



Rudolf Magnus Institute of Neuroscience

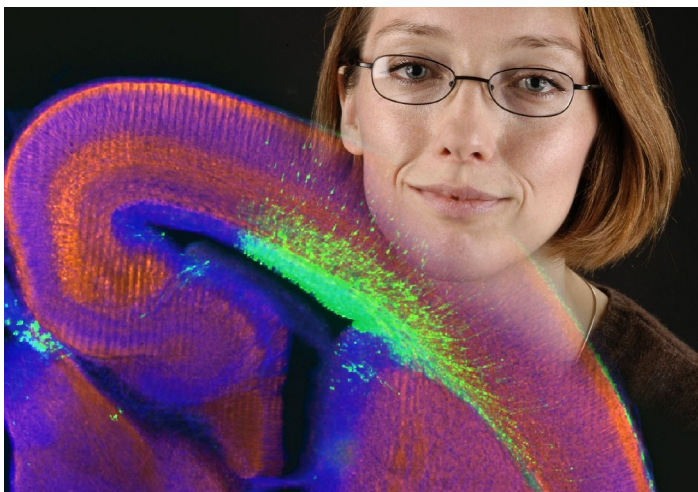
Rudolf Magnus Bulletin 13
May 2005

interview

Making up your mind

... is the somewhat provocative title of the VENI grant that Sharon Kolk has received for her original and innovative research proposal. While reading through this interview you will see why the committee in charge of selecting the winning VENI grants 2005 had no trouble making up its mind regarding this project.

The subtitle of the project reveals the specific goal; 'Molecular determinants in the development of the mesocortical circuitry'. The central question is how the axons of neurones find their way around in the developing brain, ending up making connections to neurones in the right structures. As Kolk explains these neuronal outgrowths are guided by various guidance molecules, proteins that often act as ligands and receptors. These molecules function context specific, they need to be expressed at the right time, at the right position, and in the right combinations. Kolk has narrowed down the general questions regarding this phenomenon to a particular neuronal circuit, the mesocortical pathway, that can be studied by sophisticated methods. However, the mesocortical pathways is also of particular interest from a more clinical viewpoint.



The mesocortical pathway involves dopaminergic neurones which lie in the ventral tegmental area (VTA) and which form axonal outgrowths ('projections') towards the prefrontal cortex. These projections are of particular interest as they mediate higher cognitive functions, affective/emotional and locomotor behaviours. Miswiring of these projections is

implicated in mental disorders, such as schizophrenia. Kolk will use knock out mouse strains that lack certain homeobox genes, and therefore show a disturbed midbrain development, involving the mesocortical pathway. As a result of these mutations the mice show very specific abnormalities in behaviour and motor functions. Her hypothesis is that these mutants have a disturbed expression of guidance molecules, and therefore are unable to form the right projections from the VTA to the prefrontal cortex.

While she was at Yale University, Kolk learned to master a revolutionary technique, *in utero* electroporation (IUE), which allows transfection of brain cells *in situ* in mouse embryos. The DNA of interest is brought to the desired position in the brain by a micropipette and is then 'shot' into the cells by electroporation using two very small electrodes at opposing sides of the cells that are to take up the DNA. Thus, Kolk is able to transfer the DNA to precisely defined groups of cells in mouse embryos at embryonic days 12.5-15.5 within a sub-millimetre volume, and in up to six embryos per mouse. By carefully localised injections at various timepoints during brain development she plans to express various combinations of neuronal guidance molecules in order to rescue ('cure') the mutant phenotype.

Kolk, "In this way, we may be able to regain lost functions within a perturbed mesocortical pathway which will have great implications in treating disorders associated with dopaminergic control of cortical functions." But, as Kolk is quick to say, "any therapeutic practice is still way off." However, imagine that a particular mental disorder could be corrected by expressing a particular guidance molecule at the right time and position. Wouldn't it be wonderful if you could prevent illness by one injection?

Sharon M. Kolk (Biology, Utrecht University, 1996). She worked at the Nijmegen University (Eric Roubos' group) on her thesis entitled, 'Dynamic expression and regulation of proteins involved in exocytosis'. She worked at Yale University, New Haven, USA, for two and a half years as a postdoc with Maria Donoghue, where she learned to electroporate mouse embryos *in utero*. Since December 2004 she is a postdoc (grant, 'Hersenstichting Nederland') at the Department of Pharmacology and Anatomy in the Section Neurodevelopment.

2005-17

Functional neuroimaging and OCD

May 13, 2005

Nic J.A. Van der Wee

Windows on the brain. Functional neuroimaging studies in obsessive-compulsive disorder

R.S. Kahn, H.G.M. Westenberg, H.J.G.M. Van Megen
supervisors

Using functional neuroimaging techniques Nic Van der Wee investigated several cognitive and neurochemical aspects of obsessive-compulsive disorder (OCD) in drug-naïve patients. He showed a mild dysfunction of the working memory system in OCD to be associated with an altered brain activity pattern. Most interesting was the finding of abnormalities in the dopamine system in OCD, which may lead to new treatment approaches and refinement of current models of OCD.

Patients suffering from OCD have recurrent, persistent and intrusive thoughts or images that cause anxiety or distress and cannot be suppressed (obsessions), and repetitive behaviours or mental acts aimed at reducing the distress or anxiety (compulsions). In oculomotor tasks Van der Wee tested the hypothesis that OCD patients do have in general a lower ability to suppress behaviour. However, OCD patients showed normal error rates on the inhibition tasks, indicating that impaired inhibition is not parsimoniously involved in cognitive disturbance in OCD.

In functional MRI studies Van der Wee tested the spatial working memory of OCD patients and found that the OCD patients performed more poorly than healthy controls. As both groups used their working memory system in a similar way, this malfunction in OCD could not be pinpointed to a specific working memory region. However, the anterior cingulate, involved in strategy and monitoring, was hyperactive in OCD. Patients who responded to pharmacotherapy show improved performance on the working memory tasks, indicating that the spatial working memory deficits are related to the OCD symptomatology.

Involvement of serotonergic systems in OCD has long been suspected, as selective serotonin reuptake inhibitors are often effective in improving symptomatology. Van der Wee however demonstrated that the dopamine system in OCD patients is abnormal. He used a tracer for serotonin and dopamine transporters and measured its densities in regions where the dopaminergic and serotonergic systems are localised, using MRI and SPECT co-registration. OCD patients had significantly higher binding of the tracer in dopamine-rich left basal ganglia regions. In a similar study Van der Wee demonstrated that the dopamine D2 receptor was possibly down-regulated in the left caudate. Both studies suggest that the dopamine system may be more active in OCD patients than in healthy controls.

Nic Van der Wee (March 9, 1965, Bergen op Zoom). Secondary school, 1983 (Roncalli Scholengemeenschap, Bergen op Zoom); Medicine at Utrecht University, 1992. Resident in psychiatry till 1999, UMC Utrecht. The thesis was prepared as member of staff of the Department of Psychiatry, UMC Utrecht, 1999-2002. Presently he works as psychiatrist at the University Hospital, Leiden.

2005-18

Dopamine misfires

May 18, 2005

Daniel S. Mathon

Regulation of the midbrain dopamine system. Alterations induced by genetic mutations.

J.P.H. Burbach, W.H. Gispen, G.M.J. Ramakers
supervisors

The midbrain dopaminergic system has been ascribed a number of functions, including the physiology of reward. Dysfunction of this system can lead to pathological states such as drug addiction. Daniel Mathon examined the midbrain dopamine system of genetically modified mice that lack the μ -opioid receptor. These mice were shown to be relatively insensitive to develop cocaine addiction, which is likely due to an increased inhibition of dopaminergic cell function.

Mathon and others showed that the μ -opioid receptor (MOR) knockout mice have a highly interesting phenotype in that they display a diminished response to the reinforcing properties of drugs of abuse. As MORs have been suggested to regulate the inhibitory and excitatory synaptic input to midbrain dopaminergic neurons in the ventral tegmental area Mathon examined this input and observed an enhanced inhibitory input to dopaminergic cells in MOR knockout mice. He furthermore found that the *in vivo* firing activity of these neurons is decreased and that the dynamics of dopamine output in target areas of these neurons are altered. These findings suggest a decreased amount of dopaminergic neuronal activity in MOR knockout mice, likely resulting from an increased inhibitory input. These changes provide a possible explanation for the 'drug-resistant' phenotype of these mice.

Daniel Mathon (June 2, 1979, Brussels, Belgium). Secondary School, 1996 (Laar & Berg, Laren); Pharmacology at University of Dundee, Scotland 2000. From 2000 until 2004 he worked on the project described in this thesis. November 2004 he started at the Department of Physiology, UCL, London.

2005-19

Antibodies attack neurones

May 20, 2005

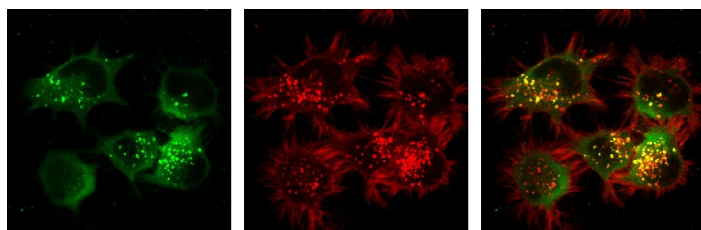
Nina M. Van Sorge

Autoantibodies, Fc receptors, and complement in inflammatory neuropathies. Impact on pathogenesis and therapy

J.H.J. Wokke, J.G.J. Van de Winkel, W-L. Van der Pol, L.H. Van den Berg
supervisors

The Guillain-Barré syndrome (GBS) is characterized by inflammatory damage to peripheral nerves. Nina Van Sorge demonstrated that auto-antibodies against gangliosides expressed by neurons play a critical role in the pathogenesis of GBS. In particular she established a role for IgG receptors in the binding of these auto-antibodies and the subsequent activation of leukocytes, which eventually contributes to nerve damage.

GBS often develops as complication of bacterial infection, such as by *Campylobacter jejuni*. This bacterium carries oligosaccharide structures that are identical to the carbohydrate structures of gangliosides; membrane glycolipids in peripheral neurones. Auto-antibodies against gangliosides develop as response to infection. These auto-antibodies possibly exert their pathogenic effect by interacting with different IgG receptors (FcγR) on inflammatory cells. The studies by Van Sorge provide solid evidence that the pro-inflammatory activity, i.e. leukocyte activating capacity, rather than antibody concentration, is critical for onset and subsequent nerve damage in patients with GBS. Interestingly, FcγR-mediated leukocyte activation by ganglioside-specific IgG was inhibited by addition of therapeutically used pooled gammaglobulin (IVIg).



Anti-ganglioside antibodies of GBS patients (green) bind to neurones (red) in tissue culture (Illustration, thesis Van Sorge)

Polymorphisms in three FcγR, which determine the efficacy of leukocyte activation by IgG antibodies, may predispose for GBS. However, Van Sorge demonstrated that FcγR polymorphisms in humans are not associated with increased susceptibility to GBS. Yet, a segment of chromosome 1 may contain several candidate genes, including FcγR, that influence GBS disease severity.

The occurrence of pathogenic ganglioside-recognizing antibodies following *C. jejuni* infection results from a complex interplay of the individual's predisposition and variation of *C. jejuni* strains. Besides the requirement for the presence of ganglioside-mimicking structures on the bacterium, Van Sorge also defined characteristics of the host innate immune system (dendritic cells in the intestine), and of *C. jejuni* (different glycosylation patterns) that possibly contribute to occurrence of GBS.

Nina Van Sorge (September 17, 1976, Den Haag). Secondary school 1994 (Stedelijk Gymnasium, Arnhem); Pharmacy at Utrecht University, 1998, Pharmacist's diploma, 2001. In 2001-2005 she worked as PhD student on the work described in the thesis. Presently she is a postdoc at the Department of Immunology, UMC Utrecht.

2005-20

Genes in psychiatric disease

May 31, 2005

Steven C. Bakker

Unravelling the genetics of schizophrenia and ADHD

P.L. Pearson, R.S. Kahn, R.J. Sinke
supervisors

Psychiatric disorders such as schizophrenia and ADHD have a large basis in genetics. Steven Bakker studied the possible contributions of known and unknown genes to each of these diseases. For schizophrenia he found that neuregulin 1, RGS4, and

PIP5K2A were associated with the disease. For ADHD he performed a linkage study involving 106 families, and identified two chromosome regions, 7p en 15q, that could contain genes that are involved in the disorder. Thus, both diseases clearly have genetic correlates.

Bakker developed a new method for analysis of pooled DNA samples by microsatellite analysis. Using this technique, Bakker sought to determine associations of genes involved in dopamine neurochemistry with schizophrenia. Twelve separate genes were systematically screened, but no associations were found. Further association studies with 5 more candidate genes were more successful, whereas distinction was made between deficit and non-deficit schizophrenia. Deficit schizophrenia is characterized by persisting negative symptoms, such as loss of initiative and interest and loss of social contacts. Interestingly, of these genes neuregulin 1 and RGS4 appeared specifically associated with the non-deficit group, whereas PIP5K2A was associated with both groups.

Similar to schizophrenia, Bakker was unable to demonstrate a association between ADHD and genes involved in dopamine neurochemistry (DAT1, DRD4, DRD5, and DDC). However, using linkage analysis he was able to demonstrate the linkage between ADHD and the chromosomal regions 7p and 15q. The overall conclusion is that there are specific genes associated with schizophrenia, while progress has been made in identifying such genes in ADHD. In addition, the results indicate that a more uniform definition of patient groups or more specific endophenotypes may help to further identify genetic variations associated with either disease.

Steven Bakker (December 3, 1970, Woerden). Secondary school, 1989 (Murmellius Gymnasium, Alkmaar); Medicine at Leiden University, MD diploma 1998. In 1999-2004 he worked at the Department of psychiatry on the work described in the thesis. Since 2004 he is resident in Psychiatry at the UMC Utrecht.



Iris Sommer and Sharon Kolk win VENI Grant

The grant (€200,000) of Sommer is entitled, 'Structure, activity and connectivity of cortical language areas in healthy hallucinators'. In the project, language activation, structural deviations and connectivity will be assessed in healthy individuals who sometimes experience auditory hallucinations. Healthy volunteers will be asked about their hallucinatory experiences. Persons with high scores or low scores will be invited to participate in an MRI study. If these healthy hallucinating subjects can be demonstrated to show similar abnormalities as described for schizophrenia patients, a causal role for these cerebral deviations can be presumed in the occurrence of hallucinations, which can serve as an endophenotype for genetic studies on schizophrenia. (for grant of Sharon Kolk, see interview)

Rudolf Magnus Graduate School Certificates

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

Marieke Van Asselen (April 28, 2005)

Damiaan Denys wins Ramaer Medal

Denys has won the biannual Ramaer Medal that is awarded by the Netherlands Society of Psychiatry to young psychiatrists who made exceptional contributions to research in Clinical Psychiatry. Denys received the Medal for his 2004 PhD thesis on OCD.

Inge Wolterink runner up in Wichers Award

During the meeting of the Netherlands Society of Biomedical Laboratory Workers, Inge Wolterink was presented with the second prize of the Anna Wichers Award for her professional publication on the development of a model for schizophrenia, which appeared in 'Analyse'.

Ale Algra Professor

As of February Ale Algra (Dept of Neurology and Neurosurgery and Julius Centre) has been appointed professor of 'Clinical epidemiology of thrombosis treatment and prevention' at the Leiden University for a day a week.

Preservation of the Rudolf Magnus Legacy

The K.F.Hein Foundation, under the auspices of the Utrecht University Foundation, has granted € 10,000. The funds were raised as part of a scheme to preserve the legacy of Rudolf Magnus and his predecessors Ulbe Bijlsma and David De Wied, as part of the collection of the Utrecht University Museum.



May 10, Evening Lecture Psychiatry

Jogin H.Thakore (St.Vincent Hosp. and Trinity Coll., Dublin, Ireland), 'Antipsychotics and diabetes: what does the data say?'

19:45- 22:00, 'Roze collegezaal', UMC Utrecht
(contact, e.schreurs@azu.nl)

May 17, Rudolf Magnus Seminar

Gerard J.M.Martens (Nijmegen Ctr Mol. Life Sci.), 'Gene dosage effect on gamma-secretase component Aph-1b in a rat model for neurodevelopmental disorders'

9:00-10:00, Room 4.208, Stratenum Building, UMC Utrecht
(contact, h.c.vanvlaarding@med.uu.nl)

May 20, 2005, Helmholtz Lecture

Earl Miller (Massachusetts Institute of Technology) 'The prefrontal cortex: categories, concepts, and cognitive control'

16:00-17:00, 'Rode Zaal', Ruppert Building, Leuvenlaan 19, Utrecht
(contact, v.maassen@fss.uu.nl)

June 16, 2005, Rudolf Magnus Symposium Behavioural Genetics

Jonathan Flint (Oxford), **Dorret Boomsma** (Amsterdam), **Berry Spruijt** (Utrecht), **Bobby Koelman** (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, UK), '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.