



# Rudolf Magnus Institute of Neuroscience

## Rudolf Magnus Bulletin 37 January 2008

### **Fourth IoP and RMI workshop**

#### **An impression**

The fourth workshop in the framework of the international collaboration between the Institute of Psychiatry London (IoP) and the Rudolf Magnus Institute of Neuroscience (RMI) took place the 26<sup>th</sup> and 27<sup>th</sup> of November 2007 in Utrecht. During the two days four different topics were addressed and discussed by researchers of both Institutes.

The workshop was opened by Jan M. van Ree, the director of the RMI. Van Ree highlighted the current collaborations and emphasized the success and usefulness of the combined research efforts.



The first topic, biomarkers, was addressed from different view points by Iain Campbell and Leonard Schalkwyk from the IoP and Leonard van den Berg and Christiaan Saris from the RMI. Campbell discussed the use of biomarkers as indicators for a biological state and as aid to predict and prevent disease and by that improve clinical decision making. Schalkwyk presented data on a search for biomarkers for depression using mouse strains. He explained how inbred and chromosome substitution strains can be used to perform phenotypical analysis which can lead to the discovery of useful biomarkers for human disorders. The session was closed by Van den Berg and Saris who presented their view on the use of biomarkers in the diagnosis of ALS. Saris presented data on genome-wide expression profiling of human blood of ALS patients. The aim of this study is to identify biomarkers in the blood of ALS patients, which can be used for the diagnosis, progression of the disease and to monitor the effect of therapy.



After a nice lunch the day was continued by a session on epilepsy and epileptic surgery. The kick-off of this session was by Antonio Valentin (IoP), he gave a lecture on new electrophysiological techniques for epileptic surgery. He highlighted the pros and cons of new techniques. Mark Richardson (IoP) was the second to present. He focused on the electrophysiology of human cognition. He explained that with single neuron stimulation and recording, it is possible to distinguish two types of responses, behavioural responses and electrophysiological responses. The session was completed by Nick Ramsey, Mariska van Steensel and Dora Hermes (RMI). In their presentation the focus was on electrocortical research in epilepsy patients to study basic brain function. This work is part of the large Brain Computer Interfacing (BCI) study of Ramsey. Van Steensel and Hermes presented preliminary data of two epilepsy patients who underwent the BCI program.



The day was completed by a keynote lecture on schizophrenia by Prof René Kahn, head of the department

of Psychiatry of the UMC Utrecht and the RMI. Kahn started the lecture with an overview on the clinical features and diagnosis of schizophrenia. He then moved on to the imaging research done with the Tesla machines that helped to understand the disorder better and to improve the diagnosis. He showed data on brain volume and the relation between brain volume and schizophrenia and finished his presentation with a note on the genetic background of schizophrenia. The keynote lecture was followed by an entertaining drink and a dinner in restaurant Stadskasteel Oudaen.



After a cup of coffee or tea with cake the second day of the workshop was opened with a session on the theme addiction. Louk Vanderschuren (RMI) opened the session. He presented data and his view on neurobehavioural mechanisms of compulsive drug use. The main question he posted during his presentation was: 'what makes the differences between a drug user and a drug addict?' The session continued with a presentation by Emma Dempster (IoP). She approached the theme of addiction not from a behavioural point of view but rather from a molecular point of view. By studying gene-environmental interactions in addictions, primarily in alcohol addiction, she tries to understand the molecular basis of addiction. Dempster presented data on animal stress and alcohol studies and array experiments in which she showed that the CRHR-1 gene could be a potential candidate gene in alcohol addiction.

The final session, topic pharmaco-imaging, was the most extensive session with 6 presenters. The session was opened by Gerry Jager (RMI). She presented studies done at the RMI on cannabis and the effect on cognitive functions in cannabis users. By using fMRI she tries to

determine which working areas of the brain are affected by cannabis use. Mitul Mehta (IoP) was next to present.



He gave a much more methodological talk in which, he emphasized the use of fMRI not only to understand the activation of brain regions in psychiatry, but also to use fMRI to understand the effect of pharmaca on brain activity, and thus use MRI as pharmacological MRI. The presentation by Mehta was complemented by Matthijs Bossong and Erika van der Hell (both RMI). They stayed for six weeks at the IoP in the group of Mehta and learned to perform and to analyse pharmacological experiments. The results of their visit were presented in this session. The final two presentations of the session and thus the workshop were by Emma Barkus and Quinton Deeley, (both IoP), who presented respectively data on cognitive symptoms predicting psychoses and schizophrenia before the disorder has manifested itself and data of an fMRI study of the effects of acute tryptophan depletion on facial motion processing in healthy controls and autism spectrum disorder patients.



The fourth workshop was a great success with a good overview of collaborating research and the development of many new research plans. In the near future no new workshop will take place. However, in 2009 a workshop will be organized in which the results of the collaboration between the IoP and the RMI will be presented and will be discussed in what format the collaboration between both institutes will continue.

For those of you taking part in a collaboration between the IoP and the RMI, or those who want to start a new collaboration: remember that there are travel grants available for short exchange visits of staff and PhD-students between both institutes and for 1-2 months' visits for performing experiments at the partners' Institute. More information on these possibilities can be obtained with Mariken de Krom (m.dekrom-3@umcutrecht.nl)

December 6, 2007

Paul van Vught

### Genetic Susceptibility factor in ALS

L.H. van den Berg, F. Baas

supervisors

Paul van Vught started his PhD in 2002 after he had finished his studies in biology. He performed his PhD work in the department of Neurology and Neurosurgery and completed his thesis in the section of Neuromuscular diseases.

ALS is a neurological disorder that is characterized by the selective death of motor neurons in cortex, brainstem and spinal cord. Initial manifestations are weakness of limbs or weakness in the bulbar region leading to abnormalities of speech, swallowing difficulties and facial weakness (bulbar onset). Muscle weakness may be mild at first, but gradually progresses and spreads to other regions of the body. The patient eventually becomes paralyzed and approximately 50% of patients die within 3 years after initial manifestations of symptoms, usually as the result of respiratory failure. To date, there is no effective treatment for ALS. ALS can occur at anytime in adulthood with a median age of onset in the mid-fifties and has a slightly higher incidence in males (about 1.5:1), though this sex difference diminishes with age. The estimated incidence of ALS is approximately 2-4 per 100,000. ALS is thought to be a complex disorder, implying that both genetic and environmental factors predispose the disease.

In this thesis, several genetic association studies have been undertaken to identify genetic variations that may be associated with ALS susceptibility. We first choose to screen the coding region of candidate genes for genetic variants to determine an association with ALS. We could however, not detect a relation between genetic variation in several candidate genes and ALS. To ascertain the credibility of published positive results, we replicated previous studies which showed an association between ALS and polymorphisms in the *VEGF*, *HFE* and *CNTF* genes. In a Dutch population, we found a relation between a *HFE* polymorphism and ALS, but not in the *CNTF* and *VEGF* genes. Meta-analysis in 10 populations in the *VEGF* gene, however, showed an increased risk for ALS in males homozygous for a SNP in the promoter region. Patients carrying this genotype also had an earlier disease onset and shorter survival. We further investigated genetic susceptibility factors using an unbiased genome wide genotyping approach (GWA). We found a SNP in the *ITPR2* gene, which showed a significant association with ALS after genotyping additional samples from several European countries. Combining our data with a recent GWA study in an US population revealed a SNP in the *DPP6* gene to be associated with ALS susceptibility. Also, this was confirmed in additional populations. In addition to the genetic association studies, we have performed gene expression analysis in blood from ALS patients and controls, in order to identify differentially expressed genes. We identified groups of genes that were co-expressed (modules), 2 of them were differentially expressed in ALS patients. This may lead to a greater understanding of ALS

pathogenesis, but also may serve as diagnostic markers. In conclusion, we identified several genes related with ALS. It is hoped that these findings will shed new insights in the mechanism leading to ALS and may form targets for future drug intervention.

2008-01

January 14, 2008

Leonie de Visser

### Home sweet home; Home case testing for behavioural phenotyping of mice

B.M. Spruijt, R. van den Bos

supervisors

Leonie de Visser started her PhD in 2003 after she had finished her master studies. She performed her PhD work at the department of Veterinary Sciences in the programme emotion and cognition and completed her thesis in the section Behavioural Genomics.

Behaviour is the ultimate expression of the interaction between genes, the brain and the environment. In order to unravel its underlying neurobiological and genetic processes, behavioural phenotyping of inbred and genetically modified mice deserves full attention. Maybe trivial, but it is also one of the most challenging tasks in behavioural neuroscience as behaviour is highly dynamic and complex and at the same time unpredictable and sensitive to confounding environmental factors that are either unaccounted for or practically unavoidable. Current behavioural assays have the advantage of an extensive literature backup and pharmacological validation, but are limited in the ability to study long-term effects on behaviour, circadian rhythms and address multiple interacting motivational systems in a single test setup. Moreover, factors like handling and transport have considerable, but not well quantified impact on experimental outcomes in short-lasting tests. To tackle these problems, a system is developed that allows continuous registration of mouse behaviour in a home cage environment. Testing animals in their home cage environment yields several advantages; it allows observations of habituation to the new home cage over consecutive days and the evaluation of both challenge-induced and baseline behaviours. Home cage testing also minimizes human intervention. Apart from detailed analysis of baseline activity and circadian rhythmicity, this set-up could be used to study approach-avoidance behaviour.

The research presented in my thesis is aimed at investigating the possibilities and limitations of home cage testing as a novel method for the behavioural phenotyping of mice. The general approach is as follows: (1) the general organization of home cage behaviour is investigated in different inbred strains to determine the discriminative power of home cage testing with respect to genetic differences. Furthermore, the influence of different environmental manipulations (novelty, running wheel, stress) on home cage behaviour are investigated to determine the discriminative power of home cage testing with respect to environmental challenges.

(2) A paradigm to test for approach-avoidance behaviour is introduced to extend the possibilities of home cage testing by addressing the behavioural domain of anxiety.

(3) Between- and within-laboratory reproducibility of home cage testing was determined. It was concluded that home cage testing is a valuable tool for behavioural phenotyping of mice. Continuous, automated recordings of mouse behaviour in an ethological context allow detailed investigation of circadian processes and long-term effects of genetic, pharmacological and environmental manipulations. Importantly, home cage testing is suitable to detect trait characteristics. It has the potential to detect behaviour that is dysfunctional or maladaptive, thereby contributing to the development of animal models for human behavioural disorders. Future developments directed at pharmacological validation, the implementation of cognitive tasks, the coupling of the home cage with novel environments and the integration of behaviour and physiology would further extend the possibilities of home cage testing.

2008-02

**January 31, 2008**

**Sabine Uijl**

### **Decision making in temporal lobe epilepsy surgery**

**A.C. van Huffelen, K.G.M. Moons, F.S.S. Leijten**  
supervisors

**Sabine Uijl started her PhD in 2002 after she had finished her studies in biomedical health sciences. She performed her PhD work at the department of Clinical Neurophysiology and completed her thesis in the section Brain function and plasticity.**

Epilepsy surgery is a successful treatment option for patients with drug resistant temporal lobe epilepsy. To decide whether patients are surgery candidates, a complex presurgical work-up is performed, starting with basic diagnostic tests (patient history, MRI, video EEG monitoring), followed by tests with increasing invasiveness (PET, intracranial EEG monitoring). In my thesis, we assessed the added value of a selection of tests used in the presurgical work-up: patient history, MRI, video EEG monitoring, FDG-PET, and the bilateral intracranial amobarbital procedure (IAP or Wada test). Furthermore, we assessed whether postoperative seizure freedom can accurately be predicted and we assessed whether epilepsy surgery is utilized to its full extent in the Netherlands. We conclude that the presurgical work-up for temporal lobe epilepsy surgery could be more efficient: the combination of MRI, interictal EEG and ictal EEG can select a subgroup of patients who are eligible for surgery, without the need for further testing; FDG-PET can be performed in more patients, especially when MRI and video EEG monitoring are inconclusive; and IAP can be performed unilaterally instead of bilaterally in most patients. Furthermore, the model we derived to predict postoperative seizure freedom one year after surgery had a moderate ability to predict seizure freedom. Finally, we conclude that epilepsy surgery should be considered in more patients currently treated in secondary and tertiary care in the Netherlands.

### **Prof Backx appointed professor**

**In January 2007 Frank Backx MD PhD, sports physician at the Department Rehabilitation and Sports Medicine of the Neuroscience Division in the University Medical Center Utrecht (UMCU) was appointed professor in Clinical Sports Medicine. His inaugural speech entitled: 'Sport is healthy; reach for limits to optimize effects' was held on December 6 in the Aula of the Academic Building, Domplein.**

Nowadays, sport is hot and exercise is a must. In most western countries sports and exercise are promoted intensively knowing that 12% of the yearly deaths is related to physical inactivity. Prevention seems to be the best health investment. In the Netherlands promotional actions as 'The Netherlands on the Move' were initiated to stress that 30 minutes exercise a day is necessary for a healthy lifestyle. Although critics point at the registration of nearly 1.5 million sports injuries and 200 sudden cardiac deaths in sports a year, on balance, sports and exercise are beneficial to our health.

In his speech Backx described sports medicine as a horizontal medical specialism without beds, perpendicular in other domains. He outlined the history of sports medicine in Utrecht, with predecessors as prof Jongbloed (1942-1965) and Mosterd (1987-1999). In Zeist there were also important initiatives, such as the formation of the first Sport Medical Center by the Royal Netherlands Football Association (KNVB). In 2002 the UMC Utrecht and the KNVB created the foundation University Center of Sports Medicine (UCS), a joint venture between our university hospital and the largest sports federation in Holland. Within this UCS Backx initiated a new knowledge development program, named Load & Capacity. This program comprises the following research lines:

1. improving medical care by development of evidence-based treatment methods for acute and chronic sports injuries, including establishing early diagnosis and treatment of chronic systemic overload in recreational and elite sportsmen;
2. development of the most effective rehabilitation programs induced by physical training for patients with chronic diseases and reduced exercise tolerance.

Based on the niches in research, ZonMw developed a special funding program Sports, Exercise and Health. Four universities (i.e. UMC Groningen, Vu UMC Amsterdam, UMC Maastricht en UMC Utrecht) were selected to initiate a new infrastructure and applied studies. At the same time a firm base for sports and exercise medicine research was created under the umbrella of LOSO (Landelijk Overleg SportgezondheidsOnderzoek), a platform of the four research groups already mentioned. Their primary goal is aimed at bridging the gap between practice and science. In close harmony with the other three partners Utrecht has focused on the body region of low back, pelvis and hips. Nowadays projects are running on specific sports problems as groin injuries and hamstring muscle strains (especially in soccer) but also on kinking of the iliac arteries (in endurance sports). Other topics of research line 1 are:

- the cost-effectiveness of acute ankle sprains treated with tape or brace,

- head and brain injuries in field hockey and
- compression socks for the under leg in case of muscle strains or cramps.

In the last decades patients with chronic illnesses have been encouraged to take part in sporting activities as part of their rehabilitation. Adult patients with chronic diseases such as heart failure, stroke, schizophrenia and morbus Parkinson are the primary target groups in research line 2. In the future other patient populations (e.g. recovering from cancer) will be trained (pre- and post-surgery) following the "better-in, better-out" principle. Special interest has been addressed to the most effective exercise program for reconditioning, i.e. the dose-response relationship.

Backx continued his oration with his other tasks concerning patient care and education, together with science the so-called Trias academica. In the department of Rehabilitation and Sports Medicine patient care consists of two sports medical products: injury consultations and pre-participation examinations. Target groups are not only elite athletes, but predominantly competition and recreational athletes with overuse injuries, acting in different types of sports. More media attention caused by sudden cardiac death of top-level soccer players has led to an increased demand for health checks with maximal exercise testing and ECG-control. Backx emphasized the importance of the central registration of cardiac data (named SportCor) and the use of an AED (acute external defibrillator) on the spot.

Finally, he explained the increased interest of medical students in sports medicine. In addition, a lot of post-academic courses aimed at family physicians, physical therapists and occupational doctors will be given. He finished his speech with five take home messages aimed at looking for the boundaries of our physical abilities and avoiding unnecessary health risks to keep sports healthy. His last words contained an expression of his heartfelt thanks to his family, the Board of Directors of UMC, KNVB and the Advisory Board of UCS and naturally his colleagues in the department of Rehabilitation and Sports Medicine.

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## Article in Nature Genetics

**Michael van Es, working in the group of Leonard van den Berg, in the department of Neurology and Neurosurgery has recently published a paper in Nature Genetics.**

Amyotrophic lateral sclerosis (ALS) is a severely disabling and lethal disorder caused by progressive degeneration of motor neurons in the spinal cord and brainstem. ALS affects 1-3 per 100,000 and average survival is 3 years. To date, no effective treatment is available. Familial ALS accounts for up to 10% of patients with approximately 20% of families linked to mutations in SOD1. Mutations in ALS2, DCTN1, VAPB and ANG have been found in rare cases of familial ALS. Sporadic ALS accounts for >90% of patients and is considered to be a multi-factorial disease with an estimated heritability ranging from 0.38 - 0.853. Several associations with variants in genes have been reported including ANG, VEGF, HFE, PON, and copy number variations in SMN1/SMN2. However, replication of these findings in other populations has frequently failed. To identify novel ALS susceptibility genes we performed a

genome-wide association study using Illumina 300K Beadchips in 461 cases and 450 healthy, age, gender and ethnically matched controls from The Netherlands. We combined our data with a previously published genome-wide association study of 276 ALS cases and 271 controls from the US. We followed up on all SNPs with  $P < 0.01$  in each study independently, and for which the allelic association was unidirectional (i.e. same direction of the allele associated). Fifteen SNPs fulfilled these criteria and were analyzed in three additional independent populations consisting of 272 cases and 336 controls from The Netherlands, 467 cases and 437 controls from Sweden and 291 cases and 420 controls from Belgium. Using this approach we identified 1 SNP in the DPP6 gene that is consistently strongly associated with susceptibility to ALS in different populations of European ancestry with an overall P-value of  $5.04 \times 10^{-8}$  in 1,767 cases and 1,916 healthy controls and with an odds ratio of 1.30 (95% CI 1.18-1.43). Our finding is the first report of a genome-wide significant association with sporadic ALS and may be a target for future functional studies.

Van Es et al, 2008 Genetic variation in DPP6 is associated with susceptibility to amyotrophic lateral sclerosis, Nat Genet. Jan;40(1):29-31

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## Awards received at the 45<sup>th</sup> Biotechnical Days

At the 45<sup>th</sup> Biotechnical Days researchers from the Institute received several awards. Saskia Plomp, Jan Brakkee\*, Sjaak Klis and Martijn Agterberg, from the departments of Pharmacology and Anatomy\* and KNO, received an award for the best article in 'Biotechniek' entitled 'Zijn dove cavia's actiever dan horende' (Are deaf guinea pigs more active than normal-hearing guinea pigs). Furthermore Inge Wolterink, technician in the group of Pierre de Graan of the department of Pharmacology and Anatomy, received an award in the area of alternative animal experiments, for her work on epilepsy. She implanted temperature sensitive transponders in ten day old mouse pups. This technique has improved the welfare of the animals and made the experiments much more accurate.

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## Rudolf Magnus Graduate School Certificate

The Director and the Research Training Committee of the Graduate School have taken pleasure in presenting the Rudolf Magnus Graduate School Certificate to the following Doctor:

Paul van Vught (6 December, 2007), Leonie de Visser (14 January 2008)

## **agenda and announcements**

### **January 30, 2008 CSCA Lecture**

**Chris de Zeeuw**

'Regulation of sensorimotor integration in mouse mutants'

Doelenzaal (UB) Singel 425, Amsterdam  
16:00-17:00, afterwards informal drinks  
more information: <http://www.cscs.nl>

### **February 1, 2008 M-BIC Lecture**

**Pieter Roelfsema**

'Cortical algorithms for perceptual grouping'

13.30 hr, UNS50 0402, Maastricht University  
more information:

<http://mbic.unimaas.nl/redirect.asp?page=Lectures>

### **February 13, 2008 Research Lunch**

**Research lunch department of psychiatry**

Aula Psychiatry, UMC Utrecht

12:00-13:00, lunch provided

contact, [i.sommer@umcutrecht.nl](mailto:i.sommer@umcutrecht.nl)

### **February 15, 2008 Helmholtz lecture**

**Alvaro Pascual Leone (Harvard University, USA)**

'Studying and guiding the changing human brain'

16:00 hr 'Ruppert Building Zaal rood', Utrecht

contact, Veronica Maassen, [helmholtz@fss.uu.nl](mailto:helmholtz@fss.uu.nl)

### **April 21-22, 2008 Summer school RMI**

**Summer school for all PhD students of the RMI**

Location Akersloot, Van der Valk Hotel Akersloot

### **May 13-16, 2008 '100 jaar Farmacologie Nederland'**

**Visit the website for details on the program and registration for the symposia**

**[www.100jaarfarmacologie.nl](http://www.100jaarfarmacologie.nl)**

