Rudolf Magnus
Institute of Neuroscience

Rudolf Magnus Bulletin 29
February 2007

interview

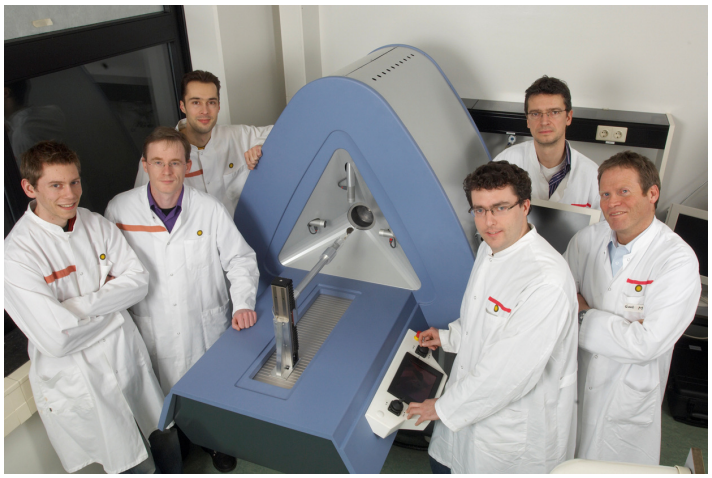
The marriage between physics and biology

The opening of the U-SPECT molecular imaging facility and the granting of the IoP Photonics project to Freek Beekman, in collaboration with his company MILABS, TU-Delft and Dalsa, is a big step in further development of U-SPECT and its research applications within the Rudolf Magnus Institute and Imago. It will enable biologists to be the first to use the knowledge of advandced physics and engeneering research to understand better the dynamics of diverse biological systems.

Freek Beekman, physicist by training, very enthusiastically tells about the major events taking place at the moment within the Rudolf Magnus Institute and Imago on the field of molecular imaging. First of all the U-SPECT imaging facility will be officially opened January 30th. He tells that this facility will enable researchers to perform very specific molecular imaging addressing all kind of questions regarding the dynamics of biological processes in an *in vivo* system, not possible before. This will open a whole new research area within neurobiology and the Institute. Virtually everything can be visualised using the U-SPECTII as long as there is an appropriate tracer and animal model available. Some tracers are even already commercially available, like for the serotonin and dopamine system and some GABA-ergic molecules. Many other interesting molecules, says Freek, are not available as SPECT tracers but one could consider labelling those oneself.

One of the big advantages of the U-SPECT-system compared to other SPECT systems is the very high resolution and the high sensitivity, the best you can get at present according to Freek, a statement supported by several awards he and his group received the last years for the best animal SPECT images. The high resolution really makes it possible to address questions about interactions between ligands and targets at the spatial level of subcompartments in the murine brain, which couldn't be answered before.

Some pilot experiments with dopaminergic tracers have shown that the data obtained in mice and rats can readily be translated to the human situation. The dynamics of the tested molecules resembled those observed in human imaging studies. Another advantage of these experiments is the longitudinal character of the studies, which remarkably limits the number of animals needed for a study.



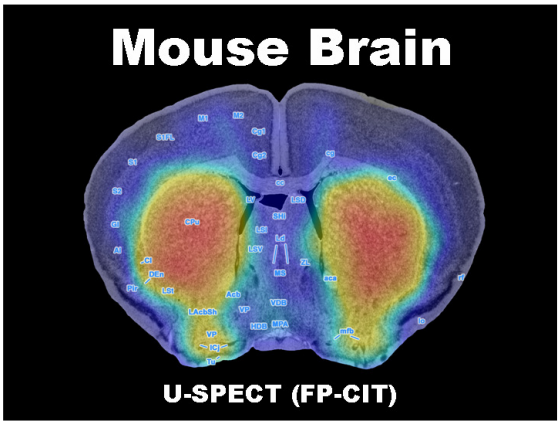
Part of the U-SPECTII development team
Left to right: Wout-Jan Brander-Horst, Mart Rentmeester, Brendan Vastenhouw, Frans van der Have, Norben Gehéniau and Freek Beekman

The other big event is the granting of 2.5 million euros for the IoP Photonics project. This project is a joint effort of the UMCU, TU-Delft and the companies Dalsa and MILABS, the company recently founded by Freek and the UMC Utrecht. The aim of the project is to build the U-SPECTIII, which will be a smaller scanner producing even nicer images than the U-SPECTII. The main differences with the U-SEPCTII will be the camera's used in the system, which will be optimised in the current project.

Although all the imaging currently is focusing on animal work, mice and rats, with future grants Freek also wants to aim to build a U-SPECT-like system suitable for human studies. However, this will not yet be available in the near future.

What about this marriage between physics and biology? What are the real possibilities for the researchers in the Rudolf Magnus Institute? This question is very promptly answered by Freek: “Everything is possible, however, the research is very expensive and complexcostly due to costly tracers, animals and dedicated personnel involved. Therefore ad hoc studies are almost impossible to organise. Of course we are more then willing to team up and write and participate in grants, to enable making nice molecular imaging programs including high level physics and image processing support possible. A nice example of such a joint effort is the HIPO grant rewarded to Marten Smidt and me”.

Visit www.milabs.com to see for yourself the possibilities of the U-SPECT-system.



U-SPECT image of the dopamine transporter distribution combined with overlay of the mouse brain atlas

PhD theses

2007-01
January 18, 2007

Bernard Lo

Activation of hemostasis after off-pump coronary artery graft surgery

C.J. Kalkman, R. Fijnheer and A.P. Nierich
supervisors

Bernard Lo started his PhD in September 2001 after he finished his medical training. He works at the department of Anaesthesiology and the department of Neurology and Neurosurgery and completed his thesis in the section of Cerebrovascular Disorders.

My thesis describes among other things the impact of activation of hemostasis during two types of heart surgery: with and without use of cardiopulmonary bypass. In contrast to what has been thought for many years, our research has shown that surgical trauma plays at least as an important role in activation of hemostasis as the use of the cardiopulmonary bypass system. This may be of clinically significance in case of off-pump surgery (therefore without cardiopulmonary bypass), as the used strategies to prevent coagulation are less aggressive than with on-pump surgery. Furthermore, there are a number of anti-coagulation effects as a result of the use of the cardiopulmonary bypass, which may be clinically important and are lacking with off-pump surgery. We showed that this can have obvious consequences by demonstrating a clear association between the activated hemostasis after off-pump surgery and cognitive dysfunction in the early postoperative period. In addition, we also investigated anti-thrombotic effects of several local anesthetics. Finally we have shown that a small elevation (clinically not noticeable) of the pre-operative inflammation marker C-reactive Protein levels predisposes a risk factor for the occurrence of atrial fibrillation after heart surgery. This applies to cardiac surgery both with and without cardiopulmonary bypass.

2007-02
January 25, 2007

Herman R. Holtslag

Prospects after major trauma

Chr. van der Werken, E. Lindeman, M.W.M. Post and E.F. van Beek
supervisors

Herman Holtslag started his PhD in January 1999, after his training as physiotherapist and his medical training. He is currently employed as rehabilitation physician at the department of Rehabilitation and Sports medicine. He did his PhD training in collaboration with the department of Neurology and Neurosurgery and completed his thesis in the section of Cerebrovascular Disorders.

Co-morbidity appeared, beside the direct impact of lesions by the accident, the most important predictor for almost all used outcome measures. Herman Holtslag, rehabilitation physician working in the UMC Utrecht and the rehabilitation centre ‘De Hoogstraat’ interviewed 335 patients. All patients also completed several questionnaires. The patients are all major trauma victims, who have been primarily taken care of in the UMC Utrecht in 1999 and 2000. A strong feature of this study is the prospective cohort set-up with a follow-up measurement after an average of 15 months with a high collaboration percentage (93%).The research group primarily consists of (75%) young men (37 years), who survived a traffic accident (70%), stayed one week at the intensive care unit and were dismissed after 4 weeks from the hospital. Most of the restrictions, indicated by the patients, were in the field of pain and discomfort, mobility, walking, and cognitive complaints. The consequences of these restrictions were mild to average problems in participating in the field of work, household, recreation and pastimes, and alertness behavior. Almost 40% returned partially or not at all to their job and more than 60% had stopped with their former sport or leisure activities.

The impact of external causes of injuries on health has been calculated. Individuals lost 32 years of life or lived 12 years with disability. Each victim contributed 25 disability adjusted life years (DALY), which put major trauma in the top 10 list of burden of diseases in the Netherlands.
For the daily clinical practice as well as future research it is recommended to aim at finding the correct instrument to be able to determine the seriousness and duration of the co-morbidity in measure and number. Furthermore the attention concerning trauma patients could be intensified in the chain of prevention, relief, rehabilitation up to and including labour integration.

2007-03
February 6, 2007

Alexander F.J.E. Vrancken

Diagnositc efficiency and treatment strategy in chronic axonal polyneuropathy

J.H.J. Wokke, N.C. Notermans and H. Franssen
supervisors

Alexander Vrancken started his PhD in September 1997 after he finished his medical training. He is a resident in the department of Neurology and Neurosurgery since 2000. He completed his thesis in the section of Neuromuscular Diseases.

Polyneuropathy is a common peripheral nerve disorder that often has a well known cause such as diabetes, chronic renal disease, alcohol abuse, vitamin deficiency, hypothyroidism, or use of toxic medication. Elderly people are more often affected, but the differentiation from signs of normal ageing can be difficult. It is important to diagnose a polyneuropathy and establish the cause at an early stage, because treatment can ameliorate symptoms and prevent progression. Because of the ageing population, the number of people affected by a polyneuropathy can be expected to increase. My thesis deals with questions regarding the efficient work-up and treatment strategies for chronic axonal polyneuropathy.

A description of the main study results is as follows. In about 25% of healthy elderly people older than 60 years the vibration sense at the big toes or ankles and the ankle jerks can be absent, and this should be taken into account when developing a clinical diagnostic definition for polyneuropathy. Implementation of a restrictive guideline for the workup of polyneuropathy leads to less diagnostic delay (on average 2 weeks), fewer investigations and less costs (about 30%), whilst retaining diagnostic reliability. For chronic axonal polyneuropathy, the sural and superficial personal SNAP have complementary diagnostic value and equal diagnostic accuracy. Neither ageing nor disease duration have an important influence on the disease course or prognosis of chronic idiopathic axonal polyneuropathy. Sural nerve biopsies in progressive idiopathic axonal neuropathy often demonstrate inflammatory abnormalities suggestive of vasculitis (i.e. an inflammation of arterial blood vessels), but the absence of these findings does not preclude an immune-mediated origin of this neuropathy. Based on a literature review according to the methods of The Cochrane Collaboration© there is no evidence from randomized trials on which to base treatment for chronic idiopathic axonal polyneuropathy and non-systemic vasculitic neuropathy.

2007-04
February 7, 2007

Carien S. de Kloet

Afterwards. Neurobiological alterations in veterans with and without postraumatic stress disorder

H.G.M. Westenberg, C.J. Heijnen and E. Vermetten
supervisors

Carien de Kloet started her PhD in June 2001 after she finished her medical training. She works at the department of Psychiatry and completed her thesis in the section Psychiatric Phenotypes.

Traumatic experiences can result in long-lasting psychological dysfunction. Based on epidemiological studies we can expect that approximately 3% of Dutch military personnel will develop psychopathology in the aftermath of their deployment. My thesis focuses on the alleged hypothalamic-pituitary-adrenal axis (HPA-axis) dysregulation in posttraumatic stress disorder (PTSD). In all studies described in my thesis, we included two, sometimes three groups: Dutch veterans with PTSD, veteran controls (with the same kind of trauma exposure, but no symptoms of PTSD or other psychopathology) and healthy non military controls. This design enabled us to associate alterations in biological readouts with either trauma exposure or specific features of PTSD.
The ACTH response to cognitive stress as well as baseline levels of plasma corticotrophin releasing hormone and vasopressin were specifically related to the presence of PTSD. The question remains whether these are “neurobiological markers” that develop after traumatic stress in PTSD patients or vulnerability factors that were already present before deployment.

The response to the dexamethasone suppression test, the awakening cortisol response and leukocyte glucocorticoid receptor binding showed differences between veterans who experienced traumatic stress during their deployment (both PTSD patients and control veterans) and healthy controls, and might therefore be related to trauma exposure or other military related factors.
PTSD patients with a comorbid depressive disorder (MDD) showed differences in the response to dexamethasone-CRH challenge and a cognitive challenge compared to PTSD patients without comorbid MDD. This suggests that we might be dealing with subtypes of PTSD, characterized by differences in HPA-axis and Sympathetic Nervous System regulation.
Follow up studies assessing neurobiological and psychological parameters in patient control and prospective designs, hopefully will help to answer the questions raised in this thesis and will help to understand why some do and others do not develop mental health problems in the aftermath of traumatic stress.

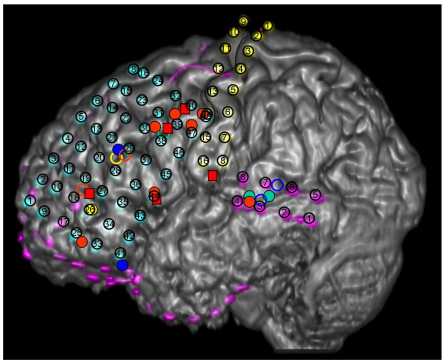
news

Nick Ramsey receives prestigious VICI grant

Nick Ramsey works at the department of Neurosurgery and received a prestigious VICI grant from NWO, the Dutch organisation for scientific research, titled "Human CNS Neuroprosthetics: substituting lost brain function".

Nick received the grant to investigate and develop techniques to help people who have lost their ability to speak or move. People can loose their ability to speak or move by an accident or a disease; this has a very big impact on their lives and that of their families. With his VICI grant Nick wants to develop techniques which allow those people to communicate and act using computers and other technical aids via sensors in their brains. By only thinking about a certain movement they will be able to actually move something.

More about this intriguing research and the VICI grant of Nick in the next bulletin.

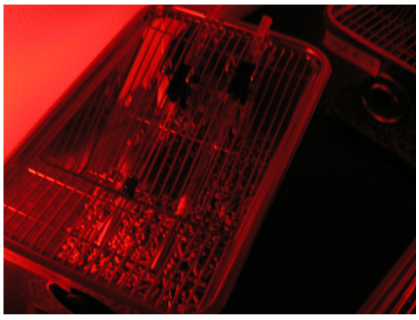


Example of sensor points in the brain

Heidi Lesscher receives 'Hersenstichting' grant

Heidi Lesscher, department Pharmacology and Anatomy, received a fellowship from the Netherlands Brain Foundation for her proposal titled "Alcoholism: neurobiological mechanisms and genetic sensitivity".

Alcoholism is a complex disease with a major genetic component. The main goal of this project is to determine how the amygdala, a brain region that is well known for its role in emotional processing, promotes alcohol consumption in mice. Mice like to drink alcohol. They develop high levels of alcohol consumption after 2-3 weeks of daily drinking. During her post-doctoral training at UC San Francisco, Lesscher discovered that the amygdala is critically involved in this process. With this fellowship, she will now identify the molecular mechanisms in the amygdala that facilitate high alcohol intake in mice. Using microarrays, molecular networks in the amygdala will be identified that are employed during the development of high alcohol intake. Subsequently, candidate genes will be functionally characterized by 'knockdown' of specific genes in the amygdala using *in vivo* RNA interference. Parallel to this work, susceptibility genes for high alcohol consumption will be identified using so-called chromosome substitution strains. These strains, where single chromosomes were swapped from one strain to another, now allow for rapid identification of quantitative trait genes – in this case for high alcohol intake. The unique combination of gene expression arrays, *in vivo* RNA interference and QTL mapping will provide novel insight into the neurobiological mechanisms that determine high alcohol consumption and alcoholism.



Example of the cages used in the experiments of Heidi

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:

Herman Holtslag (January 25, 2006)

Coordinator replaced

After about five years of full dedication Jan Dekker has left the Rudolf Magnus Institute to return to his 'old' field, the science of stomach and gut. He will be the head of a group of 20 scientists working throughout the Netherlands. Jan will be based at TNO in Zeist. He can be contacted at the following email address:
jan.dekker@tno.nl
Since January 1st, Mariken de Krom has replaced Jan Dekker. She can be contacted at +31030 2538110, or emailed: m.dekrom-3@umcutrecht.nl

agenda

January 30, 2007, Opening
Opening U-SPECT molecular imaging facility
Tuinzaal, A.A. Hijmans van den Berghgebouw,
Contact, m.merseveld@umcutrceht.nl

February 19 and 20, 2007 VCP meeting NIN
Plasticity in the juvenile and adult virtual cortex
NIN, Amsterdam
programme and registration,
www.nin.knaw.nl/IndexNIN/Meeting/ExtraPages/VCPmeeting.2007.pdf
contact, martijn@cncr.vu.nl

February 23, 2007 Helmholtz lecture
Susan Lederman, (Queen's university, Canada)
'Feeling objects, Feeling faces' *zaal Rood,* Ruppert building, Leuvelaan 19, Utrecht
16:00, contact, v.maassen@fss.uu.nl

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