



# CCRN News

Centre for Clinical Research in Neuropsychiatry

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## New Research on First-Rank Symptoms in Schizophrenia

One of the most well-known symptoms of schizophrenia is when a person reports that their own thoughts and actions are controlled by some other force or agency. What might be happening in the brain itself which causes this?

**Dr Flavie Waters** (right), NHMRC Research Fellow at CCRN, is studying first-rank symptoms of schizophrenia, which are thought to reflect what is known as a disordered 'sense of agency': ways in which the human mind provides a personal experience of being the originator of one's thoughts and actions.

In the past, the 'internal forward model' system has been used to account for these first-rank symptoms. In a healthy brain, the forward model anticipates and diminishes the sensory impact of a self-generated movement – which is why it is almost impossible to tickle oneself. Theoretically, people with first-rank symptoms are unable to 'predict' internally the consequences of their own actions, which means that actions might be experienced as originating from outside.

Yet this model does not account for the diversity of first-rank symptoms, which can include disruptions in thoughts, actions, perceptions and emotions. Nor do people with these symptoms experience the full range of deficits in motor control that might be expected if the internal forward model was solely responsible.

What might prove more fruitful is investigating other brain processes that are used to make up the sense of self-experience. The human mind constantly updates the body senses and position of the limbs as the person interacts with their environment. So the ways that the body senses such as vision and touch are integrated, and the way in which our internal 'spatial body map' is organized, can also contribute to how the world is experienced. Psychological processes that tie these all internal and external processes together can also help towards differentiating what is self from what is non-self. Research seems to indicate that people with schizophrenia may have impairments in these processes, and research must continue to help us understand the brain mechanisms contributing to these experiences.

F Waters, J Badcock (2008) First rank symptoms in schizophrenia: reexamining mechanisms of self-recognition. *Schizophrenia Bulletin*, advance publication 27 August 2008.



## Seeing autism differently—the Visual Processing study

CCRN's Adjunct Associate Professor **Johanna Badcock** (right) is currently working with a UWA School of Psychology-based research team (Associate Professor Murray Maybery, Professor David Badcock, and the University of Bristol's Dr Elizabeth Pellicano) investigating visual processing in autism.

Visual processing is the sequence of steps that information takes as it flows from visual sensors (the eyes) to cognitive processing (the way in which the brain interprets the information). Compared with typically developing individuals, people with autism do show some visual performance deficits, but they also often show superior abilities on visual tasks that involve focussing on individual parts of complex figures. This processing strength stands in clear contrast with characteristic difficulties experienced by people with autism, such as deficits in social interaction and communication.

How this ability is achieved is poorly understood, but may provide important insights into brain functioning in autism. This research project will evaluate different theoretical accounts of visual processing in autism, as well as develop new and improved tasks to assess the strengths and weaknesses exhibited while processing simple and complex figures. It will advance considerably the present understanding of atypical visual processing in autism, and may also provide cognitive and psychophysical markers that are useful in genetic studies aimed at identifying patterns of inheritance for atypical processes. Another application of the work may be in the early identification of the autism spectrum disorders, which will facilitate early intervention.



*The CCRN is a specialised research facility of the University of Western Australia's School of Psychiatry and Clinical Neurosciences, funded and operated jointly by the School and the North Metropolitan Area Mental Health Service.*

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## Seminars and Speakers at CCRN, October-November 2008

On 3 October, **Dr Kathryn Abel** (University of Manchester, UK, seen here with CCRN's **Dr Vera Morgan**, left) gave a UWA Psychiatry Research seminar presentation on **'Birth weight and adult maternal disorder – is risk confined to the smallest babies?'** Some problems with the existing data include a bias towards positive findings (those which confirm a relationship), very low numbers in positive studies (between 35-238 cases only), and the fact that the largest studies to date (700-1000+ cases) have found no significant association between low birth weight and schizophrenia. Abel's research team has linked databases in Sweden and Denmark totaling over 1.6 million live births and subsequent psychiatric admissions for schizophrenia and affective disorders to produce a data set of approximately 6000 schizophrenia and 12,500 affective disorder admissions, and 1.5 million controls. After adjusting for possible confounds such as socioeconomic status, gestational age and maternal smoking, data analysis has shown a clear linear trend linking low birth weight and all mental illnesses, with no 'threshold effect', and the strongest effect seen in the lowest birth weight strata. Limitations include a lack of maternal data on smoking, alcohol use, marital status and psychiatric history. If the data can be further refined to allow for other possible confounds such as genetic liability and maternal physical morbidity, practical interventions could be developed to improve outcomes for babies affected by foetal growth restriction and low birth weight, which may increase their resilience in later life.

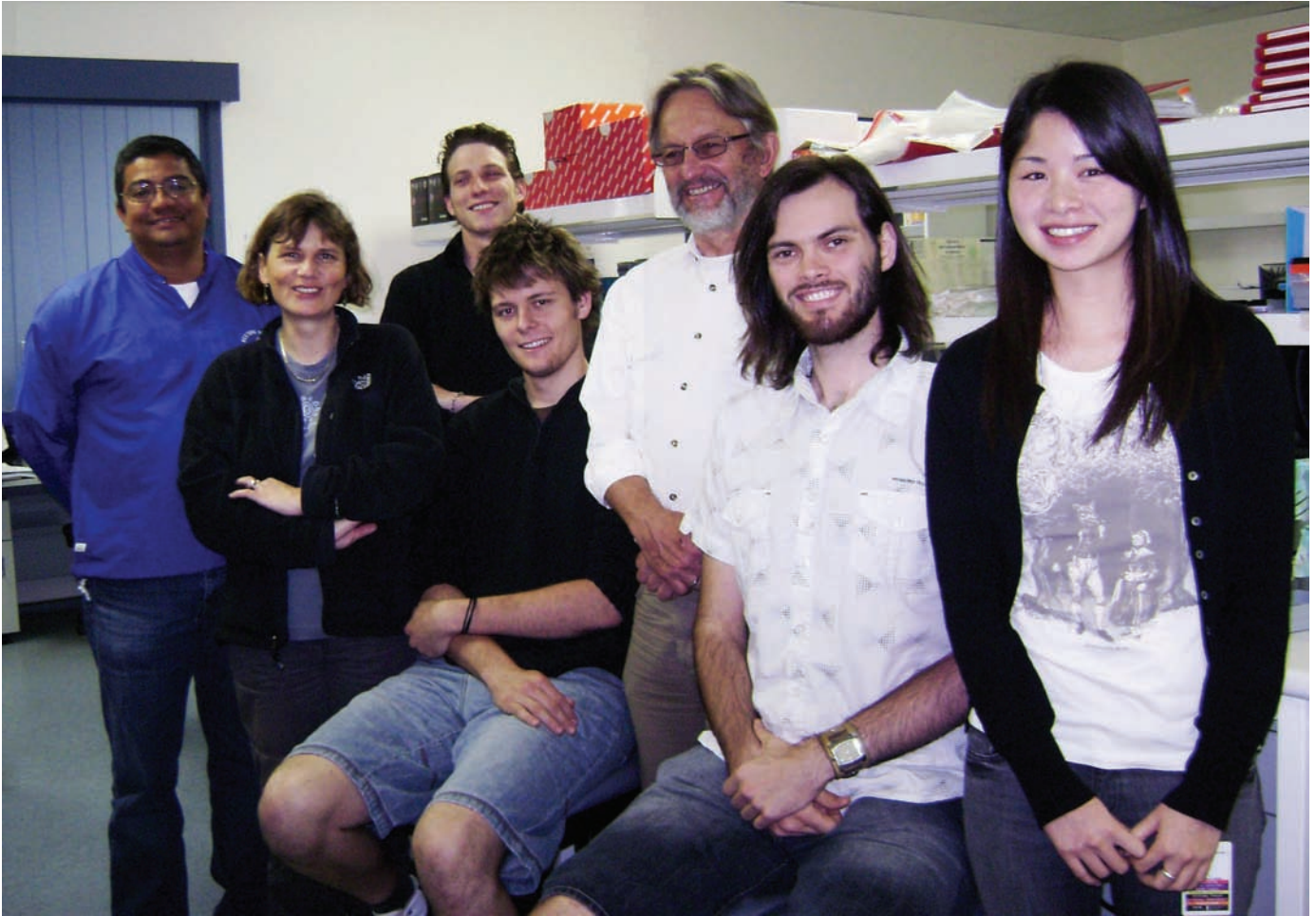


On 29 October, **Dr Katharina Wulff** (Nuffield Laboratory of Ophthalmology, Oxford University), gave a CCRN Research Seminar on **'Disturbed sleep and circadian rhythms in patients with schizophrenia'**. Dr Wulff's research examined the anecdotal relationship between irregular sleep, unemployment, and schizophrenia, by comparing the sleep profiles of people with schizophrenia with a group of healthy unemployed. Using largely non-invasive assessments such as self-rated questionnaires, recording of rest-activity with specially made 'wristwatches' and testing of melatonin levels in urine, the research found that people with schizophrenia were more likely to be 'evening' people, with consistently poorer sleep quality than the control group, as well as longer sleep duration and latency (time taken to fall asleep). The research also demonstrated a very erratic pattern of sleep-wake cycles in schizophrenia which was not present in healthy unemployed people, suggesting that irregular sleep is not a direct consequence of a lack of 'structured' activities like employment. Further research is needed to investigate the relationship between sleep disturbances in schizophrenia and medication, clinical symptoms and social functioning, and to explore whether the circadian system can be entrained to improve sleep and overall functioning. Genetic investigation may reveal an endophenotype for sleep disturbance, and there is a possibility that it may constitute a separate illness, requiring its own diagnosis and treatment.

On 7 November, **Professor Leon Flicker** (Geriatric Medicine, UWA) gave a UWA Psychiatry Research Seminar on **'Frailty and mental health in older people'**. While the media may engage in demographic scare-tactics concerning Australia's ageing population, the real concern is not ageing but the frailty associated with it, which impacts upon health spending. It can be argued that dementia is a form of 'frailty of the brain', the product of a range of health problems: studies undertaken among Indigenous populations in the Kimberley region, where overall health is very poor, found rates of dementia five times higher than that of the general population. While scientific arguments about the causes of ageing continue, and definitions of frailty may be problematic, frailty itself need not equal disability. Frailty is the basis of geriatric medicine: successful interventions need to be as comprehensive as frailty, which is complex. Iatrogenic conditions may increase frailty, as may psycho-social factors, falling hormone levels, and even genetic polymorphism. Falls, a very common disabling event among elderly people, can be the product of multiple factors: failing eyesight, medication, arthritis, and depression. All these conditions may predispose an elderly person to falling, and interventions which address the multiple causes of falls may be more effective.



## Schizophrenia, heroin dependence, and Parkinson's disease: current projects at CCRN/WAIMR Neuropsychiatric Genetics Laboratory



The Neuropsychiatric Genetics laboratory team (L-R): Dr Herbert Ludewick (postdoctoral fellow); Dr Sibylle Schwab; Llewellyn Saggars-Gray (PhD student); Alexander Barty (honours student); Professor Dieter Wildenauer; Dr Adrian Scott (postdoctoral fellow); Clarissa Ganda (research assistant). Not in picture: Jyoti Doshi (research assistant).

CCRN and WAIMR are working together to explore the genetic factors that may influence an individual's susceptibility to disabling illnesses such as schizophrenia, Parkinson's disease and heroin dependence.

Five of the major projects underway at the Neuropsychiatric Genetics Laboratory are investigating the genetic components of schizophrenia, and two of these involve identification of schizophrenia susceptibility genes in Indonesian family samples (NHMRC Project Grant 513861), an international collaboration with the University of Indonesia. Three more are examining protein expression of dysbindin (DTNBP1), PIP5K2a and AKT in both people with schizophrenia and a control group.

The lab is collaborating with Professor Gary Hulse and Dr Robert Tait from UWA's School of Psychiatry and Clinical Neurosciences, working to identify susceptibility factors for heroin dependence (NHMRC project grant 513862). Currently, the team is building up a large case control sample of around 1000 individuals with diagnosed heroin dependence in Western Australia. With an improved understanding of the pharmacogenetic aspects of heroin dependence, practical therapies can be developed to treat it more effectively. Tait and Hulse are simultaneously investigating the clinical efficacy of naltrexone in heroin dependence.

UWA's Professor Sergio Starkstein is also working with the lab on a genetic investigation of Parkinson's disease. This research may help to identify the candidate genes for this and other disorders, by tracking the identifiable co-morbidities such as depression and other psychiatric disorders which affect people with Parkinson's disease.

Already there have been significant findings from the research projects. The *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)* has recently published two studies co-authored by CCRN's Deputy Director **Professor Dieter Wildenauer**, which have indicated significant linkages of chromosome 3p26-21 to schizophrenia in Indonesian family samples. Wildenauer is also editor of the recently-released *Molecular Biology of Neuropsychiatric Disorders*, which presents some of the team's work on the molecular causes of schizophrenia.

Irmansyah, Schwab S, Heriani, Handoko H, Kusumawardhani A, Widyawati I, Amir N, Nasrun MW, Holmans P, Knapp M, Wildenauer D (2008) Genome-wide scan in 124 Indonesian sib-pair families with schizophrenia reveals genome-wide significant linkage to a locus on chromosome 3p26-21. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics* 147B(7): 1245-52.

Wildenauer D (ed) (2008) *Molecular Biology of Neuropsychiatric Disorders: Series Nucleic Acids and Molecular Biology*, Vol 23, Springer Verlag, Heidelberg.

## How close are we to finding the cause(s) of schizophrenia?

In a recent invited commentary in *Schizophrenia Research*, CCRN's Professor Dieter Wildenauer and WAIMR's Dr Sibylle Schwab reviewed the state of play in schizophrenia research, focusing on its (still largely unknown) causes.

In the expression of its symptoms, schizophrenia is unique. While some behavioral aspects of schizophrenia can be modulated in animal subjects, there are no animal or cell models currently available which can be used to validate existing theories about its causes. So research into the causes of schizophrenia must take innovative and often imaginative approaches to the disorder.

Yet the very complexity of the problem means that research makes slow progress. There are many confounding issues in schizophrenia research, one of which is phenotype definition. What phenotypes – observable traits – are truly associated with the development of schizophrenia? Current diagnoses of schizophrenia according to DSM-IV may not correlate to the disease's genotype, while tests which measure neurocognition and memory in people with schizophrenia may not produce a more accurate phenotype, as these features are not always specific to schizophrenia. CCRN's Western Australian Family Study of Schizophrenia is working towards defining a more accurate phenotype by including neuropsychological, neurophysiological and other measures.

A more serious problem exists in schizophrenia genetics. What constitutes true replication of linkage or association of a particular gene or allele with schizophrenia? Ideally, genetic studies should be carried out on reasonably large and well-defined family samples.

Finally, there is the question of functional evidence for elevated or reduced expression of genes. At present, researchers claim that mRNA- or protein analysis forms sufficient functional evidence for this change in expression. This is at best supporting evidence, and cannot stand alone. Functional evidence should effectively be demonstrated by the impact of disease-associated variants on functionality of proteins, pathways and interactions. As yet, this has not been forthcoming.

One possible way forward is through increased interdisciplinary research between neuroimaging, neurobiology, genetics, and epidemiology. This may help to set firmer standards for each field which will generate reliable datasets. Currently available technologies are already highly refined and diverse; the interpretation of the data produced by these technologies needs further development.

Schwab S, Wildenauer D (2008) Research on causes for schizophrenia: Are we close? *Schizophrenia Research*. May 7.

## News and Notes



**New Student:** Avdesh Avdesh (PhD, Pharmacology, UWA, left) will be carrying out doctoral research on 'The effect of cannabinoids on the memory loss and habituation of startle reflex in the APP-mutant mouse model of Alzheimer's disease', supervised by Associate Professor Mathew Martin-Iverson and ECU's Professor Ralph Martins.

**Staff Changes:** CCRN's Deb Faulkner (right) has been appointed by the Clinical Applications Unit as a Project Officer, working on the Vulnerable Families Project. Deb was previously employed by CCRN as a Research Associate.



**UWA School Review:** From 8-10 September 2008, UWA's School of Psychiatry and Clinical Neurosciences underwent its formal review process, and as part of the School, CCRN was reviewed on 9 September. Professor John Saunders (University of Qld/University of Sydney), Associate Professor Vladan Starcevic (University of Sydney), Professor Hans Lambers (School of Plant Biology, UWA—Panel Chair), Professor Ian Puddey (Dean) and Ms Susan Henshall (Executive Officer) spent an hour with CCRN's Senior Investigators Committee, and then met with staff and students for afternoon tea.

### Conference Attendance:

**Professor Assen Jablensky**—Biennial Schizophrenia Conference, Chennai, India, October

**Dr Vera Morgan**—Australasian Schizophrenia Conference, Lorne, Victoria, October

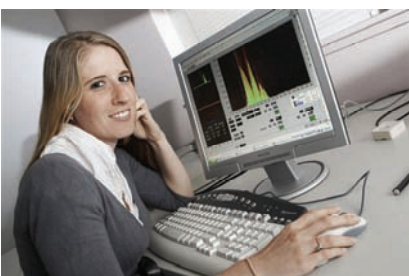
**Dr Philippa Martyr**—Our Mob, Our Minds, Our Spirits 2008: Aboriginal Mental Health, Fremantle, November

**Professor Dieter Wildenauer**—Annual Meeting of the American Society for Human Genetics, Philadelphia, USA, November

**Dr Johanna Badcock, Dr Flavie Waters**—Australasian Society for Psychiatric Research Conference, Newcastle, NSW, December, speaking at the symposium entitled: 'Voices to reckon with: New directions in hallucination research'

**Invited Speaker:** Professor Dieter Wildenauer has been invited to speak on 'Genetics of schizophrenia' at the 5th National Congress of Schizophrenia, Lombok, Indonesia, in October 2009.

**Presentations:** On 16 October, Dr Yvonne Hauck gave a paper on 'Promoting Healthy Babies for Mothers with Serious Mental Illness: a case management framework for mental health clinicians and a specialist Childbirth and Mental Illness (CAMI) clinic' at the WA Health Conference, Perth.



**Prizewinning Student:** CCRN doctoral student Kirsty Scholes (left) won a \$400 prize for Best Postgraduate Oral Presentation at the UWA School of Medicine and Pharmacology Research Day on 17 October, with a presentation entitled 'Disturbed prepulse inhibition in patients with schizophrenia is secondary to selective attention deficits'.

**Registration:** CCRN's Clinical Assessment Officer Lisa Dawson, currently supervised by Dr Flavie Waters, has been granted conditional registration by the Psychologists Board of Western Australia.

Kirsty Scholes photo: Ron Olson, WA Health Department