



# Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 18  
December 2005

## interview

### Male sexual behaviour and serotonin

**Ejaculation disorders are common human disorders. Trynke De Jong performed experimental studies in rats focussing on the psychopharmacology and neuroanatomy of the serotonergic control over ejaculation. She identified the role of the serotonin receptor 5HT<sub>1A</sub> in the neurotransmission of ejaculation, and she investigated the neuroanatomical substrate involved in ejaculation behaviour. She also used natural occurring variation in ejaculatory behaviour in rats to illuminate aspects of human disorder.**

De Jong explains: "Ejaculatory dysfunctions, such as premature or retarded ejaculation, are common human disorders. For long, it was thought that these disorders were based on psychological problems. The neurobiological origin became evident when antidepressant drugs, i.e. selective serotonin reuptake inhibitors (SSRIs) that alter serotonergic neurotransmission, appeared to relieve premature ejaculation as a 'side' effect. However, different SSRIs have different sexual effects, suggesting that different adaptive changes in the neurotransmission may occur during chronic treatment with particular SSRIs."

De Jong utilized a standardised protocol to record rat male sexual behaviour. The total number of mounts, intromissions and ejaculations were recorded over a 30 min period after the rat was introduced in an arena with a receptive female. By pharmacologically treating the male rats, De Jong identified the serotonin receptor 5-HT<sub>1A</sub> as a key

player in the ejaculatory mechanism during SSRI treatment. She was able to link different effects of various SSRIs on ejaculation to their effects on the 5-HT<sub>1A</sub> receptor. It is a well known phenomenon that the 5-HT<sub>1A</sub> receptor agonist 8-OH-DPAT strongly accelerates ejaculation. Chronic pre-treatment with the SSRI paroxetine not only delayed ejaculation, but also reduced the effects of 8-OH-DPAT on ejaculation in a dose dependent manner and worked more strongly than the SSRI, fluvoxamine. De Jong concludes; "Apparently, chronic treatment with paroxetine but not fluvoxamine impairs the functioning of 5-HT<sub>1A</sub> receptors involved in ejaculation. This could underlie the development of delayed ejaculation often reported by men treated with paroxetine, whereas fluvoxamine is relatively free of this side effect."

De Jong also studied the activation of c-fos during her psychopharmaceutical experiments. C-fos is expressed very early in the activation of the neurones, and provides 'smoking gun' traces in the central nervous system to indicate the neuroanatomical location of activation. The location of c-fos appeared very useful. However, many structures, such as hypothalamus, brain stem and spine, appear activated in her experiments and therefore the delineation of the mechanisms involved in ejaculation will require extensive follow-up studies.

In close collaboration with Dr. T. Pattij, De Jong found that Wistar rats could be grouped in 'sluggish', 'normal' and 'rapid' ejaculators. Selecting rats on this parameter revealed large and stable differences in several other parameters of sexual behaviour. De Jong: "Further exploring the neurobiological mechanisms underlying these differences may be a promising approach to gain insights into the aetiology of premature or retarded ejaculation."

Trynke de Jong (June 13, 1978, Grijpskerk) completed her secondary education in 1996 (Jan Van Egmond College, Purmerend). In august 2001 she graduated in biology and journalism at Groningen University. Since 2002, she worked as a PhD student at the department of anatomy of Radboud University Medical Centre in Nijmegen, under supervision of Berend Olivier, Lex Cools, Jan Veening, and Marcel Waldinger. On December 1, 2005, she will defend her PhD thesis entitled, *Serotonin and ejaculation: a psychopharmacological and neuro-anatomical approach*. As of January 1, 2006, she will work as a postdoc in Psychopharmacology in our Institute.



## PhD theses

2005-42

December 1, 2005

T.R. De Jong (see *interview, page 1*)

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2005-43

### When antibodies turn against nerves

December 2, 2005

Marijke Eurelings

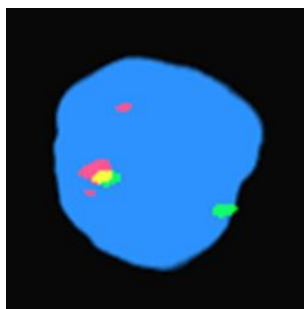
#### Polyneuropathy associated with monoclonal gammopathy, cause and consequence

J.H.J. Wokke, N.C. Notermans, H.M. Lokhorst  
Supervisors

**Polyneuropathy associated with monoclonal gammopathy is a peripheral nerve disease. Marijke Eurelings sought to improve the differential diagnosis of this disease and to better understand the relevance of diagnostic findings for the aetiology of the disease. She provides a clinical work-up for this complex disease and recommends a regular screening for these patients, who have a high risk of haematological malignancies.**

In patients with polyneuropathy associated with monoclonal gammopathy, monoclonal antibodies are present in the serum. The relation between these monoclonal antibodies and polyneuropathy is clear in some cases, as in polyneuropathy associated with IgM monoclonal antimyelin associated glycoprotein (anti-MAG) antibodies. These anti-MAG antibodies are reactive against a peripheral nerve autoantigen, thereby causing an autoimmune-mediated demyelinating polyneuropathy. But the role of the monoclonal gammopathy without anti-MAG reactivity and the role in axonal polyneuropathy is not so clear-cut.

In polyneuropathy associated with IgM monoclonal gammopathy, antibodies to myelin-associated glycoprotein (MAG), sulfoglucuronyl paragloboside (SGPG) and sulfatide have been associated with specific clinical and electrophysiological features. Eurelings studied 65 patients with polyneuropathy and IgM monoclonal gammopathy, but found that in clinical practice anti-MAG or anti-SGPG antibody tests in polyneuropathy associated with IgM monoclonal gammopathy did not have a prognostic value in terms of future neurologic deficit or outcome. Only initial symptoms and electrophysiological studies appeared independent prognostic factors. In a separate study of polyneuropathy associated with monoclonal gammopathy, anti-ganglioside antibodies were significantly associated with demyelinating neuropathy. Monoclonal gammopathy can be a sign of haematological malignancies. Eurelings



Early diagnosis of malignant transformation in a B cell nucleus with interphase fluorescence in situ hybridization (FISH) using 14q32 probes (courtesy of M.Eurelings).

found that, in patients with monoclonal gammopathy as well as polyneuropathy, malignant transformation occurs more frequent than in patients with monoclonal gammopathy without polyneuropathy. Weight loss, progression of the polyneuropathy, unexplained fever or night sweats and monoclonal protein level were independent predictors for malignancy development. She identified chromosome 14 translocations in the bone marrow B cells of about half of these patients. The chromosome 14 translocations may help in early diagnosis of these malignant transformations. Since haematological malignancies occur frequently in polyneuropathy associated with monoclonal gammopathy, Eurelings suggests that all patients should be screened at diagnosis and follow-up for malignant transformations.

**Marijke Eurelings** (June 14, 1972, Oldenzaal). Secondary school (Bataafse Kamp, Hengelo), 1990; Medicine (Utrecht University), MD 1997. The work as described in this thesis was performed during her residency (AGIKO) in Neurology (UMC Utrecht). She is expected to register as neurologist in 2007.

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2005-44

December 7, 2005

G.W.K. Hugenholtz

#### Antipsychotics in daily clinical practice: patterns, choices, and consequences

A.C.G. Egberts, W.A. Nolen, E.R. Heerdink  
supervisors

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2005-45

December 7, 2005

D. Brandsma

#### Adhesion in leptomeningeal metastasis: towards diagnosis and treatment

E.E. Voest, M.J.B. Taphoorn  
supervisors

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2005-46

### When nerve conduction slows down and blocks

December 13, 2005

Jan-Thies H. Van Asseldonk

#### Demyelination, degeneration, and deficit in multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy

J.H.J. Wokke, L.H. Van den Berg, H. Franssen  
supervisors

**Multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP) are disorders of the peripheral nervous system that are poorly understood, difficult to diagnose and treatable with immune modulating drugs. Jan-Thies Van Asseldonk was able to improve the understanding of the mechanisms underlying deficit in MMN and CIDP and to derive better neurophysiological criteria for the diagnosis of MMN and CIDP. These findings may improve identification of patients with these treatable neuropathies.**

The diagnosis of MMN and CIDP requires clinical characteristics and the finding of blocked conduction or demyelination on nerve conduction studies. Studying the temperature dependence of weakness in MMN and CIDP, Van Asseldonk was able to differentiate a demyelination block in CIDP and a depolarizing block in MMN. Since depolarizing block reflects axonal dysfunction, his results emphasise the importance of axonal pathology in MMN. This was confirmed by Van Asseldonk in a study in which the presence of axon loss, conduction block and demyelination were independently assessed and correlated with the presence of weakness to identify independent determinants of weakness in MMN. Van Asseldonk showed that axon loss in MMN is abundant and the strongest independent determinant of weakness. In addition, a strong correlation of axon loss with conduction block was found which suggests that clarification of the mechanisms underlying conduction block may lead to novel treatment strategies in MMN aimed at prevention of axon loss.

To define an optimal electrodiagnostic protocol for MMN, Van Asseldonk determined the distribution of conduction block and weakness in 39 patients with MMN. He found that conduction block was always present and most often occurred in long arm nerves innervating weakened muscles. Since conduction block was always found it is considered an obligatory finding in the diagnosis of MMN. In 135 patients suspected of CIDP, Van Asseldonk identified conduction abnormalities compatible with demyelination that predicted the presence of CIDP. He showed that electrophysiological criteria sets for CIDP that score a limited number of conduction abnormalities in a limited number of nerves may improve identification of patients with this potentially treatable disorder.

**Jan-Thies Van Asseldonk** (July 8, 1974, Veghel). Secondary education, 1992 (Woerden); Medicine (Leuven, Belgium and Utrecht University), MD 2000. From 2000 till 2005 he worked on the research project as described in this thesis. He is a resident in Neurology at the UMC Utrecht since 2004.

2005-47

**December 16, 2005**

**I.C. Van der Schaaf**

**CT angiography and CT perfusion in subarachnoid haemorrhage. There is more than meets the eye**

**W.P.Th.M. Mali, G.J.E. Rinkel, B.K. Velthuis**  
supervisors

2005-48

**When autism governs behaviour**

**December 20, 2005**

**Fabiënne B.A. Naber**

**Toddlers with autism: aspects of early behaviour**

**H. Van Engeland, J.K. Buitelaar,  
S.H.N. Willemsen-Swinkels**  
supervisors

**Autism is a developmental psychiatric disorder. Fabiënne Naber studied the social development of toddlers with autism at the age of 24-48 months. She found that already at the age of 24 months toddlers**

**with autism were capable of developing a secure attachment relationship with their parents, and that joint visual attention may be a reliable screening index for early detection of autism.**

Naber performed the first ever study on young toddlers with Autism Spectrum Disorders (ASD) that included both chronological and mental age matched control groups. She examined in toddlers (24-48 months old) with ASD the attachment relationship with the parent with the standard Strange Situation Procedure, and tested the contribution of the quality of attachment to the development of play behaviour and joint attention skills (i.e. the ability of the child to share attention with a parent or caretaker).

Naber found that children with ASD are capable of developing a secure attachment relationship with their parents already at the age of two years. However, having a higher number of autistic characteristics was related to attachment insecurity. This secure attachment relationship was found to stimulate the early development of play behaviour in children both with and without ASD. Children with a secure attachment relationship showed more and higher quality of play, regardless of their developmental level. No effect of attachment security or disorganization was detected for the development of joint attention.



Normal child's play (courtesy of F.Naber)

No differences were detected in level of play behaviour between children with or without ASD. For joint attention however, we documented that children with ASD show less joint attention compared to children with typical development at the age of two years. Although the development of joint attention behaviours of children with or without ASD was comparable, children with ASD showed less basic joint attention (i.e. pointing and gaze following), associated joint attention (i.e. checking and following pointing) and joint visual attention (i.e. looking at things together). At the age of four years, the basic and associated joint attention is not different for children with or without ASD. Naber concludes that deficits in joint attention skills are more related to ASD than deficits in basic play behaviour. Moreover, since children with ASD displayed less joint visual attention this may constitute a reliable screening index at both 24 and 42 month of age.

**Fabiënne Naber** (September 30, 1972, Zevenbergen). Secondary education, 1992; Biology (Utrecht University, 2000). From 2000 till 2005 she worked on the project of which the results are described in her thesis. As of February 2004, she is assistant professor of Pedagogy at Leiden University.

### 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:

Ron Van Empelen (November 1, 2005)  
 Barbara Gutteling (November 3, 2005)  
 Cornelle Noorlander (November 4, 2005)  
 Anne Visser-Meily (November 22, 2005)

### Louk Vanderschuren wins Rudolf Magnus Award

On November 30<sup>th</sup> the Rudolf Magnus Research Award 2005 was presented to Louk Vanderschuren (Department Pharmacology and Anatomy), for his publication in *Science* entitled 'Drug seeking becomes compulsive after prolonged cocaine self-administration'. The Rudolf Magnus Research Award is presented yearly to the member of staff of our institute who is the author of the best publication in the previous year. The nominees were judged by an independent national jury of neuroscientists. The Award (€ 3,500 and a certificate) was presented during the yearly Rudolf Magnus Symposium by Hans Stoof, dean of the Medical Faculty Utrecht.

### Rudolf Magnus Institute welcomes Primate Brain Bank

The Rudolf Magnus Institute of Neuroscience is proud to announce that the Primate Brain Bank now resides under its wings. The Institute hosts the Primate Brain Bank in which also the Faculties of Biology and Veterinary Medicine of Utrecht University participate. By collecting and conserving the brains of deceased primates and making these brains available to scientists, the Primate Brain Bank stimulates (neuro)scientific research.

The Primate Brain Bank currently holds over 170 primate brains in storage. More than 35 species are represented ranging from the tiny mouse lemur to the enormous gorilla. Of course, man's closest living relatives the chimpanzee and bonobo are also present. Experts from the Department of Pharmacology and Anatomy conserve the brains, using standardised protocols which allow a broad range of research methods. For instance, the material can be used for studies using various histological staining techniques. They can also be used for imaging (MRI, DTI) studies, as well as studies of gene expression. For more information contact Ido Toxopeus, tel. 030-253 5599; email, [PBB@rudolfmagnus.nl](mailto:PBB@rudolfmagnus.nl).



### December 5, Rudolf Magnus mini-Symposium 'Neuronal Connectivity'

Keynote, **Alex Kolodkin** (Dept Neuroscience, Johns Hopkins Univ, Sch. Med., Baltimore, USA) 'Molecular Mechanisms of Neuronal Growth Cone Guidance'  
 9:00-13:00, Boothzaal, University Library, Heidelberglaan 3, Utrecht. Programme, <http://www.rudolfmagnus.nl>  
 Contact, [j.pasterkamp@med.uu.nl](mailto:j.pasterkamp@med.uu.nl)

### December 8, Psychopharmacology Colloquium

**Jeannette Lorteije** (Functional Neurobiology, Biology, Utrecht University) 'Implied motion, from single cell to behaviour'  
 12:00-13:00, Room N014, Went Building, Sorbonnelaan 16, Utrecht

### January 20, 2006, Symposium 'Moving Forward in a Snail Shell'

On occasion of retirement of Guido F. Smoorenburg, Professor of Experimental Audiology.  
 9:30-18:00, Gertrudiskapel, Conference Centre 'In de Driehoek', Willemsplantsoen 1c, Utrecht, and Academy Building, Domplein 29, Utrecht. Programme, <http://www.rudolfmagnus.nl>  
 Registration required, contact, [s.klis@kmb.azu.nl](mailto:s.klis@kmb.azu.nl)

### April 19-27, 2006, Course on Neuropsychopharmacology

The course is accredited by the Rudolf Magnus Graduate School of Neuroscience and will be awarded by 7 credits. Venue, partly in Amsterdam, Weesp and Utrecht  
 Programme, [www.rudolfmagnus.nl](http://www.rudolfmagnus.nl)  
 Registration, Els Borghols, [eam.borghols@vumc.nl](mailto:eam.borghols@vumc.nl)

### May 4-5, 2006, Meeting of the Association of European Psychiatrists - Neuroimaging Section

'Neuroimaging Change over Time in Psychiatry'  
 Venue, Academy Building, Domplein 29, Utrecht  
 Programme and registration, [www.rudolfmagnus.nl](http://www.rudolfmagnus.nl)

### August 28-29, 2006, Rudolf Magnus-Helmholtz Summerschool

Mark your agenda for the joint Summerschool of the Rudolf Magnus and Helmholtz Graduate Schools.  
 Venue, Conference Centre Ottone, Kromme Nieuwegracht 62, Utrecht. Programme to be announced, check our website for updates, [www.rudolfmagnus.nl](http://www.rudolfmagnus.nl)