



Rudolf Magnus Institute of Neuroscience

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interview

From social behaviour to addiction and back

Louk Vanderschuren, working at the department of Pharmacology and Anatomy, has recently been awarded a TOP-grant from ZonMw (€500.000) and an RO1 grant from the National Institute on Drug Abuse (NIDA) from the USA (\$945.000). With these grants, Louk gets the opportunity to investigate drug addiction from different angles and they allow him to firmly establish his preclinical psychopharmacology group.

Louk Vanderschuren got acquainted with the Rudolf Magnus Institute doing one of his internships of his medical biology studies with Jan van Ree. He got fascinated with psychopharmacological research and continued at the Institute with a PhD project concerning opioids and social behaviour in rats. After he obtained his PhD degree he left the Institute to become a post doc at the VU medical center where he concentrated his studies on addictive behaviour in the group of Ton Schoffeleers. Next, he spent one and a half years in Cambridge where he studied the compulsive aspects of addiction in the group of Barry Everitt. That he was very successful in this latter project is testified by his Science paper, published in 2004. In that year Louk returned to the Institute to start his own research group concerning social and addictive behaviour.

I asked Louk to tell a bit more about his research and his interest in both addiction and social behaviour. "Drug addiction is a devastating disorder, but its pathophysiology is fascinating. My own research focuses on two questions: how do you get addicted, and how can you get rid of the addiction? Addressing the first question means to investigate the long-term effects of drug exposure on brain and behaviour, trying to emulate addiction-like behaviour in animals and to see what the neural substrates of addictive behaviour are. This entails lengthy and complicated experiments involving self-administration of drugs by the animals. I started with this kind of experiments in the lab of Barry Everitt in Cambridge and continued them here. This effort is essential, because only when we understand the neural underpinnings of the addicted phenotype, we can really answer the second question and design novel pharmacotherapies for addiction. Investigating how one gets addicted can also mean trying to identify vulnerability factors for addiction, some of which relate to social behaviour. Social behaviour has had my attention since my PhD studies and I find the

relationship between addiction and social behaviour very intriguing; this is why I incorporated them both in my research. But my interest in social behaviour goes beyond the possible link with addiction. It has been shown by others of the RMI that social play behaviour of young rats is important for normal social development of the rat and that social behaviour is very rewarding. However, unlike other natural rewards such as food and sex, there is relatively little known about the neural basis of social interaction."



Louk Vanderschuren

The two grants Louk has received allow him to study both social behaviour and addiction and will give him the opportunity to find out exactly how they are related. The title of the NIDA grant states this nicely: 'Social play behaviour in peri-adolescent rats in relation to later drug abuse'. Louk tells that it is well-known that humans with an antisocial personality run a greatly increased risk to develop drug addiction later on in life. With his experiments he wants to investigate the neural basis of impaired social capacities in relation to addiction, i.e. whether a neural difference between young rats causes them to be less social and also more prone to develop addiction, or whether altered social behaviour itself results in a predisposition to become addicted. Thus, with the NIDA grant Louk wants to investigate the predisposing social factors for addiction. On the other hand, in his TOP grant, the focus will be on the effects of long-term drug

exposure and it is therefore more concerned with the addiction syndrome itself.

What do these two grants mean for your future in research here at the Institute? Louk answers: "These two grants give me the opportunity to establish my research group. I can now hire several PhD students, whereas a previously obtained grant pays for a postdoctoral fellow and a technician. Furthermore, I am fortunate that Heidi Lesscher, who earlier this year received a VENI grant to investigate the genetics of alcohol abuse also works with me. With these NIDA and Top grants, a bridge may therefore be laid between social behaviour and addiction, giving my group the opportunity to study the complete spectrum of reward and addiction."

PhD theses

2007-13
June 5, 2007

Christine Wijman

Retinal ischemia and embolism. Causes and outcomes

L.J. Kappelle, J. van Gijn and V.L. Babikian
supervisors

Christine Wijman performed her PhD in the department of Neurology and Neurosurgery and completed her thesis in the section of Cerebrovascular Disorders. Currently she works at the Stanford University USA.

The ocular fundus allows direct visualization of the retinal vasculature, blood vessels that are part of the cerebral circulation. Unravelling the causes of retinal ischemia may provide further insight in the pathophysiological processes that underlie cerebral ischemia. The primary aim of the studies described in my thesis was to elucidate the causes, pathophysiology, and prognostic implications of symptoms of retinal ischemia (transient monocular blindness and retinal infarction) and the presence of asymptomatic retinal emboli in several patient populations. In addition to a retrospective cohort of patients, we prospectively studied a cohort of patients with retinal ischemia or with retinal emboli (or both). We also studied the outcome of symptoms of retinal ischemia in a cohort of patients with systemic lupus erythematosus and of migraine equivalents in the general population.

We found that the most important cause of retinal ischemia is atherosclerotic vascular disease and that the predominant pathophysiologic mechanism is embolism from a proximal vascular lesion. However, there are many other causes and mechanisms of retinal ischemia that need to be considered in the differential diagnosis of an individual patient. The presence of cerebral microemboli in a patient with symptoms of retinal ischemia increases the likelihood of finding an underlying athero-embolic lesion. We hypothesize that some of the pathophysiological vascular processes that play a role in retinal ischemia may also be important in cerebral ischemia. Examples are: in situ formation of emboli, vasospasm, and secondary microembolization from a cardiac embolus lodged in a more proximal blood vessel.

Retinal emboli, visualized on funduscopic examination,

can be found in patients with symptoms of retinal ischemia, but more often are detected in asymptomatic individuals during routine ophthalmologic examination. In patients with symptomatic retinal embolism, ipsilateral carotid artery stenosis, cerebral microemboli, and early recurrent vascular events are more common than in patients with asymptomatic retinal emboli, suggesting that there are pathophysiological differences.

Patients who present with retinal ischemia or asymptomatic retinal emboli are at an increased risk for recurrent vascular events. Therefore, a timely and meticulous work-up for an underlying cardio-vascular source of embolism is indicated in these patients and modifiable vascular risk factors should be carefully monitored and treated.

2007-14
June 19, 2007

Annemarie van Elburg

Psychoneuroendocrinological aspects of anorexia nervosa: predictors of recovery.

H. van Engeland and M.J.H. Kas
supervisors

Annemarie van Elburg started her PhD in 2000 after her training in medicine and psychiatry. She completed her thesis in the section Developmental Disorders at the department of Child and Adolescent Psychiatry. She currently holds a position as child psychiatrist at the Rintveld, centre for Eating Disorders, Altrecht Mental Health Institute.

Anorexia Nervosa (AN) is a psychosomatic eating disorder of unknown aetiology, which primarily affects adolescent girls and young women and is characterized by aberrant patterns of eating behaviour and weight regulation which result in weight loss and endocrine abnormalities such as amenorrhea, disturbances in attitude and perception about weight and shape, and an intense fear of gaining weight. This thesis is based upon a follow up cohort study of 61 young girls and women consecutively referred to two specialized eating disorder treatment centres, one for adolescents (at the Dept. of Child and Adolescent Psychiatry of the University Medical Centre Utrecht) and one for adults (Rintveld, centre for Eating Disorders, Altrecht Mental Health Institute).

The study focused on psychoneuroendocrinological changes during treatment; changes in body weight and composition, in hormones, activity level and mood states. After a follow-up of maximum one year, the patients were divided into 3 groups according to their clinical status: no weight recovery and ongoing amenorrhea (NWR, nineteen patients), weight recovery but with ongoing amenorrhea (WR, eighteen patients), and weight and cycle recovery (WCR, twenty-four patients). Approximately 5 years after the first admission a follow up was conducted to investigate the current state of illness as well as to identify potential predictors of recovery.

All hormones changed over time with weight gain, with ACTH being the only exception to this rule, if normal values were reached this occurred in the WCR group only. Several factors predicted and influenced complete physical

recovery in the first year. A novel finding is that the ovarian markers AMH, Inhibin B together with FSH predict which participants will regain a regular menstrual cycle with weight gain. Leptin levels did predict physical recovery, we detected a threshold level; an initial leptin level > 2 microgr./L increased chances for a full recovery to 75%. We replicated the finding by Holtkamp et al. (2006) that hyperactivity is related to leptin in the acute stage of AN but only when we compared an age matched group, the youngest patients in this study. Activity levels however are not predictive for treatment outcome in the first year in our study sample. Interestingly, chances for a patient that shows recovery in the first year, to relapse at 5 years are correlated with leptin and activity level at T1, a novel finding.

Without physical recovery there is no psychological recovery, but the factors that influence psychological recovery need further study. Although at 5 years FU 59% of the participants had become physically recovered and 52% did not meet criteria for an eating disorder, many still spent a lot of time and energy on thoughts concerning food or their body. Most striking are the data on the anxiety and depressive symptoms that are in line with the findings of Herpertz-Dahlmann and colleagues (2001).



news and other things

Heidi Lesscher receives VENI grant

Heidi Lesscher, from the department of Pharmacology and Anatomy, has received a VENI grant from ZonMw (the Netherlands Organisation for Health Research and Development), for her proposal entitled 'Involvement of the amygdala in the development of alcoholism'.

Alcoholism is a complex disease with major health consequences. The amygdala is a brain region that is well known for its role in emotional processing. As a post-doc at UC San Francisco, Lesscher discovered that the amygdala is also important for alcohol consumption. Mice like to drink alcohol and develop high levels of alcohol consumption after 2-3 weeks of daily drinking. However, local knockdown of a specific protein kinase C, PKCepsilon, in the amygdala by *in vivo* RNA interference

prevented the development of high alcohol intake in mice. The focus of Lesscher's research is therefore on the amygdala and the main goal of this project is to determine molecular mechanisms in the amygdala that promote high alcohol consumption in mice.

Lesscher will perform a detailed gene expression study to identify which molecular pathways are recruited during the development of high alcohol intake. One of the known downstream targets of PKCepsilon is CRF and neuropeptides including CRF have been implicated in alcohol consumption. Therefore, this project will focus in particular on neuropeptides and their regulators. Lesscher will determine the role of specific differentially expressed genes in the development of high alcohol consumption using *in vivo* RNA interference. Specific genes will be 'knocked down' in the amygdala in mice and subsequent tests for alcohol consumption will reveal whether specific genes are important for the development of high alcohol consumption in mice. Using this multidisciplinary approach, novel molecular mechanisms that contribute to the development of high alcohol intake and alcoholism will be identified.

Nick Ramsey receives Smart Mix grant

Nick Ramsey, the department of Neurology and Neurosurgery, participates in the Smart Mix grant that has been rewarded to the research platform into BCI research.

The BrainGain consortium has been rewarded with a large grant in the latest Smart Mix call, an initiative of the ministries of EZ and OCW. The BrainGain consortium consists of 4 universities, 6 companies and 3 patient organizations. The goal of the consortium is to use recent developments in the area of brain measurements and techniques to influence brain activity to enhance the quality of life of patients and improve the performance of healthy individuals.

The Brain-Computer Interface group of Nick Ramsey is part of the consortium and the grant enables Nick Ramsey to hire two additional researchers. The researchers will investigate the possibilities to implant electrodes in brains of paralyzed patients, which can be used to steer a computer. The focus of research is mostly on the characteristics of the electrodes themselves, and the methods to determine the right place for the electrodes using functional MRI on the new 7 Tesla scanner of the UMC Utrecht.

Prof van Gijn retired

After being 24 years head of the department of Neurology of the UMC Utrecht Prof Van Gijn will give his lecture emirates June 8th in the Domkerk, Utrecht, with the title 'Hersenspingsels'.

Third Mind the Brain symposium master Neuroscience and Cognition

Each year 9 students from the master Neuroscience and Cognition organise a two day symposium. During these two days the students present their data from their internships either on a poster or orally. Furthermore two renowned scientists in the field are invited to give a keynote lecture.

This years symposium took place on the 22nd and 23rd of May at the UMC Utrecht. During both days there was a very good atmosphere. The students were very enthusiastic, the presentations were of high quality and during the poster sessions there were a lot of scientific discussions. The presence of two poster judges during the poster sessions gave the students the opportunity to learn how to present a poster, to discuss their data with someone of the neuroscience field besides their supervisors and to get feedback on their posters and performance. The poster judges rewarded each day one poster with a small price as the best poster of the day.

The keynote lectures were given by prof dr. Heutink from the VU Amsterdam, he discussed the use of genetics to discover genes involved in neurodegenerative disorders, and prof. dr. Della Sala from the University of Edinburgh, UK, who discussed anarchy in the brain. Both lectures were of high quality and have inspired the students to continue their efforts in neuroscience and cognition research.

RMI exchange visit of Nick Ramsey

Recently Nick Ramsey visited the Institute of Psychiatry to establish a research collaboration in concordance with the IoP-RMI collaboration.

Nick Ramsey visited two research groups at the IOP: the Cognitive Neuroimaging Center (CNS, Steve Williams) and the epilepsy surgery group (Mark Richardson at the Academic Neuroscience Center). He discussed options for collaboration with both. The CNS agreed to host several PhD students of Ramsey's group to train them in the latest acquisition and analysis techniques for pharmacological MRI. The CNS group is interested in collaborating on THC projects involving appetite and pain. The epilepsy group agreed to start sharing cognitive paradigms in their patients. This will hopefully expand to include more groups within Europe, and to mature into a European paradigm exchange network. A second epilepsy research group, at the institute of Neurology in London, also agreed to participate in this emerging network.

Rudolf Magnus Graduate School Certificate

The Director and the Research Training Committee of the Graduate School took pleasure in presenting the Rudolf Magnus Graduate School Certificate to the following Doctor:
Sophie van Rijn (May 24, 2007).

agenda and announcements

June 1, 2007 Helmholtz lecture

David Heeger, (New York University, USA)
'Functional magnetic resonance imaging of human visual cortex'
zaal Groot Aardwetenschappen, Budapestlaan 4, Utrecht
16:00, contact, v.maassen@fss.uu.nl

June 4, 2007 Neuroscience seminar

Reza Shadmehr,
'Internal models, adaptation, and uncertainty'
ErasmusMC, Rotterdam, Colloquium room K
16:00, tea and coffee from 15:45
more information: <http://www.erasmusmc.nl/neuro/>

June 4, 2007 Neuroscience lecture

George Perry,
'Is oxidative stress the initiator of Alzheimer Disease?'
Utrecht
more information: j.vanhorsen@vumc.nl

June 5-18, 2007 ENP meeting

6th Dutch Endo-Neuro-Psycho meeting 2007
Doorwerth, the Netherlands
More information: <http://www.enpmeeting.nl>

June 8, 2007 Neuroscience symposium

Symposium on Emotion & Passion
Amsterdam
More information: <http://www.imaginggenetics.org>

June 14, 2007 Swammerdam lecture

Martin Schwab, (Brain Research Institute, University and ETH Zurich, Switzerland)
'Mechanisms of structural and functional repair of the injured adult CNS'
ONWA Amsterdam
more information: <http://www.onwa.med.vu.nl/swammerdam>

June 26, 2007 'refereeravond' psychiatry

JD Blom, (Parnassia Groep Den Haag)
'Onderzoek naar Hallucinaties. Historische en conceptuele aspecten'
17:15 Aula volwassen psychiatrie (A01.107 UMC Utrecht)
more information: 030-2506020, Opleidingszaken Psychiatrie Volwassenen UMC-Utrecht



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