

# Rudolf Magnus Institute of Neuroscience

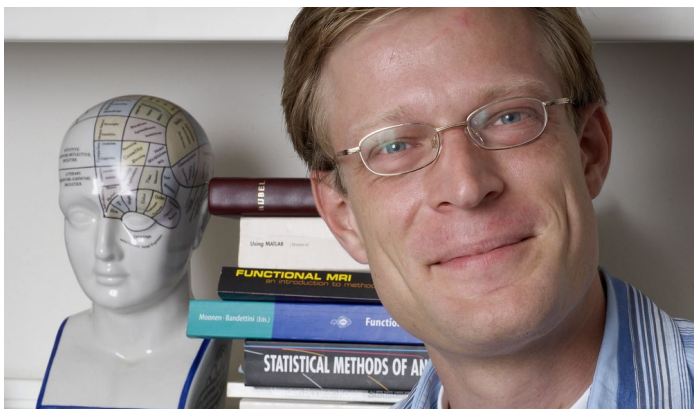
Rudolf Magnus Bulletin 26  
October 2006

## interview

### Controlling Psychotic Symptoms in Schizophrenia

**Matthijs Vink (Dept of Psychiatry) has received a VENI grant in July for his project entitled, 'Controlling psychotic symptoms in schizophrenia'. The subtitle gives away what this project is all about: 'a new approach to an old problem'. It has been shown, among others by the work of Vink himself, that schizophrenia patients have little inhibitory control. Vink now will use very advanced imaging techniques, combined with methods to manipulate inhibitory control, to determine how cortical and subcortical systems contribute to the development of psychosis in schizophrenia.**

Schizophrenic patients in general seem unable to filter out irrelevant information in daily life. In the work described in his thesis of last year, Matthijs Vink examined inhibitory control in healthy subjects, schizophrenic patients, and their unaffected siblings. A distinction was made between inhibitory control over incoming information (perceptual inhibition) and outgoing information (motor inhibition). The main finding of Vink was that patients are impaired in both aspects of inhibitory control. Siblings, tested on motor inhibition, displayed functional brain abnormalities in the striatum similar to those of patients, despite normal behavioural performance. This finding suggests that functional brain measures may be a more sensitive marker of (genetic) risk factors for the development of schizophrenia than behavioural measures.



The work of the VENI grant of Vink will in fact commence where his thesis work ended. Vink explains the new ways to address an old problem that he will be exploring: "In the early 1990's, a new model of schizophrenia was put forth to unite the dopamine hypothesis (i.e. subcortical dopamine hyperactivity leading to psychosis) with the hypofrontality hypothesis (i.e. cortical dopamine hypoactivity leading to deficient social and cognitive functioning). It was postulated that in schizophrenia cortical control over subcortical systems fails, and that this failure gives rise to psychosis and related symptoms. Data from animal research supports this hypothesis in that frontal regions regulate (dopamine) activity in the subcortical areas, especially the striatum. As of yet, this model has not been tested directly in humans."

"The aim of my project is therefore to validate this model in healthy subjects, siblings of schizophrenia patients, and schizophrenia patients. This approach requires both a read-out measure of striatal activity and a method to manipulate cortical activation. Brain responses in the striatum during various levels of activity will be measured using functional MRI. Next, frontal regions controlling the striatum are identified as those regions whose activity covaries with that of the striatum and which evidence direct connections with striatum as determined with Diffusion Tensor Imaging. Activity in these frontal regions will be disrupted using repetitive Transcranial Magnetic Stimulation (rTMS), so that reduced frontal control can be mimicked in healthy controls and in siblings of patients. The effects of disrupting frontal activity will be assessed in terms of subclinical manifestation of psychotic symptoms, performance on a task sensitive to striatal functioning, and striatal activity during this task as measured with functional MRI directly after rTMS treatment. By including siblings of patients, we will determine whether abnormalities in the frontal-striatal network are already present prior to the manifestation of schizophrenia, or rather caused by the potential degenerative effects of psychoses or by effects of antipsychotic medication."

Matthijs Vink (December 22, 1976) studied psychology at Groningen University (1999). From 2000 until 2005 he worked in the Dept of Psychiatry of our Institute as PhD student on his thesis (June 1, 2005), entitled '*On inhibition: studies in schizophrenia*'. After a brief period as a postdoc he is now an assistant professor at this department.

## PhD theses

2006-31

October 10, 2006

A.C.H. Houben

**The effect of amplitude compression of the perception of speech in noise by the hearing impaired**

G.F. Smoorenburg  
supervisor

2006-32

October 13, 2006

Erno J. Hermans

**Defy or ally. Neuroendocrine regulations of human socio-emotional behaviour**

J.L. Kenemans, E.H.F. De Haan, J. Van Honk, N.F. Ramsey  
supervisors

2006-33

**The War Within**

October 24, 2006

Elbert Geuze

**The war within. Neurobiological alterations in posttraumatic stress disorder**

H.G.M. Westenberg, E. Vermetten  
supervisors

**A subgroup of veterans suffers from posttraumatic stress disorder (PTSD), a psychiatric illness that hampers many aspects of daily life. Elbert Geuze studied PTSD in veterans by structural and functional imaging. He found that the abnormalities in PTSD were complex and comprised thinning in particular regions of the cortex of PTSD patients, reduced numbers of GABA<sub>A</sub> receptors in PTSD, reduced pain sensitivity in PTSD, and memory deficits in PTSD.**

Geuze examined 25 male Dutch veterans with deployment-related PTSD and 25 male veterans without PTSD matched for age, year and region of deployment with structural MRI. Individual cortical thickness maps were calculated from the MR images. Veterans with PTSD revealed reduced cortical thickness in the bilateral superior and middle frontal gyri, the left inferior frontal gyrus, and the left superior temporal gyrus. Cortical thinning in these



regions may correspond to functional abnormalities observed in these areas in patients with PTSD. Preclinical and psychopharmacologic studies have provided support for a role of the GABA<sub>A</sub> system in PTSD. Geuze assessed differences in the benzodiazepine-GABA<sub>A</sub> receptor complex in Dutch veterans with and without deployment-related PTSD using [<sup>11</sup>C]-flumazenil and PET. Nine drug naive male veterans with PTSD, and seven male veterans without PTSD, were recruited, and matched for age, region and year of deployment. Each subject received a [<sup>11</sup>C]-flumazenil PET scan and a structural MRI scan. Results revealed significantly reduced [<sup>11</sup>C]-flumazenil binding in PTSD subjects throughout the cortex, hippocampus, and thalamus. This provides support for the role of the benzodiazepine-GABA<sub>A</sub> receptor in the pathophysiology of PTSD and is consistent with previous animal research and clinical psychopharmacological studies.

In addition, Geuze performed a functional MRI (fMRI) study of the neural correlates of pain processing in Dutch veterans with deployment-related PTSD. The experimental procedure consisted of a psychophysical assessment and neuroimaging with fMRI. Two conditions were assessed during fMRI in both experimental groups: one with administration of a fixed temperature of 43 °C (fixed temperature condition), and one condition with an individual temperature for each subject but with a similar affective label, equal to 40% of the subjective pain intensity (individual temperature condition). Twelve male veterans with PTSD, and 12 male veterans without PTSD, were recruited, and matched for age, region and year of deployment. Veterans with PTSD rated temperatures in the fixed temperature assessment as less painful compared to control veterans. In the fixed temperature condition, veterans with PTSD revealed increased activation in the left hippocampus, and decreased activation in the bilateral ventrolateral prefrontal cortex, and the right amygdala. In the individual temperature condition veterans with PTSD showed increased activation in the right putamen, and bilateral insula, as well as decreased activity in right precentral gyrus, and the right amygdala. These data provide evidence for reduced pain sensitivity in PTSD. The witnessed neural activation pattern is proposed to be related to altered pain processing in patients with PTSD.

Geuze examined memory performance and processing in Dutch veterans with and without deployment-related PTSD. He examined the neural correlates of associative learning and memory in veterans with PTSD and control veterans with fMRI. Twelve male veterans with PTSD, and 12 male veterans without PTSD, were recruited, and matched for age, region and year of deployment. Changes in the fMRI BOLD response were assessed to encoding and retrieval of non-emotional word pairs reflecting deactivation and activation of brain areas involved in associative memory processing. Veterans with PTSD revealed under-activation of the frontal cortex, and over-activation of the temporal cortex during the encoding phase. Retrieval of the paired associates resulted in under-activation of right frontal cortex, bilateral middle temporal gyri, and the left hippocampus/parahippocampal gyrus in veterans with PTSD. These data support the long held assumption that altered activity in fronto-temporal circuits is related to deficits in memory performance in veterans with PTSD. Neuropsychological assessment in 50 veterans (25 with deployment-related PTSD and 25 without PTSD matched for age, and year and country of deployment) with a comprehensive revealed that although veterans with PTSD had similar total IQ scores compared to veterans without

PTSD, they displayed deficits of figural and logical memory. Veterans with PTSD also performed significantly lower on measures of learning and immediate and delayed verbal memory. Memory performance accurately predicted current social and occupational functioning.

**Elbert Geuze** (August 13, 1979, Barneveld). Secondary education, Mount Cheam Christian School, Chilliwack, BC, Canada (1996), Neuropsychology, Radboud University, Nijmegen (2002). PhD training from 2002-2006 resulted in the work as described in his thesis. As of October 1, 2006, he is employed as senior researcher at the Research Centre of the Military Mental Health Division of the Ministry of Defence.

2006-34

## Drugged memories

October 31, 2006

Gerry Jager

### Functional MRI studies in human ecstasy and cannabis users

**R.S. Kahn, W. Van den Brink, J.M. Van Ree, N.F. Ramsey**  
supervisors

**Cannabis and ecstasy (MDMA) are among the most widely used recreational illicit drugs in the world. Gerry Jager investigated whether ecstasy and cannabis cause sustained effects on cognitive brain function in humans, using fMRI. Her findings indicated that heavy use of ecstasy was associated with reduced performance and altered brain activity for associative memory, but had little effect on working memory and attention.**

Cannabis and ecstasy have generated concern about their neurotoxic potential for brain and brain function, but there is also interest in the possible beneficial actions of both drugs, e.g., as an analgesic or anti-emetic drug (cannabis) or to reduce anxiety, tension or agitation (ecstasy) in patients with post-traumatic stress disorder or in last stage cancer patients. Jager studied the sustained effects of frequent cannabis use in at least one-week abstinent cannabis on working memory and attention, both in terms of performance and related brain activity in the network of brain regions involved in these cognitive processes. No firm evidence was found for long-term deficits in working memory and attention. In addition, Jager found sustained effects of frequent cannabis use on brain activity patterns related to associative memory function. However, as changes in brain activity were unrelated to memory performance or brain structure, it is not clear whether altered brain activity signifies neurocognitive impairment.

Heavy ecstasy users invariably use other drugs as well, which makes it difficult to disentangle the effects of ecstasy from the effects of other drugs. Jager investigated the sustained effects of ecstasy on human cognitive brain function in the context of poly-substance use, i.e. in a large stratified sample of subjects with substantial variations in type and amount of drugs used, i.e. cannabis as well as amphetamine, cocaine, alcohol and tobacco, in addition to ecstasy (median 250 tablets; range 15 – 2000 tablets lifetime). Subjects were examined on working memory, attention and associative memory brain function after at least two weeks of abstinence. In the statistical analyses all drugs mentioned, together with non-drug variables such



as gender and IQ were included as separate predictors in a regression model to predict variation in task performance and brain activity. Jager's findings indicated that drug use was associated with reduced performance and altered brain activity for associative memory, but had little effect on working memory and attention. Importantly, associative memory performance was affected by amphetamine more than by ecstasy. Both drugs affected brain activity, but the effects were consistently in opposite directions. Jager: "These findings suggest that previously reported sustained effects of ecstasy on memory might be due to concomitant use of amphetamine rather than to ecstasy. The finding that ecstasy and amphetamine use affects brain activity differently indicates that separate mechanisms are at play, possibly associated with their differential effects on serotonin (ecstasy) versus dopamine (amphetamine) systems."

**Gerry Jager** (May 9, 1966, Rotterdam). Secondary education, *Christelijke Scholengemeenschap Comenius*, Capelle aan den IJssel (1984); Psychology, Utrecht University (2002). In 1984-2001, she worked as an operation theatre nurse. From 2002-2006 she worked at the Dept of Psychiatry on the project as described in her thesis. She presently works at this Department as a postdoctoral fellow.

## news

### Rudolf Magnus Graduate School Certificates

The Director and the Research Training Committee of the Graduate School took pleasure in presenting the Rudolf Magnus Graduate School Certificate to the following Doctors:

Renate Siebes (May 19, 2006)  
Filip Van den Bergh (June 1, 2006)  
Gert-Jan Geerse (June 6, 2006)  
Mascha Van 't Wout (June 7, 2006)  
Meg Van Bogaert (June 16, 2006)  
Ynte Ruigrok (June 16, 2006)  
Mathijs Raemaekers (September 1, 2006)  
Marieke Wermer (September 29, 2006)

## Young Investigator Award for Sanne Manschot

On September 12, 2006, Sanne Manschot (Dept of Neurology) received the Young Investigator Award of NEURODIAB during its yearly meeting in Sweden for her research on diabetic encephalopathy. EURODIAB is a study group of the European Association for the Study of Diabetes (EASD) with a special responsibility for Diabetic Neuropathy. Its aims are to promote the advance of knowledge on all aspects of diabetic neuropathy through an active cooperation between interested diabetologists and other specialists. Manschot received a PhD for this research in May of this year (Rudolf Magnus Bulletin 23).



## UMC Utrecht Host to European Childhood Epilepsy Surgery Group

On September 7, 2006, the European Childhood Epilepsy Surgery Group met in the Wilhelmina Children's Hospital. This is a study group of clinical neuro(physio)logists involved in the brain surgery on children with epilepsy. This is very selective group since epilepsy surgery is very complex and only performed in its full range in a few specialized centres in Europe, among whom Utrecht takes a prominent position. Onno Van Nieuwenhuizen and Frans Leijten received guests from London, Oxford, Grenoble, Strasbourg, Munich, Freiburg, and Milano.



## agenda

### October 5, Rudolf Magnus Seminar

**Deryck Beyleveld** (Sheffield Institute for Biotechnological, Law and Ethics, UK) 'Should Patents be Excluded on Grounds of Immorality? If So, When?'  
*Roze collegezaal*, UMC Utrecht, 16.00-17.00  
contact [F.Ohl@vet.uu.nl](mailto:F.Ohl@vet.uu.nl)

### October 5, Presentation P&L printers

**How to make a PhD thesis?**  
UMC Utrecht, Stratum Building, Room S41, 14.00-16.00  
contact, [Joke Ploos van Amstel](mailto:Joke.Ploos.van.Amstel@p-l.nl), [utrecht@p-l.nl](mailto:utrecht@p-l.nl)

### October 20, 28<sup>th</sup> PUK Symposium Psychiatry

**'Genes in Psychiatry: facts over fiction'**  
*Roze collegezaal*, UMC Utrecht, 9.30-17.00  
contact, [e.schreurs@umcutrecht.nl](mailto:e.schreurs@umcutrecht.nl)

### November 2, Inaugural address

**Leonard Van den Berg**  
Academy Building, Domplein 29, Utrecht, 16.15

### November 8, Rudolf Magnus Symposium

Including the Rudolf Magnus Lecture 2006 by **Frans De Waal** (Emory Univ. Atlanta, USA) 'On the Possibility of Empathy in Other Animals' and the announcement of the winner of the Rudolf Magnus Research Award 2006.  
UMC Utrecht, 13.30-17.15, Check our website for programme, <http://www.rudolfmagnus.nl>, contact, [k.m.poel@med.uu.nl](mailto:k.m.poel@med.uu.nl)

### November 8, Rudolf Magnus Evening

A unique mixture of social and scientific events is organised following the Rudolf Magnus Symposium. UMC Utrecht, 18:00-21:30, programme will include diner, details to be announced. The evening programme is only (and freely) accessible for all members of the Rudolf Magnus Institute. Registration is required, contact, [k.m.poel@med.uu.nl](mailto:k.m.poel@med.uu.nl)

### November 16-22, Introductory Course for PhD students in Neuroscience

Information and registration, <http://www.rudolfmagnus.nl>

### November 7, 2006, Helmholtz Lecture

**Alumith Ishai** (University of Zurich, Switzerland) 'fMRI studies of Face Perception: Effects of Memory, Emotion and Beauty'  
*Zaal A*, Ruppert Building, Leuvenlaan 19, Utrecht, 16:00-17:00  
Contact, [v.maassen@fss.uu.nl](mailto:v.maassen@fss.uu.nl)

### November 20-21, 2<sup>nd</sup> Workshop RMI-IoP

Theme, **Neuroimaging**  
Location and programme to be announced  
Only accessible to staff of the Rudolf Magnus Institute  
Check our website for updates, <http://www.rudolfmagnus.nl>

### November 23-24, Annual Meeting PhD students

Conference Centre Woudschoten, Zeist.  
Information and registration, <http://www.rudolfmagnus.nl>

### December 14, Symposium Rehabilitation

**'Functional prognosis after CVA'** (meeting in Dutch)  
*Blauwe collegezaal*, UMC Utrecht, 9.30-13.00  
programme and registration, <http://www.dehoogstraat.nl>  
contact, [n.v.keulen@dehoogstraat.nl](mailto:n.v.keulen@dehoogstraat.nl)