



# Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 15  
September 2005

## interview

### Translational research on anorexia nervosa

Patients with anorexia nervosa are possessed by a morbid fear of becoming fat and often show excessive hyperactivity. Jacquélien Hillebrand investigated several biological aspects of this disease using the activity-based anorexia model in rats. She showed that olanzapine, an atypical antipsychotic drug, reduced the characteristic hyperactivity of the anorexic rats as well as in anorexia nervosa patients. Interfering with two other aspects, the hormone leptin and heat, also appeared effective in reducing behavioural hyperactivity in rats.

Whereas reduced food-intake is the most characteristic hallmark of anorexia nervosa (AN), the wider clinical, genetic and behavioural aspects of the disease are very complex. A number of these aspects can be faithfully reproduced in the activity-based anorexia (ABA) model in rats. In this model rats receive food for one hour a day and are allowed to run in a wheel voluntarily. Although the rats are able to eat enough within an hour to maintain a healthy body weight, they eat less than the required amount and demonstrate increased wheel running, as a consequence of which they lose body weight and subsequently show hypothermia, activation of the HPA axis and decreased leptin levels, similar to AN patients. Each of these characteristics of the ABA model could be further studied in order to get more insight in aetiology and treatment of AN.



Hillebrand demonstrated that voluntary access to a warm plate in the ABA model reduced hypothermia and hyperactivity, and slowed down body weight loss in rats (*Physiol. Behav.*, June 2005). Because of this result, Hillebrand suggests that maintaining body warmth may be beneficial for AN patients. In a separate study, Hillebrand investigated if leptin treatment would influence development of hyperactivity. Rats were treated chronically with leptin while exposed to the ABA-inducing regime. The results showed that leptin treatment indeed reduced hyperactivity in ABA rats. However, at the same time the rats showed increased thermogenesis and decreased food intake, and the overall result was an even stronger negative energy balance (*Biol. Psychiatry*, July 2005). Hillebrand concludes that leptin might still have potential as a medication of severe hyper-activity in AN patients, although great caution should be taken regarding energy intake and temperature regulation.

The results of the following study were even more interesting from a clinical point of view. When she administered the atypical antipsychotic olanzapine to rats, it reduced their hyperactivity, hypothermia and body weight loss, thereby slowing down the development of ABA (*Biol. Psychiatry*, epub July 2005). When used in hyperactive AN patients in a small open label study, olanzapine significantly reduced hyperactivity levels. These results seem to warrant larger controlled studies to establish if AN patients can benefit from olanzapine prescription.

Hillebrand presently participates in an ongoing multidisciplinary collaboration on translational research on AN, involving Roger Adan (molecular pharmacologist), Martien Kas (behavioural biologist), Mariken de Krom (molecular biologist), Annemarie Van Elburg and Wijbrand Hoek (psychiatrists). She is responsible for organizing clinical research aimed at determining the role of biological factors in the development, treatment, and recovery of AN.

Jacquélien J.G. Hillebrand (Nutrition and Health, Wageningen University, 2000) worked as a PhD-student in the Department of Pharmacology and Anatomy under supervision of Roger Adan and Martien Kas. Her thesis, entitled, "Hypothalamic signalling in and animal model of anorexia" (2005), included the papers as described in the interview. Presently she is a postdoc at Rintveld Eating Disorders (Altrecht GGZ, Utrecht).

## PhD theses

2005-24

September 7, 2005

S.I. Correia de Oliveira Santos

Seeing the invisible

B.A. Van Oost, J.T. Lumeij  
Supervisors

2005-25

Attention on pain

September 8, 2005

Judy (D.)S. Veldhuijzen

Effects of pain and its pharmacological treatment on driving ability and cognition

J.L. Kenemans, B. Olivier, C.J. Kalkman, E.R. Volkerts  
supervisors

Chronic pain hampers cognitive performance in daily life of many patients. Judy Veldhuijzen studied the driving ability of patients suffering from chronic pain and the influence of psychotropic medication on driving, as well as the interaction between chronic or experimental pain and attention. Pain patients had difficulties focussing their attention both in automated tasks like driving and in controlled cognitive laboratory tasks. Medication with amitriptyline in some conditions worsened the performance of pain patients, warranting further safeguarding of its use.

Veldhuijzen used a specially adapted car to assess the driving abilities of sufferers of chronic pain and the effect of medication. Patients were asked to drive a standard highway track of 100 km in real traffic at a constant speed of 95 km/h in the centre of the right lane. A driving instructor with access to dual controls safeguarded the test drive. The deviations from the centre position in the lane were taken as readout for the ability to drive safely. Veldhuijzen found that pain patients drove more unsafely than controls. Also acute medication with amitriptyline worsened their driving abilities. However, chronic (> 2 weeks) use of this medication did not alter driving abilities. Conclusions from these studies are that the effects of pain on safe driving are generally underestimated and that changes in medication may also be potentially dangerous.



Car used in driver's test (courtesy of Judy Veldhuijzen)

Car driving is an automated task. Veldhuijzen also tested the effects of chronic and experimental pain on attention in non-automated cognitive tasks, using electroencephalography (EEG) and Event-Related Potentials (ERP). She tested the effect of pain, induced by immersing the non-dominant hand of healthy volunteers in cold water, while they were performing a visual location task. It appeared that the pain perception was attenuated when more demanding tasks were performed. She also measured the attention capacity in chronic pain patients in primary visual tasks that were 'probed' by visual distractors. Healthy volunteers showed decreasing attention capacity with increasing difficulty of the test, but chronic pain patients showed no capacity problems, indicating that the difficulties that pain patients experience are in focussing their attention, but are not a capacity problem. Acute administration of amitriptyline had adverse effects on the reaction time in patients, but sub-chronic administration had a positive effect on attention capability.

**Judy Veldhuijzen** (January 19, 1975, Tiel). Secondary school (RSG Lingecollege, Tiel), 1994; Psychology at Utrecht University, 2000. In 2001-2005 she worked as a PhD-student at Psycho-pharmacology (Pharmaceutical Sciences, Utrecht University) on the work described in her thesis. As of October 1, 2005, she will work as a postdoc at the University of Maryland (Baltimore, USA).

2005-26

September 16, 2005

M.C. Toet

Cerebral monitoring in neonatal intensive care

L.S. De Vries, A.C. Van Huffelen, F. Groenendaal  
supervisors

2005-27

Glutamine synthetase as marker

September 23, 2005

Ineke (W.)M. Bos

In search for peripheral markers for epilepsy and ALS – focus on glutamatergic signalling in blood cells

O. Van Nieuwenhuizen, J.P.H. Burbach,  
P.N.E. De Graan  
supervisors

In epilepsy and amyotrophic lateral sclerosis (ALS), glutamate neurotoxicity may play a major role in pathogenesis. To find peripheral markers for ALS and epilepsy, Ineke Bos determined the expression of proteins that are involved in avoiding high extracellular concentrations of the neurotransmitter glutamate in the synaptic cleft in blood cells. Glutamine synthetase (GS) was found a potentially useful peripheral disease marker for both diseases. In ALS patients, the amount of GS protein in platelets appeared enhanced, whereas GS mRNA was decreased in children with epilepsy. The latter appeared independent of treatment by antiepileptic drugs.

Glutamate mediates most of the excitatory synaptic neurotransmission in the brain. High concentrations of extracellular glutamate are neurotoxic and can cause signal spillover to neighbouring synapses. Therefore it is essen-

tial for normal brain functioning that extracellular glutamate levels are kept low. Glia cells tightly control removal of extracellular glutamate from the synaptic cleft by means of glutamate transporters (excitatory amino-acid transporters, EAATs), which is subsequently converted into glutamine by glutamine synthetase (GS). Bos studied EAATs and GS in blood platelets and leukocytes, to determine if the expression of these proteins could be identified as peripheral markers of ALS or epilepsy. She showed that the glial EAAT2 is the predominant glutamate transporter in blood platelets. Her data suggest that the protein levels of GS in platelets, but not of the EAATs, may be a peripheral marker of ALS. Microarray and PCR analysis showed that leukocytes also express genes implicated in glutamatergic signalling. Of all genes implicated in glutamatergic transmission, only GS mRNA expression was significantly reduced in children newly diagnosed with epilepsy. Treatment with anti-epileptic drugs did not restore patient leukocyte GS expression. Bos' data indicate that GS might be a putative early peripheral marker for epilepsy and a target for treatment of epilepsy.

Bos also studied the role of glutamate transporters and GS in experimental epilepsy, the pilocarpine-treated rat. The brains of these rats showed a transient increase in the rat glutamate transporters, GLAST and GLT1, in particular cells of the hippocampus, whereas GS expression was unchanged in these cells. The increased GLAST and GLT1 expression may be related to epileptogenesis.

Ineke Bos (September 4, 1975, Groningen). Secondary education (Wessel Gansfort College, Groningen), 1993; Biotechnology (Noordelijke Hogeschool, Leeuwarden), 1997; Biology (Groningen University), 2000. From 2001-2005 she worked as PhD student on the work as described in her thesis.

2005-28

**September 27, 2005**

**D.J. Russell**

**The gross motor function measure: impact on childhood disability research and clinical decision-making**

**P.J.M. Helders, P.L. Rosenbaum, J.W. Gorter**  
supervisors

2005-29

**Autistic children see things differently**

**September 29, 2005**

**Manon A. Boeschoten**

**Global and local information processing in autism**

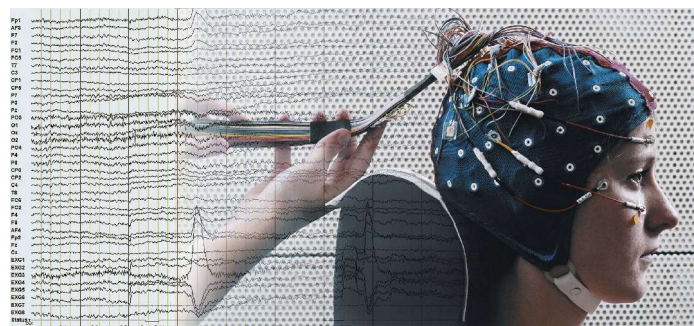
**H. Van Engeland, C. Kemner, J.L. Kenemans**  
supervisors

Autism is often accompanied by specific abnormalities in visual information processing, for instance of faces. Boeschoten aimed to identify the underlying neurophysiological mechanism. By event-related potential (ERP) and dipole source studies in healthy controls and children with pervasive developmental disorder (PDD), she found that abnormal face processing in PDD was associated with abnormal processing of spatial frequency information. Her data imply that abnormalities in visual information processing may play a major role in social perception deficits in PDD.

Studies indicated that autistic or PDD individuals process faces differently than healthy controls. While healthy controls process faces in a global manner and objects in a local manner, PDD subjects seem to process both faces and objects in a local manner. Differences in processing mode for faces seem influenced by the spatial frequency content of faces. Boeschoten tested the hypothesis that the atypical processing mode of PDD subjects for faces was related to abnormal spatial frequency processing. For both healthy controls (adults and children) and PDD children she compared the brain activity in response to faces and objects to the brain activity in response to simple gratings consisting of high and low spatial frequencies. She analyzed brain activity in response to faces and objects of which either the low or high spatial frequencies were removed. And Boeschoten tested whether abnormalities in face processing and the role of spatial frequency processing were related to the social status of faces or expertise. The brain activity related to the processing of faces was compared not only to the brain activity related to the processing of objects but also to that of stimuli for which PDD children had special expertise (for instance sports cars).

In healthy children, as in adults, after 200 ms the processing of the high and low spatial frequency content of faces was associated with different brain areas, but that of objects was not. Instead, at this latency in PDD the processing of different frequency contents of faces was not associated with different brain areas. In PDD the processing of different frequency contents of objects of expertise was not related to activation of specific brain areas. It is not probable that the atypical brain activation pattern in response to faces in PDD is related to lack of face expertise. It is more likely that the diminished specialized processing of low and high spatial frequency information in faces in PDD is related to a basic abnormality in spatial frequency processing. This notion was supported by source localization findings in response to simple gratings in the same subjects. Whereas around 80 ms healthy children, like adults, activated specific brain areas for the processing of gratings consisting of low and high spatial frequencies, PDD children did not. This showed that a diminished specialized processing of spatial frequency information already occurs at an early level in the visual processing in PDD. This implies that the visual pathways in PDD may be less specialized for the processing of specific, spatial frequency related, stimulus characteristics.

**Manon Boeschoten** (October 24, 1975, Apeldoorn). Secondary education, 1994 (Hendrik Pierson College in Zetten); psychology, 1999 (Radboud Univ., Nijmegen). From 2000 to 2005 she worked as a PhD student on the studied global and local information processing in autism as described in her thesis. Presently she works as a postdoc in the subdivision of Child and Adolescent Psychiatry.



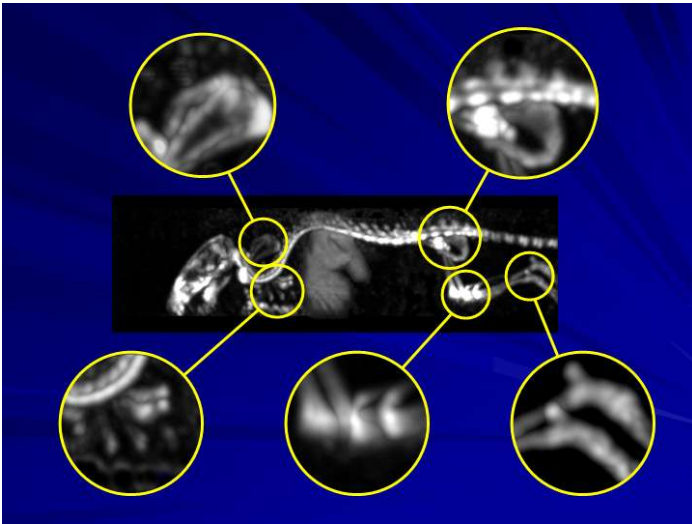
## Rudolf Magnus Graduate School Certificates

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:

Matthijs Vink (June 1, 2005)  
 Gudrun Nys (June 3, 2005)  
 Corine De Rijke (June 7, 2005)

## Brendan Vastenhouw wins Young Investigator Award

On June 21, 2005, Brendan Vastenhouw has won the Young Investigator Award for his presentation at the Society of Nuclear Medicine Meeting in Toronto, Canada. The title of the winning presentation was 'Sub-millimeter total body mouse imaging with U-SPECT-I'. Brendan held his presentation in a special session for nominees in the category 'Instrumentation and Computers'. Brendan is scientific programmer and research associate of Freek Beekman, and is affiliated to the Imaging Science Institute and the Department of Pharmacology and Anatomy of our Institute.



Total body bone scan of a living mouse by Single Photon Emission Computer Tomography using the U-SPECT I (courtesy of Brendan Vastenhouw)

## Leonard Van den Berg Professor

As of July 1, 2005, Leonard Van den Berg (Department of Neurology and Neurosurgery) was appointed as professor of 'Experimental Neurology'.

## Chantal Kemner Professor in Maastricht

Chantal Kemner has been appointed on April 1, 2005, as professor of 'Biological developmental psychology; with emphasis on developmental psychopathology' at Maastricht University for a day a week.



## September 2, Rudolf Magnus Seminar

**Mary F. Dallman** (Univ. California, San Francisco, USA)  
 'The role of corticotrophin releasing hormone: factoring the energy balance?'  
 14:00-15:00, Room 4.208, Stratum Building, UMC Utrecht  
 contact, s.lafeur@med.uu.nl

## September 5, Special Helmholtz Symposium

'On conscious vision'  
 13:00-15:30, Boothzaal, University Library, Heidelberglaan 3  
 programme, <http://www.rudolfmagnus.nl>

## September 5, Rudolf Magnus Seminar

**Hans-Rudolf Berthoud** (Louisiana State Univ., Baton Rouge, USA)  
 'Interactions between homeostatic and reward mechanisms in the control of food intake'  
 16:00-17:00, Room 4.208, Stratum Building, UMC Utrecht  
 contact, r.a.h.adan@med.uu.nl

## September 8, Special Helmholtz Symposium

'Feeling your way through the world: Somatosensory processing of the self and the environment'  
 13:30-17:00, Hall 001, Van Unnik Building, Heidelberglaan 2  
 programme, <http://www.rudolfmagnus.nl>  
 contact, v.maassen@fss.uu.nl

## September 9, UIPS-lecture

**E.L.H. Spierings** (Harvard Medical School, Boston, USA)  
 'Triptans in the treatment of migraine: experimental and clinical pharmacology'  
 14:00-15:00, Room N020, Went Building, Sorbonnelaan 16  
 contact, E.R.Volkerts@pharm.uu.nl

## September 12-13, Rudolf Magnus Summer School

Keynote, **Trevor W. Robbins** (Univ. Cambridge, U.K.)  
 Conference Centre Ottone, Kromme Nieuwegracht 62, Utrecht  
 Programme and registration, <http://www.rudolfmagnus.nl>

## September 14, Seminar

**Trevor W. Robbins** (Univ. Cambridge, U.K.) 'Fractionating impulsivity; neural and neurochemical substrates'  
 12:00-13:00, location to be announced  
 contact, m.vadenadort@med.uu.nl

## September 20, Rudolf Magnus Seminar

**Harm Krugers** (Univ. Amsterdam) 'Corticosteroid modulation of hippocampal synaptic efficacy'  
 13:00-14:00, Room 4.208, Stratum Building, UMC Utrecht  
 contact, g.m.j.ramakers@med.uu.nl

## September 28, Rudolf Magnus mini-Symposium

'Face and spatial frequency processing in autism'  
 13:30-17:00, Van Geuns Building (11<sup>th</sup> floor), Bolognalaan 48  
 programme, <http://rudolfmagnus.nl>, contact, c.kemner@azu.nl

## November 24-25, Annual Meeting PhD students

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

## November 30, Rudolf Magnus Symposium 2005 and Rudolf Magnus Research Award 2005

Keynote, **Michael Gazzaniga** (Hanover NH, USA)  
 'Brain Mechanism of Conscious Experience'  
 13:30-18:00, Green Lecture Hall, UMC Utrecht  
 Programme, <http://www.rudolfmagnus.nl>  
 Deadline for nominations Research Award, 23 September 2005

## November 28 – December 2, Introductory Course for PhD students

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