



# Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 14  
June 2005

## interview

### The science of phenotyping

**On May 20<sup>th</sup>, 2005, Frauke Ohl, professor of Laboratory Animal Science, held her inaugural address. She and her group are part of the Programme 'Emotion and Cognition' of the Faculty of Veterinary Medicine, which has just joined our Institute. Time to learn in some detail what she has in stock for our joint research efforts.**

The title of Ohl's inaugural address 'Animal and Science' mentions animals, and not laboratory animals. This simple distinction characterises the attitude of Ohl towards animals as used in research. Her point being that we should take more interest in the animal itself and not just in the use of the animal, for sake of both animal and scientist. Ohl's research concentrates on behavioural phenotyping of inbred and genetically modified mouse strains, which is a two-edged sword. If animals, on the one hand, are housed in such a way that they can display their full repertoire of behaviours their welfare is improved. On the other hand, close characterisation of (differences in) behaviours will refine our current animal models to a new level especially with respect to behaviour.



(Photograph, MCD, Faculty of Veterinary Medicine, Utrecht)

Classically, many tests of animal behaviour seem rather simple and often do not allow proper interpretation of the results. Ohl: "Although attempts have been made to develop standards in behavioural phenotyping procedures,

fundamental differences exist between laboratories regarding testing procedures and criteria to assess phenotypic characteristics. Most of the procedures are unidimensional, being predictive for one specific motivational system, such as avoidance behaviour or exploration. It is virtually impossible to assess the biological relevance of the data obtained. Biological relevant behaviour always results from interacting motivational systems. E.g., differences in behaviour of a mouse in the elevated-plus-maze may be due to different exploratory strategies – only the test set-up does not allow the animal to display those strategies. An example of such an ethological approach, is the modified hole board test, which plays a central role in our behavioural screening protocols for mice, enabling us to investigate a variety of motivational systems by use of a single test. This type of test not only allows for the identification of alterations in avoidance behaviour, locomotor activity, exploration, social affinity, and feeding, but also for conclusions whether or not those alterations are adaptive (non-pathological) or maladaptive (pathological)."

Ohl and her group are part of the Department of Animal, Science and Society of the Faculty of Veterinary Medicine, which also includes Berry Spruijt, with whom Ohl closely collaborates and who has also joined the Institute (see *News*). Ohl's scientific interests are focussed on anxiety in all its aspects, and she already closely collaborates on behavioural phenotyping with Berend Olivier and Martien Kas. Therefore the inclusion of Ohl's research in the Section Behavioural Genomics seems a logical choice. One of her ambitions in the long run is to standardise behavioural phenotyping of mice and to create public databases on phenotyping procedures and data.

Frauke Ohl (Biology, Univ. Kiel, Germany, 1993). From 1996 until 1999 she performed her PhD project at the German Primate Centre, Göttingen, Germany (Prof. Dr. E. Fuchs) entitled, 'Stress-induced changes on cognitive functions in male tree shrews'. Subsequently she was postdoc (2001-2002) and head of the research group 'Behavioural Phenotyping' (2002-2003) at the Max-Planck-Institute of Psychiatry, Munich, Germany. She was appointed as professor of Laboratory Animal Science at the Faculty of Veterinary Medicine, Utrecht (January 1, 2004).

2005-21

### No breaks in schizophrenia

June 1, 2005

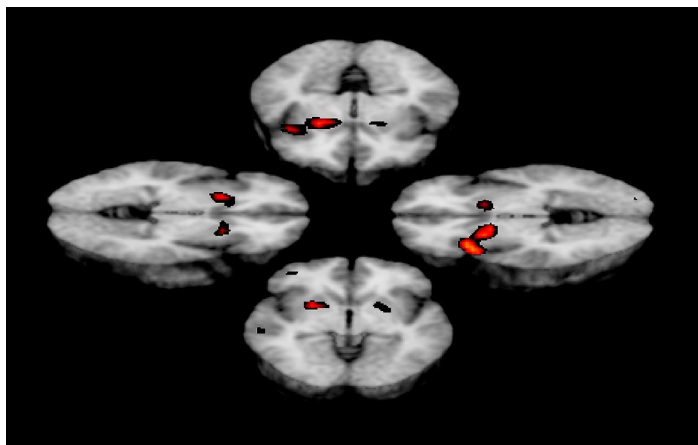
Matthijs Vink

On inhibition: Studies in schizophrenia

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

**Schizophrenic patients seem unable to filter out irrelevant information in daily life. 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 is 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.**

Vink studied perceptual inhibition in healthy controls and schizophrenic patients. Schizophrenic patients are thought to be impaired in filtering out irrelevant information that can cause an 'information overload', which may underlie several clinical symptoms, such as thought disorders or hallucinations. To measure the ability to filter out irrelevant information, Vink developed a spatial task, in which subjects have to press the button that corresponds to the location of the larger (i.e. target stimulus) of two simultaneously presented dots. It has been consistently shown that in healthy controls, presenting relevant information (e.g., a target stimulus) in a location which was previously irrelevant (e.g., occupied by a distracter stimulus) causes a slowing in responding to that relevant information ('negative priming'). The main finding was that schizophrenic patients show a reduced spatial negative priming effect compared to matched healthy controls. These data provide evidence for a reduced ability to distinguish relevant from



Similar striatal activation (red) during four different task conditions, showing that the striatum has a function beyond inhibition and execution of motor responses (Illustration, Matthijs Vink).

irrelevant information in schizophrenic patients, which probably underlies clinical symptoms of attentional dysfunction.

Motor inhibition in schizophrenia was investigated by Vink in an fMRI study, which examined what happens when controls, schizophrenic patients and their unaffected siblings, have to inhibit an automated response. Vink investigated whether impaired inhibitory control is associated with abnormal striatal activation. In healthy controls, striatal activation increased proportionally to the likelihood of having to inhibit a response. In contrast, in both schizophrenic patients and their siblings, striatal activation was unaffected by this likelihood. The level of striatal activation was reduced in the patients as compared to controls. Behaviourally, only controls and siblings became more cautious in responding, and consequently became more accurate in inhibiting their response as the likelihood of having to inhibit the response increased. Thus, despite a normal behavioural response in the first-degree relatives, Vink found their striatal activation to be abnormal. This suggests that functional brain measures may be a sensitive marker of (genetic) risk factors for the development of schizophrenia.

**Matthijs Vink** (December 22, 1976, Hengelo (O.)). Secondary school, 1995 (Menso Alting College, Hoozeveen); Psychology, Groningen University, 1999. From 2000 until 2005 he performed the work as described in his thesis. Presently he works as a postdoc in the subdivision of Psychiatry, UMC Utrecht.

2005-22

### Making sense of stroke

June 3, 2005

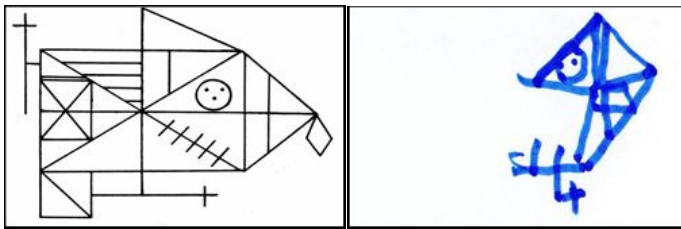
Gudrun M.S. Nys

The neuropsychology of acute stroke

L.J. Kappelle, E.H.F. De Haan, M.J.E. Van Zandvoort,  
P.L.M. De Kort  
supervisors

**Cognitive and emotional manifestations often occur after stroke, which may be overlooked in clinical practice. Gudrun Nys performed a longitudinal study in patients with a first symptomatic stroke. Cognitive disorders within the first three weeks after stroke appeared powerful predictors of long-term dependence in daily life, cognitive impairment, and reduced quality of life. Cognitive testing has additional independent prognostic value to other medical indicators. Therefore, Nys' work warrants detailed neuropsychological assessment as a standard evaluation in the stroke unit.**

The patients were admitted to stroke units of three hospitals in the Netherlands in a period of three and a half years. Nys examined the patients in the cohort with a mean interval of eight days post-stroke. In addition to a neuropsychological examination covering multiple cognitive domains, demographic data, lesion characteristics, clinical factors at admission, and pre-existent vascular risk factors were recorded. The follow-up examination was done after six to ten months, in which Nys examined cognitive, functional, and emotional outcome, and quality of life. A demographically matched healthy control group was also examined.



A drawing (Rey-Osterrieth Complex Figure) by a patient with unilateral visual neglect following right-sided stroke. Neglect is a disabling disorder in which patients frequently ignore the left half of the world (Illustration, Gudrun Nys).

Cognitive disorders in the first three weeks of stroke appeared powerful predictors of long-term dependence in daily life, long-term cognitive impairment, and a reduced quality of life, and have additional prognostic value to other well-known medical predictors. Particularly disorders in executive functioning and visual perception and construction predict poor outcome in the long term. Whereas it has previously been suggested that depressive pathology after stroke results in cognitive impairment (the so-called pseudo-dementia), the studies by Nys show that cognitive impairment in the early stage may also result in depressive symptoms in the long term. Altogether, based on the powerful predictive value of acute cognitive predictors, Nys recommends a detailed neuropsychological assessment as a standard evaluation on the stroke unit.

Only recently, stroke has become a treatable disease by means of thrombolytic intervention, which is aimed at restoring cerebral blood flow before major ischaemic brain damage has occurred. Nys demonstrated for the first time that thrombolytic treatment administered within the first three hours after stroke does not only exert a beneficial effect on basic dependence in daily life activities, as previously demonstrated, but also on more complex dependence in daily life, such as household management or grocery shopping. In contrast, Nys could not demonstrate a beneficial effect of the treatment on long-term cognitive outcome. Nevertheless, her findings emphasise the need for immediate care in neurological services. Public education is essential to learn to recognise a stroke and to seek immediate care.

**Gudrun Nys** (October 31, 1977, Roeselare, Belgium). Secondary education, 1995 (Bisschoppelijk Lyceum, Roeselare, Belgium), Psychology, Catholic University, Leuven, Belgium, 2000. From 2001 till 2005 she worked at the UMC Utrecht and the Dept Psychonomy, Utrecht University, on her thesis project. Now she is a postdoc at the Department of Psychonomy, Utrecht University.

2005-23

## Neurobiology of anorexia

June 7, 2005

**Corine E. De Rijke**

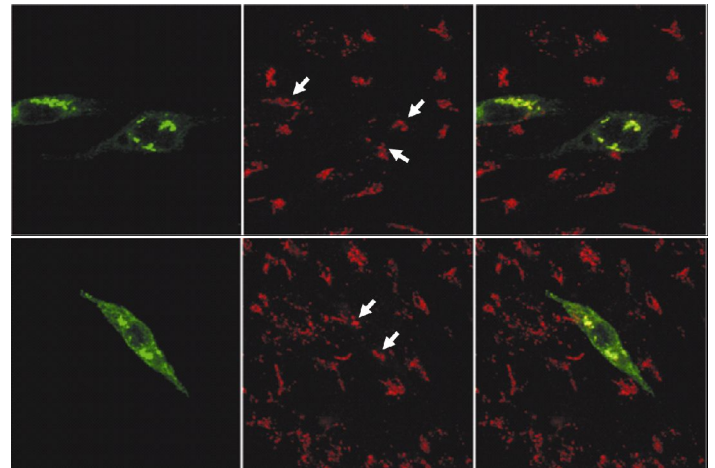
**Molecular studies on the melanocortin system in relation to anorexia**

**R.A.H. Adan**  
supervisor

**The melanocortin system is involved in regulation of feeding behaviour and energy balance. Corine de Rijke investigated the involvement of this system in**

**Anorexia Nervosa, a disease that involves 0.3% of young women, and leads to the untimely death of about 10% of patients.**

De Rijke studied the effects of a polymorphism in AgRP that has been associated with Anorexia Nervosa. AgRP is the endogenous inverse agonist of melanocortin receptors and stimulates food intake. Since the polymorphism had no effect the cellular localisation or function of the peptide, the data suggest that expression levels of AgRP in carriers of the AgRP gene variant is decreased. De Rijke found evidence suggesting that a polymorphism in the melanocortin 3 receptor may be involved in Anorexia Nervosa, but this has to be confirmed in a larger study.



Two forms of AgRP, polymorphic at amino acid position 67 (Ala67; top, Thr67; bottom), co-localise to the Golgi apparatus of transfected cells (arrows). Immunofluorescence, green; AgRP, red; Golgi marker (Illustration, De Rijke).

She also studied neuropeptide expression in the activity-based anorexia (ABA) animal model. In this model rats have access to a running wheel and are fed for only one hour per day. The presence of the running wheel makes the rats eat less than the maximal amount and lose weight, while inducing hyperactivity. During the development of anorexia in this model, the expression of AgRP was strongly elevated and inversely correlated with body weight. Previously it was found that administration of AgRP increases survival of rats in ABA, suggesting excessive melanocortin signalling in ABA, which promotes the development of anorexia. As it was also found that following an acute stressor (foot shocks) AgRP expression in rats is decreased, De Rijke speculates that during the development of ABA AgRP expression is blunted through stress induced by the model, leading to relatively excessive melanocortin signalling and concomitant hyperactivity, anorexia, and weight loss.

**Corine de Rijke** (April 22, 1977, Alkmaar). Secondary education, 1995 (Christelijke Scholengemeenschap Jan Arentsz, Alkmaar), Chemistry and Pharmacochemistry at 'Vrije Universiteit', Amsterdam, 2000. From 2001 until 2005 she worked on the PhD project as described above. As of May 2005 she is one of the coordinators of the IOP Genomics programme (SenterNovem, Den Haag).

## 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:

Nic Van der Wee (May 13, 2005)  
 Daniel Mathon (May 18, 2005)  
 Nina Van Sorge (May 20, 2005)  
 Steven Bakker (May 31, 2005)

## Institute Grows Further

By decision of the Director of our Institute, the research programme 'Emotion and Cognition, thresholds for emotions as critical factors for adaptation' of the Faculty of Veterinary Medicine has joined the Institute. These researchers join the Section Behavioural Genomics and include professors Berry Spruijt and Frauke Ohl (*see interview*). The inclusion of these investigators in the Rudolf Magnus Institute is the formalisation of an existing collaboration with Martien Kas and Berend Olivier in the field of the genetics of animal behaviour. The admittance of this programme further strengthens our position as a Utrecht University interfaculty Institute, since now members from three Faculties are included, i.e. the Faculties of Medicine, Veterinary Medicine, and Pharmaceutical Sciences. The PhD students of the joining research programme will be included in the Rudolf Magnus Graduate School.

## Neurogeneticist Appointed

Roel A. Ophoff is appointed as associate professor at the Division Biomedical Genetics. He will also work within the Department of Pharmacology and Anatomy of our Institute and will, in close collaboration with our Institute, further shape the field of Neurogenetics in Utrecht. Ophoff is presently at UCLA and will start coming autumn.

## Denys and Sommer receive Award

On May 18<sup>th</sup>, 2005, Damiaan Denys en Iris Sommer, Department of Psychiatry, have both independently received the award of the De Girard de Miolet van Coehoorn Foundation for their PhD theses. The award is presented yearly to young scientists, selected from those who receive their PhD diploma 'cum laude'.

## Note

The next issue of the Rudolf Magnus Bulletin will appear on September 1, 2005.



## June 2, 2005, Lecture

**Caroline Van Heugten** (Institute for Rehabilitation Research, Univ. Maastricht) 'Cognitive Revalidation, who is learning what?' (in Dutch)  
 16:30-17:30, 'Rembrandtzaal', De Hoogstraat, Rembrandtkade 10, Utrecht  
 (contact, kenniscentrum@dehoogstraat.nl)

## June 9, 2005, Rudolf Magnus Seminar

**Patricia di Ciano** (Univ. Cambridge, U.K.) 'Multiple mechanisms of associative control over drug seeking: a behavioural and neuroanatomical analysis'  
 13:00-14:00, Room 4.208, Stratum Building, UMC Utrecht  
 (contact, h.c.vanvlaardingen@med.uu.nl)

## June 16, 2005, Rudolf Magnus Symposium Behavioural Genetics

**Jonathan Flint** (Oxford), **Dorret Boomsma** (Amsterdam), **Berry Spruijt** (Utrecht), **Bobby Koeleman** (Utrecht) **Martien Kas** (Utrecht). Admittance to the symposium is free, however registration is required.  
 12:30-17:00, 'Groene zaal', Went Building, Sorbonnelaan 16, Utrecht  
 Programme and registration, <http://www.rudolfmagnus.nl>  
 Attendance at the symposium will be awarded by the Rudolf Magnus Graduate School by 1 credit.

## September 12-13, Rudolf Magnus Summer School 2005

Keynote, **Trevor W. Robbins** (Univ. Cambridge, U.K.) 'Neural systems of emotion: insights from animal and human studies'  
 Conference Centre Ottone, Kromme Nieuwegracht 62, Utrecht  
 Programme and registration, <http://www.rudolfmagnus.nl>  
 Attendance including presentation at the Summer School will be awarded by the Rudolf Magnus Graduate School by 2 credits.

## November 24-25, 2005, Annual Meeting PhD students

Conference Centre Woudschoten, Zeist  
 Information and registration, <http://www.rudolfmagnus.nl>  
 Attendance including presentation at the Annual Meeting will be awarded by the Rudolf Magnus Graduate School by 2 credits.

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

Keynote, **Michael Gazzaniga** (Hanover NH, USA) 'Brain Mechanism of Conscious Experience'  
 13:00-18:00, UMC Utrecht  
 Programme and nominations for the Research Award, <http://www.rudolfmagnus.nl>

## November 28 – December 2, 2005, Introductory Course for PhD students

Information and registration, <http://www.rudolfmagnus.nl>  
 The course is accredited by the Rudolf Magnus Graduate School of Neuroscience and will be awarded by 5 credits.