plan research with the Chair

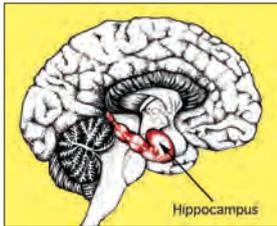
With the finishing touches being put in place on Prof. Cyndi Shannon Weickert's lab in the Prince of Wales Medical Research Institute, the scientists from the Institute's Developmental Neurobiology Panel arrived for a day-long conference to share information and develop plans for future research.

As Australia's first University Chair of Schizophrenia Research, Prof. Shannon Weickert will occupy the new space as her operational base, initially accompanied by Dr. Sinthuja Sivagnanasundaram, and ASRB Clinical Assessment Officers Yen Lim and Julie Houston.

With the new Sydney research centre and a nationwide ASRB project, schizophrenia research is poised for new advances in Australia.



Prof. Cyndi Shannon Weickert (in the light blue suit) welcomes the members of the Developmental Neurobiology Panel to her new lab within the Prince of Wales Medical Research Institute.



Differences in the Hippocampus

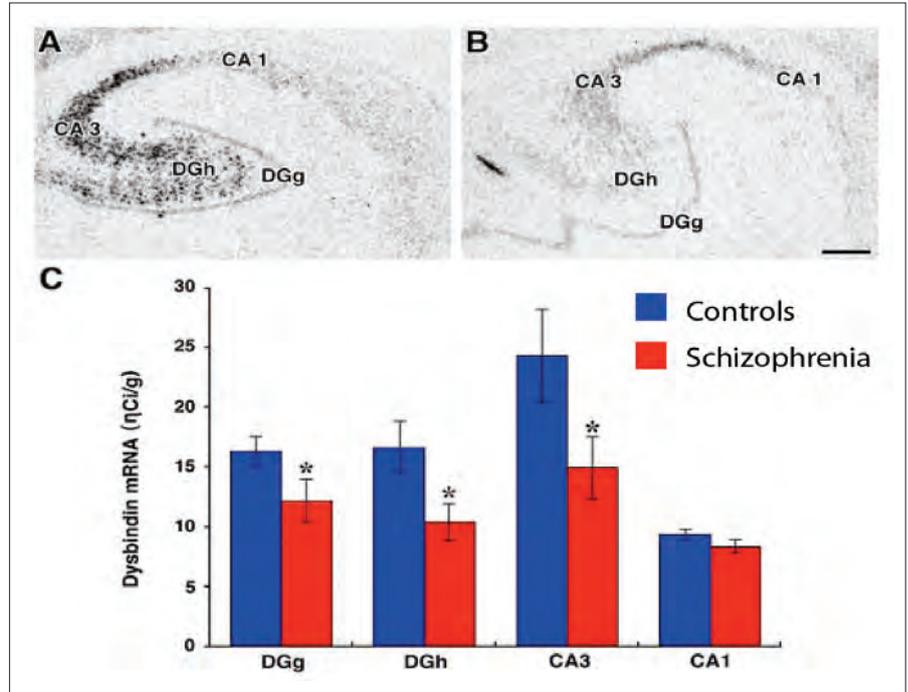
Further evidence implicates the dysbindin gene in schizophrenia.

A 2003 review of genes likely to increase risk of schizophrenia listed seven candidates. More recently, research has focused on two of these candidates as carrying the strongest risk. They are known as dysbindin (DTNBP1) and neuregulin (NRG1). The hunt is now on to find out how these genes are differently expressed in various areas of the schizophrenia-affected brain.

The Institute's Professor of Schizophrenia Research, Cyndi Shannon Weickert, has targeted the hippocampus – a part of the limbic system in the centre of the brain, which processes emotion and memory.

Using postmortem hippocampus sections, Prof. Shannon Weickert detected a 20-40% reduction of dysbindin-1 mRNA in the brains of patients who suffered from schizophrenia.

Earlier studies have found reductions of dysbindin-1 *proteins* in the hippocampus in schizophrenia. As mRNA is the biological agent which transcribes the coding from the gene

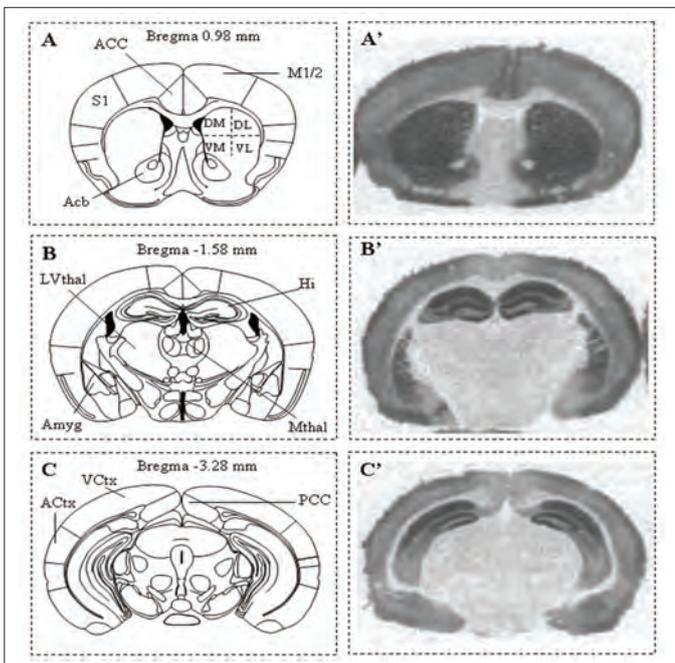


In situ hybridization detection of dysbindin-1 mRNA in the hippocampus. A: Normal levels in control sections. B: Reduced levels in schizophrenia sections. C: Relative levels in 4 areas of the hippocampus.

to build those proteins, this study has given us a broader understanding of how the expression of the dysbindin gene can go wrong to produce the abnormal neuronal connectivity in the

hippocampus which contributes to schizophrenia.

Weickert C, Rothmond D, Hyde T, Kleinman J, Straub R. Reduced DTNBP1 (dysbindin-1) mRNA in the Hippocampal Formation of Schizophrenia Patients. Schizophrenia Research (in press).



A' B' C': Autoradiographs of mouse brain sections showing density of M1/4 receptors (darker tints) in various brain areas.

Muscarinic Meds

Wollongong rats and mice aid the quest for better treatments.

Prof. Xu-Feng Huang's team at the University of Wollongong are continuing their investigations of the brain's muscarinic receptor system as a promising candidate for new schizophrenia treatments.

Current frontline medications effectively suppress symptoms by modulating the brain's dopamine neurotransmission, but side effects include weight gain, and reduced volition. New medications based on the muscarinic system may restore more normal functioning.

Current antipsychotics work by blocking the relevant receptors on the surface of brain cells. This causes the cells to produce more receptors, thus the supply of dopamine in the brain can be modulated by medication dosage levels. Evidence suggests that the muscarinic cholinergic receptors may be treated in a similar way to upregulate the brain's acetylcholine activity, balancing the undesirable side effects

The Divided Brain

The University of Sydney team investigates the corpus callosum.

The corpus callosum (CC) is a bundle of nerve fibres which bridges the gap between the two hemispheres of the brain, allowing them to communicate with each other and to act and perceive as a single consciousness. In rare cases where the CC is severed, the brain actually does divide into two consciousnesses, which can only communicate by reference to the outside world.

For example, in most people the left hemisphere deals with language and numbers, while the right deals with spatial relationships and aesthetics. So people with a severed CC cannot name objects held in their left hands (which connect to the right hemisphere) without looking at them. This is because the left hemisphere which deals with language connects to the right side of the body - which cannot feel the object.

Many earlier studies have reported structural abnormalities of the corpus callosum in schizophrenia, such as smaller size and decreased density of nerve fibres, and it has been suggested that these deficiencies may disrupt

inter-hemispheric communications, producing some of the symptoms of schizophrenia.

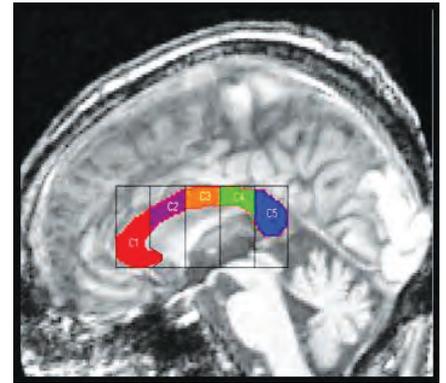
Dr Sinthuja Sivagnanasundaram and the team at University of Sydney have examined the differences in the levels of proteins in the CC of 10 post-mortem schizophrenia brains compared to 10 controls in order to gain some insight into the factors and cascade of biological events, which may help explain the abnormalities of the CC in schizophrenia.

The team found 34 proteins to be differentially expressed in schizophrenia CC, with a majority showing decreased expression.

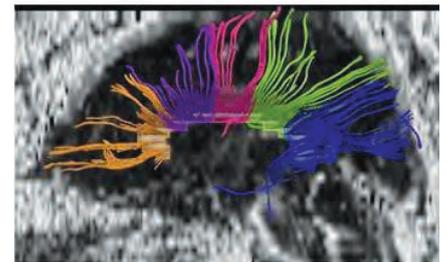
Genes encoding 8 of these proteins map directly to chromosomal regions that have shown strong or moderate linkages to schizophrenia.

Dr Sivagnanasundaram will continue this research after joining Prof. Cyndi Shannon Weickert's team at the Prince of Wales Medical Research Institute.

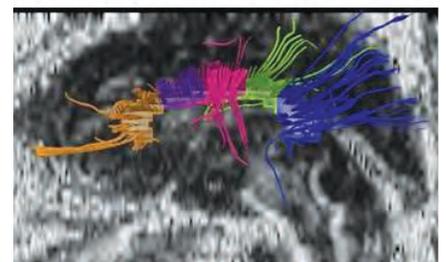
Sivagnanasundaram S, Crosset B, Dedova I, Cordwell S, Matsumoto I. Abnormal pathways in the genu of the corpus callosum in schizophrenia: a proteome study. Proteomics (in press).



Side view of corpus callosum (CC)



Neuronal tract performance of CC in controls



Neuronal tract performance of CC in schizophrenia

• The above images are from a 2005 study by John West, Andrew Saykin, Laura Flashman, Paul Wang: Corpus Callosum Fiber Tractography in Schizophrenia.

of dopamine-based medications. At Wollongong, two recent studies have explored this possibility:

Mice on PCP

Kelly Newell has used a mouse model to investigate muscarinic M1/4 receptors¹, which are found to be abnormally reduced in schizophrenia. Such animal models are valuable to research because they are ~85% genetically identical to humans, and have similar brain structures.

Following a well-established procedure, mice were dosed with phencyclidine (PCP) for 14 days to induce schizophrenia-like symptoms. Half of the mice were then examined to determine short term effects, while the other half were examined 14 days later to determine longer term effects.

The findings were that the densities of M1/4 receptors were increased in the PCP-treated mice in the short term group, but decreased in the long term group. Significantly, the different densities in specific brain areas of mice in the long-term group were similar to the low M1/4 densities found in postmortem brains of schizophrenia patients.

These findings suggest that this animal model may be used to trial the ability of new drug treatments to reverse the M1/4 changes in the schizophrenia brain.

Weight gain in medicated rats

Dr Chao Deng at Wollongong has investigated the link between current 'atypical' medications, muscarinic M2 receptors, and weight gain.

Following the evidence that the dorsal vagal complex (DVC) in the brain stem is involved in hunger and satiety signals, Dr Deng has investigated whether olanzapine acts on muscarinic receptors in the DVC to influence appetite.

A number of rats were divided into three groups which were dosed respectively with olanzapine, haloperidol, and a non-active 'vehicle'. After 12 weeks dosage, only the olanzapine treated rats had gained weight, and subsequent research showed a significant reduction in muscarinic M2 densities in the DVC of these rats, but not in the haloperidol treated rats.

This is the first study² to show that olanzapine may cause weight gain by blocking muscarinic M2 receptors in the DVC of the brain stem.

1. Newell K, Zavitsanou K, Huang X: Oposing short- and long-term effects on muscarinic M1/4 receptor binding following chronic phencyclidine treatment. *J. Neuroscience Research* 85:1358-1363 (2007).

2. Deng C, Katrina L, Weston-Green, Mei Han, Huang X: Olanzapine treatment decreases the density of muscarinic M2 receptors in the dorsal vagal complex of rats. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 31: 915-920 (2007).

Spark of Genius 2007

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Volunteers: Ann Devine, Anne Marie Neylan, Ariane Blanch, Arthur Elefante, Cedric De Air, Chris Carr, Chris Timmons, Christina Woods, Christopher Modica, Colin Carr, Connie Chan, Courtney Nicholls, David Flower, Debbie Simmons, Dorothy Prociuk, Elizabeth Tian, Emily Cappas, Emily Cunich, Fiona McDonald, Glenn Leighton, Greg Payne, Hala Azzi, Jason West, Jenny Boardman, Jesse Gardiner, John Alvarez, Julie Houston, Julie Prociuk, Karina Chui, Katie Kirk, Kim Montgomery, Kim Drury, Kimberley Chiswell, Kristen Edwards, Kulbir Singh Malhotra, Kylie Benson, Lauren Rouse, Liesl Duffy, Lynn Croft, Mary Juco, Melissa Green, Melissa Pigot, Michael Devine, Michael Legzdins, Michael Yacoub, Noelene Kinnear, Pramod Sreekumaran, Rebecca Goodwin, Renee Kinnear, Rhona Anthony, Richard Villarroel, Rodney, Sarah Canabady, Sinthuja Sivagnanasundaram, Sonia Longo, Sonja Grozdanovski, Steve Nicholls, Tracie Goon, Trish Flaherty, Val Vassall, William Linton, Yen Lim.



InterContinental GM Alvaro Rey (centre) and Elizabeth Masselos, with the Institute's Peter Maher, Louise Fisher, and Alex Rivers.



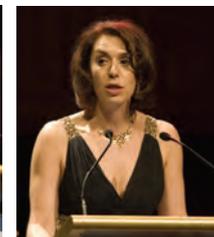
Prof. Cyndi Shannon Weickert.



Bob Ansett with Prof. Vaughan Carr.



The Hon. Paul Lynch M.P.



Heloise Waislitz.



Angela Greensill.



Naomi Simson with MC James O'Loughlin.



Spark of Genius banners fly around the Town Hall specially illuminated by GE Lighting.



Allan and Irene Moss, with Sam Lipski of the Pratt Foundation.



Richard and Jeanne Pratt.



John Symond with David Waislitz.



Mikey Robins.



Julie White of Macquarie Bank Foundation.

