



Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 36 November 2007

RMI symposium and evening

An impression

This year the Rudolf Magnus symposium and evening took place the 31st of October, Halloween's eve. As each year the symposium highlighted exciting research within the institute with four excellent presentations. The program of the symposium was completed by a keynote lecture of Judith Rapoport, an outstanding scientist in the research field of psychiatry.

The first four speakers had the difficult job to give an overview of the research going on in the institute at this moment. The kick off was by Jacob Vorstman, of the department of Psychiatry, who gave a lecture on the research which is currently done on autism, a collaboration between the department of psychiatry and the department of neuroscience and pharmacology. He presented data on a DIAPH3 a novel autism candidate gene. Jacob's lecture was followed by a lecture of Nick Ramsey, of the department of Neurology and Neurosurgery. Nick has been very successful this year in obtaining funding for his Brain Computer Interface (BCI) research. In his lecture he gave an overview of BCI research up till now and he presented his ideas and plans on the development of BCI in the (near) future. The third lecture was given by Martien Kas, of the department of Pharmacology and Anatomy, who has received a VIDJ grant of NWO. He explained how animal models can be used for the discovery of human candidate genes for phenotypic traits observed in psychiatric patients. The series of four lectures was closed by Edward de Haan, who recently has been appointed part time as professor at the department of Neurology and Neurosurgery. He presented data and his view on the neuropsychology of colour vision.

The keynote lecture was presented by Prof Judith Rapoport, a child psychiatrist and researcher at the National Institutes of Health in Washington, USA, renowned for her longitudinal studies with children. In her presentation she showed imaging data both on studies with healthy children and studies of children with ADHD or Childhood Onset Schizophrenia (COS). During the first part of her presentation she focused on the development of the brain of healthy children. She used imaging data of prospective longitudinal MRI scans acquired of the brains of healthy children in the age of 5 up to 20 years. She used movies to visualize the data, showing changes of the thickness of the cortex over time. Globally, the movies showed that this change in time takes place in a 'wave'

from rostral to frontal. In the first years (up to 8-11 years) a gradual thickening of the cortex takes place, afterwards a gradual reduction of the thickness of the cortex. A fascinating finding was that the I.Q. of young children correlated negatively with the thickness of the cortex (the thinner the smarter) as from the age of 8.5 years I.Q. was positively correlated with the thickness of the cortex. This phenomenon could possibly be explained by the fact that the maximum thickness of the cortex with smart children was reached at a later age in comparison to children with a lower I.Q. (with a higher I.Q. maximum cortex thickness was reached at the age of 11 and with a lower I.Q. at the age of 8).



Judith rapoport

In the second part of the lecture Rapoport presented similar imaging data now on the brains of children with ADHD or COS. The development of the cortex of children with COS was characterised by a "shift to the left" which corresponds with an advanced maximum cortex thickness in time and a correspondingly earlier start of cortex reduction. In contrast the ADHD group was characterised by a "shift to the right" or a later maximum of cortex thickness. When the ADHD group was divided in good outcome and poor outcome patients it appeared that the cortex thickness of the first group in time caught up with normal development of the cortex, while in the poor outcome group the development of the cortex remained deviant. Interestingly, it was shown that the use of ADHD medication (like methylphenidate) was associated with a normalisation of the development of the cortex within the ADHD group.

After the lectures it was time for the announcement of the winner of this years' Rudolf Magnus Research award. This reward is given to the most exciting research paper written by researchers of the institute. A national jury had judged the applications and selected the winner. This year was special; there were not one but two winners. The winning paper had a chaired first authorship, Simone Smits and Frank Jacobs, respectively postdoc and PhD student at the department of Pharmacology and Anatomy. The winning article was: Retinoic acid counteracts

developmental defects in the substantia nigra caused by Pitx3 deficiency. *Development*. 2007 Jul;134(14):2673-84.



The winners of the RMI research award

With the ending of the symposium the start of the evening was given. Everybody involved in research done in the institute was invited for a nice evening in the 'Kroonluchter' of the Hijmans van den Bergh building. The evening program started with drinks and a scientific poster session. The quality of the posters was very high and at the posters lively discussions were taking place, whilst drinking a glass of wine and enjoying some appetizers.



Poster session and drinks

The poster session was followed by a dinner buffet with a variety of dishes. A chef was preparing warm ham, furthermore there were several salads, tapas and fish.



Enjoying a bite of fish...

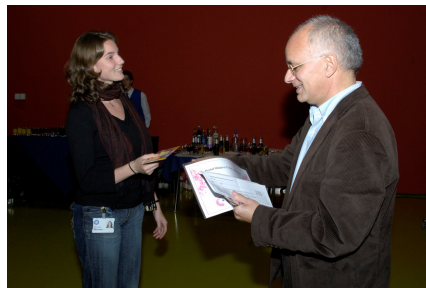
During dinner the Wolf Consort, with Anne Kan PhD student of the department of Pharmacology and Anatomy, gave a very nice concert. They enlightened the evening with several classical duets accompanied by piano. After the music, it was time to enjoy a terrific dessert buffet, which nobody, even if you tried, could resist.



The Wolf Consort

The grand final of the evening was the announcement of the winners of the Rudolf Magnus Poster awards. Peter

Burbach, as chair of the poster judges, had the honor to present the prizes. The third prize was for the poster of Suzanne Koudijs, the second prize was for Erika van Hell, who had also won with the same poster the ECNP poster award, and the first prize was for Micheal van Es. All three poster award winners work at the department of Neurology and Neurosurgery.



Erika receives the second prize

PhD theses

2007-19

November 15, 2007

Mechteld Hoogendoorn

Schizophrenia: a study on genetic aspects of a brain disease

R.S. Kahn, J.P.C.J. Selten, R.A. Ophoff, R.J. Sinke
supervisors

Mechteld Hoogendoorn started her PhD in 1999 after she had finished her studies in psychology. She performed her PhD work in the department of Psychiatry and completed her thesis in the section of Developmental Disorders. Currently she works at the AMC in Amsterdam and there she divides her time between the clinic and research.

The thesis of Mechteld Hoogendoorn: "Schizophrenia: a study on genetic aspects of a brain disease" outlines schizophrenia as a complex disorder, most probably involving multiple genetic and environmental factors that interact with each other. In this thesis, the focus was on genetic factors that contribute to the risk to develop schizophrenia. With a sample of over 300 patients and over 800 control subjects, it was possible to detect, and/or to replicate associations with several positional and functional candidate genes.

In three of the studies, it was demonstrated that some candidate genes (NRG1, PIP5K2A & RGS4) and the interaction between them were differentially associated with specific subtypes of schizophrenia: distinguishing between patients with and without the Deficit syndrome of schizophrenia was a valuable tool for 'narrowing down' the phenotype of schizophrenia. Furthermore, by combining two different approaches of association analyses, we were able to detect association between specific myelin- and oligodendrocyte-related genes and schizophrenia, as well as association between these same genes and brain structure volume deficits that are found in schizophrenia. However, we failed to detect association between schizophrenia and genes that are part of the dopamine system; although from numerous lines of

evidence it has been suggested that this neurotransmitter system is involved in the risk to develop schizophrenia. We also tested for a chromosomal abnormality in our patients (the 22q11.2 deletion), a deletion that is associated with a very high risk for schizophrenia. This chromosomal deletion was not detected in any of the patients, ruling out the possibility that some of the susceptibility factors in our sample were due to this chromosomal abnormality.

Since the completion of the studies described in this thesis, we have carried on with the recruitment of patients with schizophrenia. Furthermore, we also go on with acquiring MRI scans of patients to further explore the relationship of schizophrenia susceptibility genes and brain structure volumes. So, to be continued...!

2007-20

November 22, 2007

Frans van der Haven

Ultra-high-resolution small-animal SPECT imaging

M.A. Viergever, F.J. Beekman
supervisors

Frans van der Haven started his PhD in 2002 after he had finished his studies in technical physics. He performed his PhD work in the IMAGO graduate school and partly at the department of Pharmacology and Anatomy and completed his thesis in the section Behavioural Genomics. Besides his PhD research Frans also worked for the company of Freek Beekman MILabs. After his promotion he will work part time for MILabs and part time as postdoc within the same departments.

The research associated with this doctoral thesis contributed to the development of a new SPECT scanner, named U-SPECT. SPECT (Single Photon Emission Computed Tomography) is a three-dimensional imaging technique used in Nuclear Medicine that is capable of visualizing very low concentrations of radioactive molecules. Until recently, its resolution was insufficient for many types of research in small animals such as mice. The thesis is about the development of a SPECT scanner for small laboratory animals with a much higher resolution than scanners had before: the U-SPECT can visualize details of one third of a millimeter. The design is such that it is also possible to follow through time where the molecules are (and at which concentration) inside an animal or organ. Now that this technology has become available, it means that sometimes things can now be measured in a living animal that could only be measured ex vivo before. In other cases, much more information can be obtained from a single animal. The system can be used in biomedical and pharmaceutical research.

news and other things

Two grants for DEXamethasone for Cardiac Surgery (DECS) trial

Diederik van Dijk and Stefan Dieleman of the subdivision of Anesthesiology have been awarded with a grant from the Netherlands Heart Foundation and from ZonMW NWO (in total 685.000 euro).

Cardiac surgery with use of the heart-lungmachine is associated with a postoperative systemic inflammatory response syndrome, which may contribute to mortality, myocardial infarction and other major complications. The inflammatory response can be suppressed with a high intra-operative dose of dexamethasone, but this can have a multitude of unwanted side effects including immunosuppression, poor wound healing, and inadequate post-operative glucose control. These side effects themselves could contribute to the rate of major complications. At present, there is no evidence from clinical trials whether steroids increase or decrease the risk of major perioperative complications. As a result, the use of steroids in heart surgery is highly controversial and varies greatly across the countries where heart surgery is performed.

Diederik van Dijk and Stefan Dieleman from the Department of Anesthesiology at the UMCU have therefore designed the DEXamethasone for Cardiac Surgery (DECS) trial. This is a large but simple multi-centre, double-blinded, randomized controlled trial of dexamethasone versus placebo in 4,500 adult patients undergoing cardiac surgery. The aim of the DECS study is to measure the effect of intra-operative administration of dexamethasone on major complications in the first month after cardiac surgery.

Two years ago, Van Dijk and Dieleman have unsuccessfully applied for a grant for the DECS study at the Netherlands Heart Foundation. In 2007, after recruiting 200 patients at the UMCU, they have re-submitted their grant application to both ZonMW and the Heart Foundation. This time they were more successful. ZonMW and the Heart Foundation have both decided to support the trial with a total amount of 685,000 euro. This enables the researchers to carry out the intended multicenter trial. Within 6 months from now, the DECS trial will recruit patients at 8 cardiac surgical sites in the Netherlands. It is estimated that the inclusion of 4,500 patients will be completed in 2010.

Two new professors appointed

Hilleke Hulshoff-Pol and Nick Ramsey have been appointed as professors at the Utrecht University. Hilleke Hulshoff-Pol is working at the department of Psychiatry in the section of Developmental Disorders and has been appointed as professor in Neuroscience with special focus on psychiatric disorders since October 1st, 2007. Nick Ramsey is working at the department of Neurology and Neurosurgery in the section of Brain Function and Plasticity and has been appointed as professor in Cognitive Neuroscience since October 1st, 2007.

Prof Albers deceased

With regret we received the message that professor Frans W.J. Albers from the subdivision otorhinolaryngology has passed away in the evening of October 30th at an age of 52 years. He completed a report on the new research program of the subdivision, that was related to the research of the section Brain Function and Plasticity. The implementation of the new research on hearing and equilibrium was just started.

Erika van Hell received the poster award at the ECNP meeting

This year, the Congress of the European College of Neuropsychopharmacology (ECNP) was organized in Vienna. The poster Erika van Hell presented there was awarded with a Poster Award, existing of 500 euros and a commemorative certificate. The title of her poster was: "Differential effects of cannabis and nicotine on the human reward system". (Van Hell H.H., Jager G., Vink M., Ossewaarde L., Kahn R.S., Ramsey N.F. (2007) Differential effects of cannabis and nicotine on the human reward system. *European Neuropsychopharmacology* 17(Suppl 4): S554)

In the research project, presented on the poster, they investigated the reward system with a monetary reward task, during which functional MRI scans were acquired. They compared cannabis users to healthy, non-smoking controls, but since the cannabis users also used nicotine, they included a smoking control group. They looked specifically at the nucleus accumbens, since this is an important brain structure in the reward system, involved in anticipation of reward. In the nucleus accumbens, nicotine and cannabis seemed to have the same effect on brain activity during anticipation of reward, whereas the specific effect of cannabis was found in the caudate nucleus.

Rudolf Magnus Graduate School Certificate

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

Mechteld Hoogendoorn (15 November, 2007)



agenda and announcements

November 21, 2007 Research lunch psychiatry

Wouter Staal

'Copy Nu,ber variations and candidate gene studies by autism spectrum disorders'
aula psychiatry, UMC Utrecht
12.00, lunch provided
more information: i.sommer@umcutrecht.nl

November 21, 2007 LIBC colloquia

Dr. Mattie Tops (UL)

'Brain motivational/emotional systems and sets of proactive vs. reactive behavioral repertoire'
11.30 hr, FSW room SB11, Leiden
more information: <http://www.libc-leiden.nl/colloquia.htm>

November 22, 2007 Swammerdam lecture

Dr. Robert Stickgold (Harvard, USA)

'Sleep, memory, and dreams: beyond consolidation'
16:40 Woudschoten Conference Center,
More information:
<http://www.onwa.med.vu.nl/pages/lectures/swammerdam.htm>

November 22 and 23, 2007 Annual PhD meeting RMI and ONWA

Woudschoten Conference Center

November 23, 2007 Helmholtz lecture

Dr. Clive DL Wynne (university of Florida)

'Do animals think? Nonhuman intelligence and the struggle for the animal mind'
16:00 hr 'Bestuursgebouw, Van Lier & Eggingk zaal', Utrecht
contact, Veronica Maassen, helmholtz@fss.uu.nl

November 26 and 27, 2007 RMI-IoP workshop

December 3, 2007 Neuroscience seminar

Dr. John Welsh

'Functional views on brain rythm'
ErasmusMC, Rotterdam, Colloquium room K
16:00, tea and coffee from 15:45
more information: <http://www.erasmusmc.nl/neuro/>

December 6, 2007 LIBC colloquia

Prof. Dr. Nick Ramsey (UMC Utrecht)

'Act it today, Think it tomorrow towards implantable neuroprosthetic brain devices'
16.30-17.30, Von Ronnenzaal, k2-052 in the LUMC
more information: <http://www.libc-leiden.nl/colloquia.htm>

December 10, 2007 Swammerdam lecture

Dr. Sacha Nelson (Brandeis Univeristy, USA)

'Physiological genomics of neuronal cell types'
16:00 Colloquiumroom Netherlands Institute for Neuroscience
More information:
<http://www.onwa.med.vu.nl/pages/lectures/swammerdam.htm>

December 13, 2007 RMI seminar

Dr. Kevin J. Mitchell

'The roles of Semaphorin and Plexin genes in specifying brain connectivity and possible involvement in psychiatric disease'
12:00 S41 stratenum UMC Utrecht
More information: Jeroen Pasterkamp,
r.j.pasterkamp@umcutrecht.nl