



# Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 25  
September 2006

## Interview

### High Potentials!

**We have received several major grants this summer. Two of ten High Potential grants of the Utrecht University have been granted to staff of our institute. Hilleke Hulshoff Pol and Geert-Jan Biessels are the recipients of these grants with their respective partners, Rick Dijkhuizen and Roy Kessels. Next to these, VIDI grants were presented to Jeroen Pasterkamp and Sarah Durston, whereas Matthys Vink received a VENI grant. You can read their stories on pages 3 and 4.**

Hilleke Hulshoff Pol (Dept Psychiatry) received a High Potentials grant, together with Rick Dijkhuizen (Image Sciences Institute), for their proposal entitled, '*Organization and mechanisms of functional brain connectivity: the CONNECT study*'. They explain the relevance of their study as follows: "Brain connectivity forms the foundation of our daily functioning. Moreover, alterations in brain connectivity during development and in diseased brain are associated with changes of functions. We want to elucidate largely unresolved patterns of functional brain connectivity. Modern MRI methodologies, e.g., Diffusion Tension Imaging-based tract tracing, functional MRI, and molecular imaging, have created exciting and unique opportunities for *in vivo* studies on functional brain connectivity. We are developing new methods to extend these possibilities. We will investigate the dynamics of functional brain connectivity during adolescence in twins and their siblings, in humans and in rodents, in a longitudinal set-up. During adolescence prominent alterations in

white matter structure occur, as measured using structural MRI. However, it is unknown how functional networks change. Importantly, these events may be critical for the onset of psychiatric diseases and may show close resemblance with plasticity after brain injury. Our unique (pre-) adolescent twin sample in humans (with Dorret Boomsma, VU Amsterdam) allows for the assessment of influences of genes and environment on developmental dynamics of functional brain connectivity. Our combined human and animal research approach with innovative MRI methodology that is now at our hands will provide important complementary and mutually enhancing information, which will lead to new insights into dynamics of functional brain connectivity."

Geert-Jan Biessels (Dept Neurology and Neurosurgery) successfully applied for a High Potentials grant with his counterpart Roy Kessels (Psychology, Faculty of Social Sciences) with their proposal, '*Vascular cognitive impairment: interactions between clinical features, brain imaging and memory*'. Biessels explains: "The term vascular cognitive impairment (VCI) refers to forms of cognitive impairment associated with, and presumed to be caused by, cerebrovascular disease. The relevance of the concept of VCI lays in the notion that vascular disease and vascular risk factors are potentially modifiable causes of cognitive decline. We will approach VCI from two angles. We will unravel neural correlates of human memory through structural and functional MR studies in patients with vascular lesions in strategic brain areas or more widespread ischaemic abnormalities. Moreover, we will characterize the nature and severity of specific types of VCI to identify structural correlates and clinical determinants. In this multidisciplinary project we will develop sensitive measures of cognition in relation to state-of-the-art structural, functional and perfusion MRI. Thereto, we will examine patients after stroke and patients with vascular risk factors, such as diabetes type 2, and we will focus on memory as one of the most sensitive domains that is highly relevant for every-day functioning."

The High Potential grants (about € 1.000.000 each) are instigated by the Utrecht University to stimulate interdisciplinary research among excellent researchers of all faculties.



From left to right, Kessels, Biessels, Hulshoff Pol, and Dijkhuizen.

2006-25

### The eyes of schizophrenia

September 1, 2006

Mathijs A.H.L.L. Raemaekers

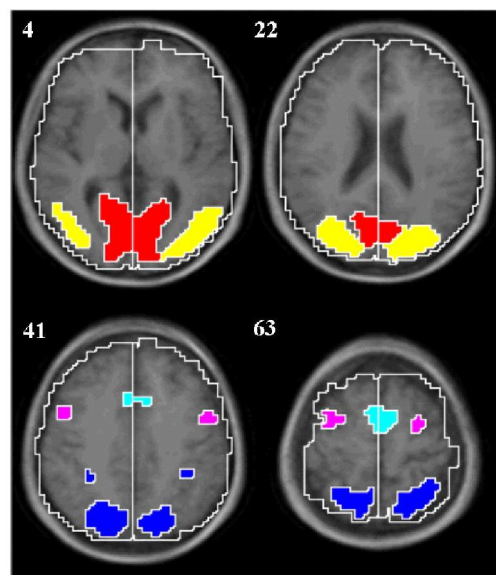
**Saccade inhibition in schizophrenia. Towards phenotyping based on brain function**

R.S. Kahn, N.F. Ramsey  
supervisors

**Despite the increasing evidence that schizophrenia has a strong genetic component, it has proven to be a difficult task to find genes associated with the illness. Mathijs Raemaekers assessed the possibility to use brain activation maps during the antisaccade paradigm as endophenotype for schizophrenia. He found that brain activation in the striatum was abnormal in both patients and their relatives, but that there were still some difficulties to overcome before using this abnormality as endophenotype for schizophrenia.**

The antisaccade paradigm may be a suitable endophenotype for schizophrenia. In the antisaccade task, subjects have to inhibit a saccade (involuntary eye movement) towards a new peripheral stimulus (i.e. prosaccade), and make a saccade in the opposite direction (i.e. antisaccade). Patients with schizophrenia and their healthy first degree relatives have difficulty suppressing eye movements towards the stimulus during antisaccades, while prosaccade performance is well within normal range. By looking directly at the functional properties of the underlying neural network during antisaccades by using fMRI, the link between genotype and phenotype may be simplified.

Event-related fMRI was used in all experiments, as Raemaekers demonstrated that it was possible to detect even the short neural events that are associated with saccadic eye movements and saccadic inhibition in healthy individuals. Raemaekers used this newly developed event-related antisaccade paradigm to detect differences in activation between patients and healthy control subjects. He found that, compared to control subjects, patients did not activate the striatum properly during inhibition of saccadic eye movements. Hence, the antisaccade deficit in schizophrenia patients could be



linked to a deficit in the striatum, or in the frontostriatal circuitry. Raemaekers also found that siblings of schizophrenia patients had abnormal striatal activation during antisaccades, yet the performance on the antisaccade task was within normal range. Hence, relatives were able to compensate for the striatal deficit. Functional brain activation measures may thus have an advantage over behavioural measures as endophenotype. However, a study on the test-retest reliability of the brain activation maps demonstrated that it was yet not possible to obtain reliable results in all subjects. Raemaekers: "Although there are still some technical difficulties to overcome, endophenotyping by using brain activation maps will undoubtedly become a very important aspect of the genetic research in schizophrenia. The results of the experiments in patients and their relatives demonstrate that brain activation maps can give more detailed information than results obtained from behavioural experiments and diagnosis alone."

**Mathijs Raemaekers** (November 30, 1974, Roermond) Secondary education, St. Ursula College, Horn (1993), psychology, Utrecht Univ. (2000). He worked on the work as described at the UMC Utrecht (2000-2005). Since 2005, Raemaekers is a postdoc in Functional Neurobiology, Utrecht University.

2006-26

### Late-life depression: two disease entities

September 5, 2006

Joost Janssen

**Late-life Depression: Structural Brain Abnormalities, Treatment and Risk Factors**

T.J. Heeren, R.S. Kahn, H.E. Hulshoff Pol  
supervisors

**Depression is highly prevalent in elderly. Age at depression onset may be a meaningful marker of disease related brain changes. Joost Janssen compared by MRI studies early-onset depression (EOD) versus late-onset depression (LOD) in the elderly, and found that EOD patients often have a smaller hippocampal volume, whereas LOD more often have subcortical white matter lesions. Therefore, two different types of depression can be described in elderly. These findings point to different aetiologic pathways to EOD and LOD.**

Janssen determined if late-life depression is associated with structural brain abnormalities and whether EOD and LOD are associated with different structural brain abnormalities. Thereto he compared late-life depressed EOD and LOD patients to normal controls. In both aged and older EOD subjects hippocampal volume was smaller compared to normal controls. Patients with LOD did not differ in hippocampal volume from the EOD group or the normal controls, but they had an increased prevalence of larger subcortical white matter lesions. Subcortical white matter lesions were not correlated to smaller hippocampal volume. From these results Janssen concludes that late-life depression is associated with structural brain abnormalities, and that EOD and LOD are associated with different structural brain abnormalities, which may reflect differences in aetiology.

Janssen also tested whether structural brain abnormalities in depression affect short-term treatment response. He determined structural brain differences between 19 older

responders and 23 non-responders to a controlled short-term antidepressant monotherapeutic trial. Responders and non-responders did not differ on any of the baseline quantitative and semi-quantitative brain measures. In addition, after one year follow-up there was no difference in baseline brain measures between patients with poor outcome and good outcome. Janssen concluded that structural brain abnormalities and response to short-term treatment are not strongly correlated.

Janssen found that his results from clinical studies, comparing elderly EOD and LOD patients, could not be straightforwardly generalized to the population. He compared aetiological risk indicators and clinical measures of 90 older EOD subjects and 39 LOD subjects, who were diagnosed using standard epidemiological instruments, and did not receive specialized care at the time of sampling. No clear pattern of neither aetiological nor clinical differences between the groups was found. Janssen concludes that differences between elderly EOD and LOD patients reported from clinical samples cannot be directly generalized to EOD and LOD subjects from the general population, who have not been diagnosed or treated in specialized psychiatric care.

**Joost Janssen** (March 5, 1976, Lottum) Secondary education, College Den Hulster, Venlo (1994), Neuropsychology, Radboud Univ. Nijmegen (1999). The work as described was performed at the UMC Utrecht (2001-2006). Presently Janssen is a postdoc at the Univ. Hosp. Gregorio Marañon, Madrid, Spain.

2006-27

**September 14, 2006**

**M.K. Meijer**

**Neglected Impact of Routine. Refinement of Experimental Procedures in Laboratory Mice**

**L.F.M. Van Zutphen, B.M. Spruijt, V. Baumans**  
supervisors

2006-28

**September 22, 2006**

**M.V. De Jonge**

**The search for endophenotypic markers in Autism Spectrum Disorders**

**H. Van Engeland, C. Kemner**  
supervisors

2006-29

**September 28, 2006**

**M.A. Gerritzen**

**Acceptable methods for large scale on-farm killing of poultry for disease control**

**B.M. Spruijt, J.A. Stegeman, E. Lambooi**  
supervisors

2006-30

**September 29, 2006**

**M.J.H. Wermer**

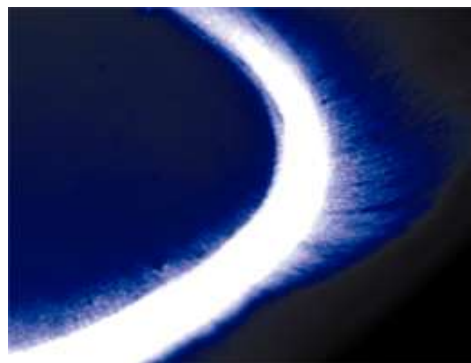
**Longterm outcome and screening for new aneurysms after subarachnoid hemorrhage**

**G.J.E. Rinkel**  
supervisor

## news

### VIDI Grant for Jeroen Pasterkamp

After having earlier received a VENI grant in 2003, Jeroen Pasterkamp (Dept Pharmacology and Anatomy) received a VIDI grant in July for his research proposal, entitled, '*Unravelling the intracellular signal transduction mechanisms that underlie axon guidance: MICALs and plexins lead the way*'. Pasterkamp: "Every aspect of mature brain function relies on a precisely sculptured neuronal network. This network forms during embryonic development when growth cones at the tips of growing axons are guided to their appropriate synaptic targets by molecular cues in the extracellular environment. These guidance molecules are sensed by receptors at the growth cone surface that subsequently trigger intracellular signalling events to modulate the cytoskeleton and consequently induce axon steering. A major challenge in neurobiology today is to define the intracellular signalling mechanisms that dictate neuronal network formation."



"By employing powerful and innovative technologies such as mouse genetics, *in vivo* proteomics, viral vector technology and *in utero* electroporation we will systematically characterize the intracellular signalling network that operates downstream of one of the best characterized subclasses of guidance molecules, class 3 semaphorins (Sema3s). To do this, we will characterize a unique and exciting new family of cytosolic signalling proteins, MICALs, recently implicated in Sema3 signalling. Furthermore, we will identify and characterize novel components of the Sema3 signalling cascades through the rapid identification of MICAL and plexinA (i.e. the Sema3 receptor) interacting proteins. These studies will allow us make a critical step forward in understanding neuronal network formation and will provide us with new avenues for studying and influencing neuronal connectivity."

### VIDI Grant for Sarah Duston

After having received a VENI grant earlier in 2003, Sarah Durston (Dept Psychiatry) received a VIDI grant in July for her research proposal, entitled, '*Profiling ADHD: Genes, brain and cognition*'. Durston: "Attention Deficit Hyperactivity Disorder (ADHD) is an impairing disorder, with a huge impact on medical and health-care services, and the associated costs are high. The disorder is heritable, with additive genetic factors explaining up to 80% of phenotypic variance. ADHD is associated with deficits in behaviour, cognition, and neurobiology, including problems with inhibitory control, reductions in frontostriatal grey matter volumes, and reduced activation in these areas. However, as yet there is no clear link between deficits at different levels, due to such issues as possible multiple aetiological pathways to ADHD, different, currently unidentified subtypes, and possible developmental differences between subtypes."

Durston will follow a novel combination of three state-of-the-art approaches, genetics, structural MRI and functional MRI to disentangle some of the phenotypic heterogeneity in ADHD. She will focus on two possible markers for ADHD-subtypes, one genetic and one cognitive. The key objectives are to investigate the effect of ADHD risk-genes on brain structure and development, to track the development of inhibitory control and associated brain-measures with age, and to investigate differences in brain activation patterns between genetically and cognitively defined subtypes of ADHD. The first two objectives will be targeted in a longitudinal, sMRI-study, where she will also acquire neuropsychological profiles of inhibitory control, and DNA for genotyping ADHD risk-genes from participants, aged 6-12 years. The third objective will be targeted using fMRI, where subjects will be selected from the first study, based on their genetic and cognitive profiles.

### VENI Grant for Matthijs Vink

Matthijs Vink (Dept Psychiatry) has received a VENI grant in July for his project entitled, '*Controlling psychotic symptoms in schizophrenia: a new approach to an old problem.*'

### Tutorial Mouse System Genetics; WebQTL

Family and twin studies have revealed that genetic factors play a major role in neuropsychiatric disorders. Within our Behavioural Genomics Section, a novel research strategy was initiated some three years ago to identify novel genes for behavioural phenotypes in mice that are relevant for psychiatric disorders. This project, partly funded by the ABC Neurogenomics programme, involves the development of novel behavioural phenotyping methods and implementation of a genetical genomics technology platform using chromosome substitution mouse strains. On-line tools are getting available to actively integrate and explore data sets on mouse genetic reference populations. WebQTL allows on-line integration of mouse genotype, phenotype and genome-wide microarray data to further generate new ideas about complex system genetics. Dr. Robert W. Williams (Univ. Tennessee Health Science Center, Memphis, USA), one of the WebQTL founders, recently visited Martien Kas (Dept. Pharmacology and Anatomy). During his visit, an ABC Neurogenomics/ Utrecht Genetics Seminar as well as a tutorial using the WebQTL website ([www.genenetwork.org](http://www.genenetwork.org)) was given. Participants originated from the Rudolf Magnus Institute of Neuroscience and the Biomedical Genetics Research programme of the UMC Utrecht. This overbooked and interactive tutorial was given in the Bioinformatics facility (computer network installed with support of the Utrecht University prestige master programme Neuroscience and Cognition) in the Stratenum Building and was very well received.

### Travel Grant for Koen Van Gassen

Koen Van Gassen (PhD student, Dept Pharmacology and Anatomy) has won a Travel Award (€ 1200) at the 7<sup>th</sup> European Congress on Epileptology (July 2-6, 2006, Helsinki). He was selected from 140 European candidates to give a lecture at the Award Symposium.



## agenda

### September 1, Neurology Seminar

**Paul Wirtz** (UMC Leiden) 'Myasthenic syndrome'  
Colloquium room, C3 Oost, UMC Utrecht, 12.45-13.30  
contact C.E.vanderWijngaart@umcutrecht.nl

### September 8, Neurology Seminar

**S.G.B. Heckenberg** (AMC Amsterdam) 'Meningitis'  
Colloquium room, C3 Oost, UMC Utrecht, 12.45-13.30  
contact C.E.vanderWijngaart@umcutrecht.nl

### September 8-9, BrainDays

A two-days meeting with (inter)national experts on the theme, '**Dynamics of (re)organisation**'.

Roze collegezaal, UMC Utrecht  
Programme and registration, <http://www.rudolfmagnus.nl>

### September 13, Rudolf Magnus Seminar

**Jim Swanson** (Univ. California, Irvine, USA) 'The Potential of the US National Children's Study: Questions to Ask about Genetic and Environmental Bases of ADHD and Other Common Disorders of Childhood'  
Room A1-107 (Aula), UMC Utrecht, 14.00-15.00  
contact, S.Durston@umcutrecht.nl

### September 15, Neurology Seminar

**Bas Bloem** (UMC Nijmegen) 'Parkinson in balance'  
Colloquium room, C3 Oost, UMC Utrecht, 12.45-13.30  
contact C.E.vanderWijngaart@umcutrecht.nl

### 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?'  
UMC Utrecht, 16.00-17.00, contact F.Ohl@vet.uu.nl

### October 5, Presentation P&L printers

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

### 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

### 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

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

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

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

Theme, **Neuroimaging**  
UMC Utrecht. 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>