



# Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 45  
June 2010

## Change of directors

On April 1 this year, RMI director Jan van Ree reached the age of 65 and stepped down from his position as director. The occasion was marked by a scientific symposium on Addiction and Van Ree's farewell lecture 'de Spiegel' in the Domkerk. The directorship was handed over to Marian Joëls.

The symposium was opened by René Kahn, head of the division of Neuroscience. All speakers of the symposium played an important role in the career of Jan van Ree as a scientist but also as manager and organiser. The first session was dedicated to scientific advances in the field of Addiction. The speakers gave impressive lectures on the past and current status of the field, in which they commemorated the role of Jan van Ree in their research or his role in general in the field of addiction.



Speakers and organisers of the symposium

During the afternoon sessions, the symposium shifted gears and concentrated more on Jan van Ree's work in the Dutch Heroin project and with regard to drug policy in the Netherlands. Jan van Ree presented the booklet he wrote on this topic "heroïne op medisch voorschrift" together with a special issue of the journal he has founded, European Neuropsychopharmacology, to the former minister of health Els Borst.

The celebrations continued in the 'Domkerk', where Van Ree held his emeritus lecture. The mirror cells of the brain served as a guideline through his lecture and with the metaphor of the mirror he talked us through his life up till now, both as a person and an academic. During the lecture a child choir presented two beautiful songs.

After the lecture, René Kahn, head of the division Neuroscience, Frank Miedema, dean of the medical faculty and Yvonne van Rooy, chairman of the Utrecht University Board, all presented Jan van Ree with honours. He was decorated as 'Officier in de Orde van Oranje Nassau' by Yvonne van Rooy.



l.t.r. René Kahn, Frank Miedema and Yvonne van Rooy

## IoP-RMI workshop

On February 4<sup>th</sup> and 5<sup>th</sup>, the fifth and final workshop between the Institute of Psychiatry London and the Rudolf Magnus Institute of Neuroscience took place in London. The workshop was organized as part of an UNCU internationalization grant. The key researchers of the collaboration projects presented their main results and the overall success of the collaboration was reviewed.

The topics discussed during the two days varied from research in the field of autism and schizophrenia to more fundamental research on pharmaco-imaging and animal models to understand behavior. The evaluation of the grant period showed that the number of steady collaborations between researchers of both institutes has increased from five to twelve. Several FP7 projects have been granted based on the standing collaboration and a number of high ranked papers have been published.

The meeting was closed with a discussion on the future and the continuation of the collaboration. It was agreed that the collaboration should be continued in the current format of workshops and travel grants. The aim should be to tighten the current collaborations and to explore new opportunities. The next workshop will be held in Utrecht February 2011. Travel grants can still be requested by filling in the travel grant form available at the coordinator of your Institute.

## PhD theses

Many of our PhD students have defended their thesis during the past months. We congratulate all of them with their doctorate degrees.

2010-02

**January 12, 2010**

**N. Moayeri**

### **Nerve identification and prevention of intraneural injection in regional anesthesia**

**C.J. Kalkman, G.J. Groen**

Supervisors

Dept. Anesthesiology

Section Cerebrovascular disorders

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2010-03

**January 14, 2010**

**E. van Daalen**

### **Early diagnosis of autism spectrum disorders**

**H. van Engeland**

Supervisor

Dept. Psychiatry

Section Psychopathology of developmental disorders

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2010-04

**January 14, 2010**

**F. Brugman**

### **Primary lateral sclerosis: diagnostic boundaries and outcome**

**L.H. van den Berg, J.H.J. Wokke, J.H. Veldink**

Supervisors

Dept. Neurology and Neurosurgery

Section Neuromuscular diseases

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2010-05

**March 4, 2010**

**S. Piepers**

### **Treatment strategies in amyotrophic lateral sclerosis and its mimics**

**L.H. van den Berg, J.H.J. Wokke, W.L. van der Pol**

Supervisors

Dept. Neurology and Neurosurgery

Section Neuromuscular diseases

This thesis explores treatment strategies of amyotrophic lateral sclerosis (ALS), lower motor neuron disorders and multifocal motor neuropathy (MMN). There are a number of disorders that mimic ALS, but have a different disease course. Progressive muscular atrophy (PMA) is a variant of sporadic ALS in which only the peripheral motor

neurons are affected. Spinal muscular atrophy (SMA) is another disease in which only the peripheral motor neuron is affected. SMA is caused by a homozygous deletion of the survival motor neuron (*SMN*)1 gene. MMN is a disease of the motor axon, but its clinical presentation may mimic ALS. The distinction with ALS is important since MMN is treatable with regular infusions of immunoglobulins (IVIg). The first part of this thesis describes the effect of symptomatic treatment of nocturnal hypoventilation using non-invasive ventilation. We performed a systematic review of the literature to analyze and summarize the scientific evidence of the effects of this treatment on the quality of life. The second part identifies the *SMN* gene in ALS and SMA as therapeutic target. Treatment with valproic acid, a histone deacetylase inhibitor, may improve disease course by increasing *SMN* expression. We used various models to investigate the effect of valproic acid on *SMN* expression. In addition 6 SMA patients were treated with valproic acid. We showed that valproic acid increased *SMN* protein expression in lymphocytes in 5 out of 6 SMA patients. The clinical significance of this up-regulation remains, however, unclear. Valproic acid did not change disease course in patients with ALS participating in a randomised sequential trial. The third part of this thesis identifies immune-mediated mechanisms in the pathogenesis of slowly progressive spinal muscular atrophy, suggesting that the disease course may share characteristics with MMN. We next investigated the role of the classical route of the complement system in MMN and speculated that targeting the complement system may be effective in treating MMN.

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2010-06

**March 9, 2010**

**E.L. van der Veen**

### **Management of chronic mucosal otitis media in children**

**A.G.M. Schilder, E.A.M. Sanders, M.M. Rovers**

Supervisors

Dept. Otorhinolaryngology

Section Brain Function and Plasticity

Chronic mucosal otitis media (COM) is one of the most common infectious diseases in children worldwide. As it causes considerable morbidity and is a major global cause of hearing impairment, establishing its most effective treatment is important. It is generally accepted that antibiotic eardrops should be the first step in treating COM, and surgery the last when optimal medical treatment has failed. What optimal medical treatment beyond eardrops entails, however, has not been established. We therefore initiated a randomized placebo controlled trial of a 6- to 12-week course of orally administered trimethoprim/sulfamethoxazole (TMP-SMX) in children with chronic active mucosal otitis media. 101 children aged 1 to 12 years with a documented history of continuous otorrhea for at least 12 weeks were randomized to receive 6 to 12 weeks of orally administered TMP-SMX (18 mg/kg, 2 times per day) or placebo and were monitored for 1 year. At 6 and 12 weeks follow-up, cure rates were 72% and 68% in

children treated with TMP-SMX and 47% and 53% in those treated with placebo. At 1 year, the cure rate was similar in both groups; 25% and 20%, respectively.

Alongside this trial we studied risk factors for COM in children. Using a case control design, we found that factors independently associated with COM in children were previous tympanostomy tube insertion, more than 3 upper respiratory tract infections in the past 6 months, low parental education level, and having older siblings. Factors independently associated with COM after tympanostomy tube insertion were more than 3 episodes of acute otitis media in the past year, attending day care, and having older siblings. The innate and adaptive immune function of children with COM was found not to differ from that of healthy controls.

Finally, we studied the effects of prolonged treatment with TMP-SMX on carriage and antibiotic susceptibility of the microbial flora in children with COM. Antibiotic resistance of the nasopharyngeal and intestinal flora increased during treatment with TMP-SMX, but returned to baseline values after discontinuation of TMP-SMX.

We concluded that a 6 to 12 week course of TMP-SMX (18mg/kg twice daily) is beneficial in children suffering from active chronic otitis media. This treatment effect is most pronounced with the shorter course, and disappears if the medication is discontinued. In light of its clinical benefit and tolerability, limited costs and reversibility of antibiotic resistance, we advise to treat children with persistent symptoms of otorrhea despite conventional management with eardrops and short-term antibiotics with a prolonged course of TMP-SMX. Ideally, interventions for COM should be aimed at prevention. At present, these are not available. It is therefore crucial that creative options based on modern insights into the pathophysiology of COM are developed.

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2010-07

**April 22, 2010**

**J. Greebe**

### **Subarachnoid haemorrhage and the life thereafter**

**A. Algra**

Supervisor

Dept. Neurology and Neurosurgery  
Section Cerebrovascular disorders

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2010-08

**April 22, 2010**

**M.A. van Es**

### **Unravelling the genetics of familial and sporadic Amyotrophic Lateral Sclerosis**

**L.H. van den Berg, R.A. Ophoff, J.H. Veldink**

Supervisors

Dept. Neurology and Neurosurgery  
Section Neuromuscular diseases

Amyotrophic lateral sclerosis (ALS) is a severely disabling, progressive disease characterized by the degeneration of motor neurons. Patients with ALS experience gradual

onset of muscle weakness which eventually leads to respiratory failure and death. ALS can occur as familial and sporadic disease.

In this thesis, all pedigrees affected by familial ALS in the Netherlands were collected and screened for mutations in known ALS genes. Mutations in *SOD1* (one of the major genes for familial ALS) are very rare in The Netherlands compared to other developed countries, suggesting genetic heterogeneity. In one pedigree a mutation in *ANG* was found to segregate with disease. One patient carrying this mutation also suffered from Parkinson disease and dementia. This is an interesting finding as there is excess co-occurrence of neurodegenerative diseases in families of ALS patients.

Despite the considerable heritability of sporadic ALS (0.35-0.80), the genetics of sporadic forms of the disease are poorly understood. To identify novel genetic risk factors for sporadic ALS, large genome-wide association studies including over 20,000 individuals were performed which resulted in the identification of four novel risk factors (*ITPR2*, *DPP6*, *UNC13A* and a locus on chromosome 9p) and an association with prolonged survival for *KIFAP3*.

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2010-09

**May 21, 2010**

**J.W. Dankbaar**

### **Complications of hemorrhagic and ischemic stroke: a CT perfusion evaluation**

**G.J.E. Rinkel, W.P.T.M. Mli, I.C. van der Schaaf, B.K. Velthuis**

Supervisors

Dept. Neurology and Neurosurgery  
Section Cerebrovascular disorders

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2010-10

**May 26, 2010**

**N.A. Sutedja**

### **Risk factors for motor neuron diseases genes, environment**

**L.H. van den Berg, J.H.J. Wokke, J.H. Veldink, K. Fischer**

Supervisors

Dept. Neurology and Neurosurgery  
Section Neuromuscular disorders

The aim of this thesis was to identify risk factors for motor neuron diseases. Several candidate genes and environmental / lifestyle factors were studied. This thesis shows that smoking, having an H63D mutation in HFE, and lean individuals with a low cholesterol level, have increased risk for ALS; that HLA-DRB1\*15 is associated with multifocal motor neuropathy (MMN); and that monoclonal gammopathy is more prevalent among patients with slowly progressive muscular atrophy (PMA). These findings suggest a possible role for oxidative stress and a higher metabolic rate in ALS; immune-mediate mechanisms in MMN and slowly PMA.

The systematic reviews in this thesis on environmental risk factors in ALS showed difficulty in attaining a high level of

evidence due to lack of high quality methodological and exposure assessment components. New population-based studies, adhering to general methodological as well as exposure assessment criteria, will elucidate risk factors for motor neuron diseases. Also, genome-wide association studies performed in by international collaboration achieved large populations with different genetic background will contribute to more insight in genetic risk factors.

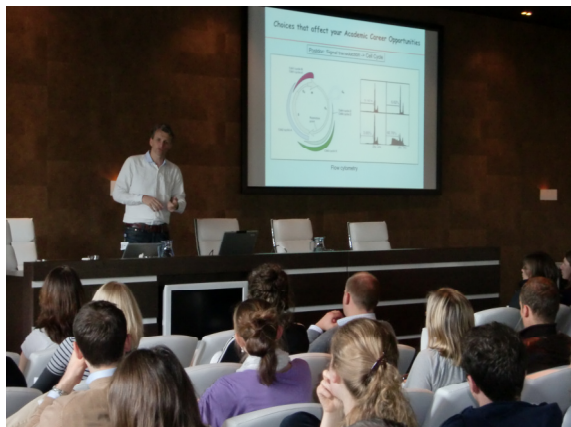
## Summerschool 2010

The RMI PhD students gathered on the 20<sup>th</sup> and 21<sup>st</sup> of April in Apeldoorn to meet for the RMI Summerschool. During two days they followed lectures and workshops.



Lecture by Jim van Os

The Summerschool was opened by the new director of the RMI and its PhD program, Marian Joëls. She introduced the lay-out of the new PhD program, effective as of September 1, 2010. From that date onwards, new courses aimed at improving general skills, in-depth knowledge of selected subjects in Clinical & Experimental Neuroscience and an overview of Neuroscience in general will start. The opening was followed by the two keynote speakers of the day. Jim van Os gave a lecture on epidemiology and genetics of psychiatric disorders. René Medema took the PhD students along his scientific career and gave tips and tools on how to become a successful group leader and scientist. The remainder of the day was filled with interesting presentations of PhD students in their final year and a workshop on techniques used in the neurosciences. The day ended with a buffet dinner.



Lecture by René Medema

The second day started with three different workshops, i.e. grant writing, poster making and scientific presenting. The program continued with a keynote speaker, André Klühkuhn, a philosopher who gave a philosophic presentation on science, art and religion. The students had the honour to close the Summerschool with a final session of student presentations. The last of these presentations was different in that it was not a scientific presentation, but rather a small course on how to handle the massive amounts of e-mail that we receive every day.

## news and awards

### FP7 grant

Leonard van den Berg, dept. Neurology and Neurosurgery, has received a cooperation grant from the 7<sup>th</sup> Framework Program of the EU entitled: European multidisciplinary ALS network identification to cure motor neuron degeneration (Euro-MOTOR). In total 16 partners are involved, with a budget of 9 million dollar.

### Agiko stipend

Metten Somers, dept. of Psychiatry, has received an Agiko stipend from NWO. He received this stipend for his project entitled: "A genetic study of left-handedness and language lateralization in extended pedigrees from a Dutch population isolated. An investigation of a possible endophenotype for psychosis".

### Rehabilitation grant

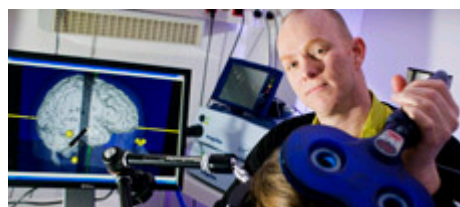
Knowledge center rehabilitation (consisting of the department Rehabilitation, Nurse Science and Sports, and rehabilitation center "de Hoogstraat") has received 300.000 Euro from the Innovation Program Rehabilitation. The grant has been given to implement guidelines for the rehabilitation of patients who have suffered from a cerebrovascular event (CVA patients).

### Young scientists' award

Ellen Hessel, dept. Neuroscience and Pharmacology and Erika van Hell, dept. Neurology and Neurosurgery, both have been rewarded with the young scientist award during the ECNP meeting in Nice. Both are now invited to give a lecture during the annual ECNP meeting, this year in Amsterdam.

### Neuronavigator NeNa put on the market

Bas Negggers of the dept. of Psychiatry has been working the last years on the development of the NeNa. NeNa is a frameless stereotactic system to navigate Transcranial Magnetic Stimulation (TMS) coils to locations indicated on an MRI scan. Together with the Norwegian company NordicNeurolab the NeNa will be put on the (medical) market. The launch took place on the 26<sup>th</sup> of April.



Bas Negggers with the NeNA

## 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 Doctors: Sanne Piepers (March 4, 2010), and Michael van Es (April 22, 2010)

## agenda and announcements

### June 15, 2010 DCCN Colloquium

#### Ken Paller (Northwestern University)

"Declarative Memory in Humans: What, Where, When, and How"

15:00-16:00 Nijmegen

more information:

[http://www.ru.nl/neuroimaging/agenda/agenda/@700881/formal\\_dc\\_cn\\_3/](http://www.ru.nl/neuroimaging/agenda/agenda/@700881/formal_dc_cn_3/)

### June 17, 2010 CSCA Frijda Lecture

#### Enst Fehr (University of Zurich)

"Neurobiological foundations of human motivation"

Amsterdam

more information: <http://www.csc.nl/>

### June 17-18, 2010

Philips Research Symposium on Neurovation:

"Innovative Applications of Brain Science"

more information: <http://neurovation.cisevents.hightechcampus.nl/>

### June 18, 2010 CSCA Symposium

"Neuroeconomics"

Amsterdam

more information:

<http://www.csc.nl/csc/symposia/neuroeconomics-june-18/>

### June 18, 2010 Helmholtz Lecture

#### Mark Johnson (University of London, UK)

"Developing a social brain"

16.00-17.00 Utrecht

Ruppert Building, Leuvenlaan 19, Zaal Wit

### June 18, 2010 RMI Lecture

#### Andrea Huber (Helmholtz Zentrum München, Germany)

"Wired for motion: molecular mechanisms governing motor system development"

16.00-17.00 Utrecht

Stratenum, room Str S41

### July 1-3, 2010 The synapse symposium

Amsterdam

more information: <http://www.synapsesymposium.nl/>

### July 1-2, 2010 FENS satellite symposium

"Translational aspects of proteolysis in neurodegenerative diseases"

Maastricht

more information: <http://satellite-maastricht.fensforum2010.eu/>

### July 2, 2010 FENS satellite symposium

"Alpha-synuclein pathology in Parkinson patients and models"

Amsterdam

more information:

<http://www.vumc.nl/afdelingen/ANW/ParkinsonSymposium/>

### July 3-7, 2010 7<sup>th</sup> FENS Forum

Amsterdam

more information:

<http://www.http://fens2010.neurosciences.asso.fr//>

### July 7, 2010 FENS satellite symposium

"Neuron-astrocyte signaling in the epileptic brain"

Amsterdam

more information:

[http://www.neuroglia.eu/\\_files/FENS\\_Sat\\_Amsterdam\\_2010.pdf](http://www.neuroglia.eu/_files/FENS_Sat_Amsterdam_2010.pdf)

### July 8-11, 2010 6th International Melanocortin Meeting

Utrecht

more information: <http://mc2010.azuleon.org/>

### July 8-10, 2010 EuroHaptics 2010 conference

Amsterdam

more information: <http://mc2010.azuleon.org/>

### September 3, 2010 NCU research day

Utrecht

more information:

<http://www.uu.nl/NL/onderzoek/focusgebieden/NCU/Current/Pages/NCUday.aspx>



