



# Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 24  
June 2006

## Interview

### First Joint Workshop Institute of Psychiatry London and Rudolf Magnus Institute Utrecht

Neuroscience institutes that are active in the fields of Psychiatry and Neurology and at both clinical and fundamental levels are rare in Europe. Yet, two such Institutes can be found only 350 km apart. The lists of research topics of the Institute of Psychiatry in London (IoP) and the Rudolf Magnus Institute in Utrecht are a close match; sufficient cause for the Rudolf Magnus Institute to apply for a grant of the UMC Utrecht to explore ways to widen and deepen collaborations between both institutes. The kick-off was a joint Neurogenetics Workshop in London, 30-31 May 2006.

In this first of a series of workshops five topics of research were discussed that are already subject to collaborative research, namely Schizophrenia, Autism, Amyotrophic Lateral Sclerosis, Eating disorders/Feeding behaviour, and Mouse Behaviour Genetics. This was complemented by a keynote seminar by Roel Ophoff (Rudolf Magnus Institute), on 'Neurogenetics: from genetic variation to phenotype'. About 40 staff of the IoP met with 15 key investigators of the Rudolf Magnus Institute. The participants of our institute enjoyed the informal atmosphere and many good discussions, and the Neurogenetics Workshop was felt as a success. Time to hear what some of our colleagues present on behalf of the IoP had to say about this initiative.

*Christopher E. Shaw (Professor of Neurology and Neurogenetics):* "From my perspective the session on Amyotrophic Lateral Sclerosis (ALS) at the Neurogenetics Workshop was a great success. It was attended by Leonard van den Berg, John Wokke, Jan Veldink and Roel Ophoff on behalf of the Rudolf Magnus Institute and Jemeen Sreedharan, Xun Hu, Bradley Smith and myself from the Institute of Psychiatry. Progress on gene hunting has been slow because so few ALS families have enough living affected individuals to track down the gene locus responsible. Despite this we have discovered the ALS6 gene locus and more recently loci for ALS-fronto-temporal dementia and distal spinal muscular atrophy, but the causative mutations have not yet been identified. We are keen to collaborate with the Utrecht group to perform linkage on Dutch families.

Leonard van den Berg gave a very entertaining and informative talk about his candidate gene studies in sporadic ALS. He has explored the effect of SMN1 and SMN2 gene copy number on susceptibility to, and clinical phenotype of, ALS and shown a highly significant association. They have also analysed Single Nucleotide Polymorphism genotypes and haplotypes in other genes including the Vascular Endothelial Growth Factor gene (VEGF), and the hemochromatosis gene (HFE), as well as the estrogen and androgen receptor genes. He expressed an high interest in using the large DNA collection in London as a replicate sample set."

*David Collier (Professor of Neuropsychiatric Genetics):* "The workshop was an excellent opportunity for IoP and RMI staff to come together for the first time as a whole group and discuss their collaborations and interactions. It was clear that there are already a series of natural and complementary interactions between the centres, which build on the strengths of each centre. This includes the excellent translational approach from clinic to laboratory and back, and the use of mouse models of behavioural disorders at the RMI, and the critical mass in clinical psychiatry and genetics at the IoP. There is already evidence that this interaction is giving rise to high impact joint publications in fields such as eating disorders, and the successful and productive exchange of MSc and PhD students. With many new interactions planned and strengthening of existing collaborations we look forward to an exciting future working with the Rudolf Magnus Institute."



## PhD theses

2006-17

June 1, 2006

F.S. Van den Bergh

Targeting Impulsivity

B. Olivier, J.L. Kenemans, R.S. Oosting, L. Groenink  
supervisors

2006-18

Stressed guts

June 6, 2006

Gert-Jan Geerse

Stress, vulnerability and visceral pain

V.M. Wiegant, R. Stam  
supervisors

Posttraumatic stress disorder (PTSD) is a common psychiatric disorder, associated with somatic disturbances such as cardiovascular disorders and irritable bowel syndrome. Gert-Jan Geerse used a rat model to assess the relation of stress, vulnerability and visceral pain. A duodenal distention model was validated as a model for visceral pain. Geerse showed that a passive coping style increases the risk of developing stress-related psychosomatic disorders.

Genetic predisposition, stressor intensity, cognitive appraisal mechanisms and coping processes influence the likelihood of developing PTSD after exposure to a traumatic event. As a model, Geerse used a single session of unpredictable footshocks to induce long-term stress-sensitisation in rats, mimicking PTSD. He selected rats with low and high open-field locomotor activity, which then underwent a single session of footshocks and were tested for behavioural sensitisation and somatic pain sensitivity 3-4 weeks later. Cardiovascular sensitisation was also investigated using a noise challenge two weeks after footshocks, followed by a transient colonic inflammation period, and a second noise challenge 4 weeks after footshocks. It appeared that low open-field locomotor activity predicted stress-induced behavioural sensitisation in the noise-test and increased somatic pain sensitivity, as well as blood pressure responses to noise after recovery from colonic inflammation. This suggests that an anxiety-prone personality or passive coping style increases the risk of developing stress-related psychosomatic disorders.

Furthermore, the involvement of the spinal melanocortin (MC) system in visceral pain was studied, since the neural mechanisms of visceral pain are unclear. A permanent intrathecal catheter was implanted in the spine for infusion of drugs and the duodenal distention-evoked blood pressure response was used as read-out parameter. Pretreatment with an MC3/4-receptor antagonist, resulted in a steeper volume-response curve than infusion of saline, suggesting that the endogenous MC-system may inhibit transduction of painful stimuli originating from the viscera. An MC3/4-receptor agonist, however, had no effect. Spinal treatment with morphine resulted in a significant reduction of the blood pressure response at all distention volumes, which supports the notion that it is pain-related, and further validates the duodenal distention model as a model for visceral pain.

Finally, Geerse investigated whether conditioned taste aversion (CTA) against a sucrose solution, could be used as an alternative measure of duodenal pain. Secondly the effect of spinal morphine on CTA was studied. CTA could be induced by a single, 20-minute duodenal distention, which did not induce passive avoidance behaviour in a light-dark box. Spinal infusion of morphine itself induced CTA, suggesting that the model is unsuitable to investigate spinal pharmacological modulation of visceral pain. Since CTA is a complicating factor in the field of chemotherapy in cancer patients and spinal morphine causes nausea and vomiting in humans, CTA may also complicate spinal drug treatment or anaesthesia.

Gert-Jan Geerse (May 31, 1978, Ede) Secondary education, 1996 (Christelijk Streeklyceum, Ede); Human Nutrition, 2001 (Wageningen University). From 2002 till 2006 he worked on the project as described at the Dept of Pharmacology and Anatomy.

2006-19

June 7, 2006

M. Van 't Wout

The nature of emotional abnormalities in schizophrenia

E.H.F. De Haan, R.S. Kahn, A. Aleman, R.P.C. Kessels  
supervisors

2006-20

June 15, 2006

(information, see Rudolf Magnus Bulletin 22 – April 2006)

M.L.D. Broekman

AAV vectors as gene delivery vehicles in the central nervous system

J.P.H. Burbach, X.O. Breakefield, M. Sena-Esteves  
supervisors

2006-21

Anxiety knocked-in

June 16, 2006

Meg J.V. Van Bogaert

Predisposed to anxiety

B. Olivier, L. Groenink, R.S. Oosting  
supervisors

Anxiety disorders are prevalent and characterized by behavioural and autonomic symptoms. Meg Van Bogaert used 5-HT<sub>1A</sub> receptor knockout mice to investigate the role of this receptor in stress and anxiety, and found that genetic background of the mice had profound effects on the anxiety phenotype. Pharmacological disturbance of 5-HT<sub>1A</sub> receptor functioning during postnatal development initiated increased levels of anxiety in adult mice.

Anxiety disorder patients not only suffer from psychological symptoms, but also display physiological changes in their autonomic nervous system. Van Bogaert investigated the role of 5-HT<sub>1A</sub> receptor in stress and anxiety, and the interaction with GABA<sub>A</sub> receptors. She used a 5-HT<sub>1A</sub> receptor knockout mouse (1AKO) in 3 genetic background strains (129S6, B6, SW). Differences in autonomic parameters (body temperature and heart rate) as well as in activity levels were observed between the 3 strains in circadian rhythm experiments and stress-induced responses. 129S6

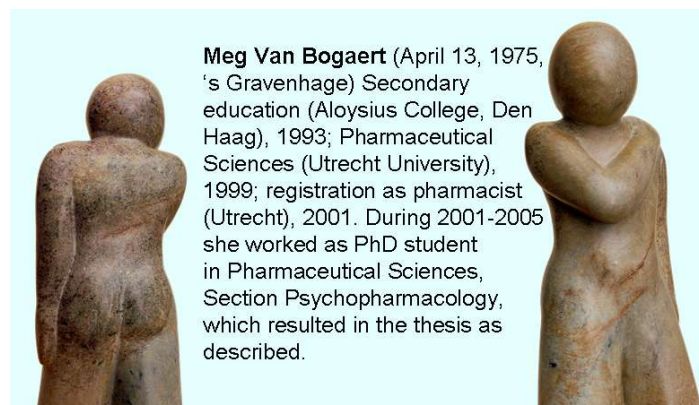
mice appeared the most anxious strain, whereas behavioural changes were present principally on the SW background. Pharmacological differences in sensitivity to anxiolytic drugs were also observed between the genetic backgrounds. Autonomic parameters showed no differences between wild type and 1AKO mice in any strain. These results led to the conclusion that 5-HT<sub>1A</sub> receptors might, to a modest extent, be involved in processes underlying anxiety-related behaviour.

Differences between wild type and 1AKO mice in pharmacological sensitivity were primarily observed in the SW strain: 1AKO mice showed reduced sensitivity towards the anxiolytic-like effects of benzodiazepines. The findings in 1AKO mice on different genetic backgrounds led to the idea that changes in GABA<sub>A</sub> receptor sensitivity in the SW strain were responsible for its anxious phenotype. By chronically blocking 5-HT<sub>1A</sub> receptors during postnatal development, effects on anxiety at adult age were assessed. Anxiety levels similar to 1AKO mice were observed already after 7 days treatment with a 5-HT<sub>1A</sub> receptor antagonist, and increased anxiety levels continued until adult age. Furthermore, these pharmacologically treated mice also showed reduced benzodiazepine sensitivity, indicating a neurodevelopmental influence of 5-HT<sub>1A</sub> receptors on GABA<sub>A</sub> receptor functioning. Hence, disturbed 5-HT<sub>1A</sub> receptor functioning during postnatal development most likely initiates increased levels of anxiety in adult 1AKO mice, possibly by changes in the GABA<sub>A</sub> receptor subunit development.



cause symptoms and remain undiagnosed. In a small subset of patients the intracranial aneurysm ruptures causing a subarachnoid haemorrhage (SAH), a form of stroke with poor prognosis. Ruigrok performed an association study analysing the gene versican, a gene coding for a structural protein of the ECM, for association with intracranial aneurysms. Several SNPs in strong linkage disequilibrium and haplotypes constituting these SNPs, were found to be associated with intracranial aneurysms. The association for the two SNPs with the most significant associations was confirmed in a second independent cohort of patients.

Ruigrok further analysed a large set of 44 additional candidate genes, involved in the maintenance of the integrity of the ECM, for association with intracranial aneurysms. In fifteen of these 44 genes, SNPs associated with intracranial aneurysms were found. In particular SNPs in *serpine1*, transforming growth factor (*beta* induced), and *perlecan* had the strongest associations. In a second independent cohort, the association for the *perlecan* gene was replicated. Combining the two cohorts, the associations for the *serpine 1*, *fibronectin*, and *collagen type 4A1* genes remained. Ruigrok's findings indicate that variation in genes involved in the maintenance of the integrity of the ECM of the arterial wall plays a role in susceptibility to intracranial aneurysms, which supports her hypothesis that diminished maintenance of the ECM of the arterial wall is important in the development of intracranial aneurysms.



**Meg Van Bogaert** (April 13, 1975, 's Gravenhage) Secondary education (Aloysius College, Den Haag), 1993; Pharmaceutical Sciences (Utrecht University), 1999; registration as pharmacist (Utrecht), 2001. During 2001-2005 she worked as PhD student in Pharmaceutical Sciences, Section Psychopharmacology, which resulted in the thesis as described.

2006-22

## Genes blowing balloons

June 16, 2006

Ynte M. Ruigrok

From intracranial aneurysm to subarachnoid hemorrhage: Unraveling the genetics

G.J.E. Rinkel, C. Wijmenga  
supervisors

**Intracranial aneurysms are probably caused by interactions of several genes and environmental factors. Ynte Ruigrok hypothesized that disruption of the extracellular matrix (ECM) of the arterial wall is a likely factor in the pathogenesis of intracranial aneurysms. By genetic analysis in large numbers of patients she demonstrated that candidate genes, each involved in the maintenance of the integrity of the ECM, are indeed associated with intracranial aneurysms.**

Approximately 2% of the general population harbours an intracranial aneurysm. Most intracranial aneurysms do not

**Ynte Ruigrok** (July 15, 1973, Wijk bij Duurstede) Secondary education, 1991 (Christelijk Gymnasium, Utrecht); study Medical Biology 1991-1995; Medicine (Utrecht University), MD 1999. Since 2001 she works as a resident in Neurology; during 2002-2006 she performed the work as described in her thesis.

2006-23

June 19, 2006

W.B. Zbijewski

Model-based image reconstruction in X-ray computed tomography

M. Viergever, F.J. Beekman  
supervisors

2006-24

July 7, 2006

J.E. Van den Bosch

Prediction of postoperative nausea and vomiting

C.J.Kalkman, K.G.M.Moons, Y.Vergouwe, W.A.Van Klei  
supervisors

**Rudolf Magnus Graduate School Certificates**

The Director and the Research Training Committee of the Graduate School took pleasure in presenting the Graduate School Certificate to the following Doctors: Anikó Körösi (April 26, 2006) and Renate Siebes (May 19, 2006)

**Gerda Croiset Appointed Professor**

Gerda Croiset (education coordinator, Division of Neuroscience) was appointed as Professor of Education (graduate-entry programme) on June 1, 2006.

**Royal Honours for Cees Van Huffelen**

Cees Van Huffelen received Royal Honours and was appointed Officer of Oranje Nassau on April 28 for his contribution to research and education.

**Jacob Vorstman wins Tegelaers Travel Stipend**

Jacob Vorstman (MD, PhD student, Child- and Adolescent Psychiatry) has won the Tegelaers Travel Stipend of € 2,500. The Stipend is awarded yearly by the Working Party on Somatic Causes of Mental illness.

**Thóra Hafsteinsdóttir wins Anna Reynvaan Prize**

Thóra Hafsteinsdóttir was awarded with the Anna Reynvaan Research Prize on May 8, for the best paper in Nursing Sciences in the Netherlands in 2005. The Prize of € 2,500 was awarded for her article in *J Neurol Neurosurg Psychiatry* (76: 788-792).

**Award Freek Beekman for best article**

The Journal of Nuclear Medicine has presented Freek Beekman (Pharmacology and Anatomy and Dept Nuclear Medicine) with the 1st place award for outstanding Basic Science Investigations for his article on the *U-Spect-1* (*J Nucl Med*, 2005, 46: 1194-1200). The Award was presented on June 5 at the annual meeting of the Society of Nuclear Medicine in San Diego.

**FIGON Award for Maike Brans**

The Netherlands Federation for Innovative Drug Research (FIGON) has presented on May 11 the 'FIGON Award for Technical Excellence' to Maike Brans (research technician Pharmacology and Anatomy, photo below). The Award, a certificate and € 1,000, is yearly presented to the laboratory worker who performed the most innovative and important contribution to drug research in the Netherlands.

**Irene Van der Schaaf wins the Girard de Miolet van Coehoorn Award**

On May 16, Irene Van der Schaaf (Neurology and Dept Nuclear Medicine) received the Girard de Miolet van Coehoorn Award (€2,000) for her PhD thesis (*cum laude*).

**June 7, Genetics / ABC Neurogenomics Seminar**

**Robert Williams** (Dept Anat. Neurobiol., Univ. Tennessee, Memphis, USA) 'A Paradigm Shift in Mouse Genetics'  
*Roze collegezaal*, UMC Utrecht, 16.00-17.00

**June 7, Rudolf Magnus Seminar**

**Jeffrey Dalley** (Univ. Cambridge, UK) 'Modelling impulsivity and substance abuse disorders in rats: new insights using positron emission tomography'  
Stratenum, room 4.208, 16.00-17.00

**June 14, Behavioural Phenotyping Meeting**

**Mechiel Korte** (Psychopharmacology) 'Why are females far more vulnerable to depression than males?'  
Went Building, Utrecht, room N022, 13.00-14.00  
Contact, M.J.H.Kas@med.uu.nl

**June 16, Symposium Gene Delivery in the CNS**

'Viral vectors as gene delivery vehicles in the nervous system', Keynote speakers, **Xandra Breakefield**, and **Miguel Sena-Esteves** (both Massachusetts General Hospital/Harvard Medical School)  
'Zaal C', Ruppert Building, Leuvenlaan 19, 13.30-17.00  
programme, <http://www.rudolfmagnus.nl>

**June 16, Neurology Seminar**

**Eleonora Aronica** (Neuropathology, AMC Amsterdam) 'What determines the sensitivity of epilepsy towards medication? The role of genes and multidrug transporters' (in Dutch)  
Colloquium room, C3 Oost, UMC Utrecht, 12.45-13.30  
Contact, C.E.vanderWijngaart@umcutrecht.nl

**June 22, Psychopharmacology Colloquium**

**Manon Boeschoten** (Child and Adolescent Psychiatry UMC Utrecht) 'Abnormal processing of spatial frequency information in social and non-social information in pervasive developmental disorder'  
Went Building, Utrecht, Room N016, 12:00-13:00

**July 7, Neurology Seminar**

**Nens Van Alfen** (Neurology, UMC St. Radboud Nijmegen) 'Neuralgic amyotrophy: a practical update' (in Dutch)  
Colloquium room, C3 Oost, UMC Utrecht, 12.45-13.30  
contact C.E.vanderWijngaart@umcutrecht.nl

**July 10-12, fMRI Course**

Starters' course, fMRI in theory and practice.  
Utrecht, programme and registration, <http://www.fmri.nl>

**July 13, Psychiatry Seminar**

**Robert I. Block** (Dept Anaesthesia, University of Iowa, Iowa City, USA) 'Does chronic marijuana use affect the human brain and human cognition?'  
*Aula*, Psychiatry (A01), UMC Utrecht, 16.00-17.00, [gjager@azu.nl](mailto:gjager@azu.nl)

**August 28-29, Rudolf Magnus-Helmholtz Summerschool**

Conference Centre Ottone, Kromme Nieuwegracht 62, Utrecht.  
Programme, <http://www.rudolfmagnus.nl>

**September 8-9, Brain Days**

A two-days meeting with (inter)national experts on the theme, 'Dynamics of (re)organisation'.  
UMC Utrecht, programme, see <http://www.rudolfmagnus.nl>

**November 8, Rudolf Magnus Symposium**

Including the Rudolf Magnus Lecture 2006 by **Frans De Waal** (Emory Univ. Atlanta, USA) and the announcement of the winner of the Rudolf Magnus Research Award 2006.  
UMC Utrecht, 13:30-17:15., see <http://www.rudolfmagnus.nl>  
Contact, [m.vandenadort@med.uu.nl](mailto:m.vandenadort@med.uu.nl)