



Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 43 October 2009

PhD theses

Many of our PhD students have defended their thesis in the last couple of months. We want to congratulate all of them with their doctorates.

2009-18

September 3, 2009

M.P. van den Heuvel

The connected Brain

H.E. Hulshoff Pol, R.S. Kahn

Supervisors

Dept. Psychiatry

Section Brain changes in developmental disorders

Our brain is a *network*. A very efficient network, to be precise. It consists of a large number of different regions, that each have their own speciality, but who are always communicating to each other. The past 30 years of functional neuroimaging has learned us an incredible amount of information about the function of each of these specific regions, but how functional communication *between* brain regions is organized remains largely unexplored. In his thesis Martijn van den Heuvel takes the reader on a journey to explore how the different regions of the brain communicate to each other and how our brain forms one integrative complex network.

organized? How do brain regions share information, do such functional communication channels overlap with physical white matter communication channels in the brain? And how efficiently can brain regions share their information? In their studies using a novel graph analytic approach to analyze resting-state fMRI data, Martijn et al explain that communication within the brain is not just a random mess, but that it is organized according to one of the most *efficient* topologies that nature has to offer and directly linked to our level of cognitive performance.

Martijn van den Heuvel received his PhD (cum laude) on the 3rd of September 2009, successfully defending his thesis 'the connected brain'.

2009-19

September 3, 2009

F.M.J. Jacobs

Pitx3 and Nurr1 in control of terminal control differentiation of Mesencephalic dopamine neurons

J.P.H. Burbach, M.P. Smidt

Supervisors

Dept. Neuroscience and Pharmacology

Section Neurodevelopment

2009-21

September 15, 2009

E. van den Berg

**Type 2 diabetes and cognition.
Neuropsychological sequelae of vascular risk factors in the ageing brain**

L.J. Kappelle, R.P.C. Kessels, G.J. Biessels

Supervisors

Dept. Neurology and Neurosurgery

Section Cerebrovascular disorders

On 15 September 2009 neuropsychologist Esther van den Berg defended her PhD thesis on cognition in patients with



the connected brain

In 'the connected brain' Martijn explores the human brain as an integrative network. Which brain regions share the most information? How are the different functional communication channels in the brain network

type 2 diabetes mellitus. Diabetes is associated with slowly progressive changes in the brain, resulting in mild to moderate decrements in cognitive functioning and an increased risk of dementia. The central topic of the thesis was to examine at which stage of the diabetes these cognitive decrements start to develop, how they progress over time and to examine the role of vascular risk factors, such as hypertension and obesity, in this relation. In one of the principal studies of the thesis, Van den Berg compared cognitive functioning between patients with recent onset type 2 diabetes, persons with the metabolic syndrome (a 'pre-diabetic' condition encompassing hypertension, obesity and dyslipidemia, but no diabetes) and a group of healthy control participants. Both patient groups showed worse cognitive performance compared to the controls, but there was no difference in performance between persons with T2DM or metabolic syndrome. The results of this study, in accordance with other studies in the thesis, indicate that diabetes-associated cognitive decrements are the result of an insidious process, starting years before the onset of the diabetes. It involves prolonged exposure to vascular risk factors, such as hypertension and obesity, and may change over time as a consequence of both exposure time and the changes in the level of these risk factors that occur with increasing age.

2009-22

September 17, 2009

P.C.M.P. Koolschijn

Brainstorm Structural brain abnormalities in schizophrenia and depression

H.E. Hulshoff Pol, R.S. Kahn

Supervisors

Dept. Psychiatry

Section Brain changes in developmental disorders

In his thesis "Brainstorm" Cédric Koolschijn described a variety of studies that explore structural brain abnormalities in schizophrenia and major depressive disorder.



This main title may need some clarification. Probably the first association you have with this word will be that of a session to generate new ideas. In a way, that is exactly what this thesis-trajectory was all about. Brainstorm also means a short-term "malfunctioning" of the brain or the "convolution of the brain" like a gyrus, but then in a more

figurative manner. In addition, taking brainstorm in a literally point of view, it can be argued that there is an actual storm going on in the brain of patients with schizophrenia (e.g. hallucinations) and patients with major depressive disorder (e.g. severe mood changes). In this thesis a variety of structural magnetic resonance imaging (MRI) studies in schizophrenia and major depressive disorder are described. The importance of genetic research by means of twin models, or the search for candidate genes and relating them to brain morphometry is highlighted. Furthermore, evidence is provided to show the importance of longitudinal (MRI) studies when investigating age-related changes or the confounding influences of antipsychotic medication on brain morphometry. In addition, the combination of different MRI techniques such as cortical thickness measurements and voxel-based morphometry can provide a better understanding of what is going on in the brain, not only cortical but also subcortical. Finally, we have shown that the application of meta-analytic methods in MRI research increases our knowledge of which brain structures are affected, and shows the path to which future research should be directed.

2009-23

September 22, 2009

M.F. Aukes

Genetics of cognitive endophenotypes in schizophrenia: a family-based study

R.S. Kahn, M.M. Sitskoorn, B.Z. Alizadeh

Supervisors

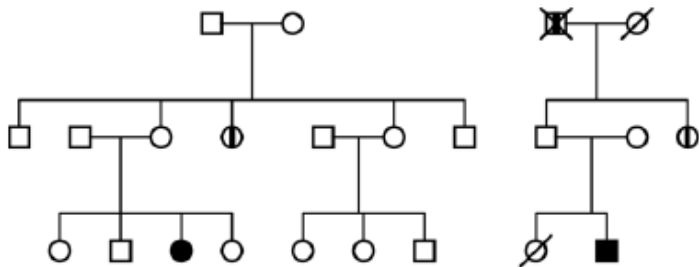
Dept. Psychiatry

Section Genetic basis of developmental disorders

Schizophrenia is a highly heritable, though complex disease; multiple genes and environmental factors contribute to its development. Most of these genes have small effects on schizophrenia. Therefore, the localization and identification of genes for schizophrenia has been difficult. An alternative method is to measure characteristics related to schizophrenia that are less complex phenomena, so-called endophenotypes. If endophenotypes are less complex clinically and genetically than schizophrenia itself, it may be easier to find underlying genes. Because of the link between endophenotype and schizophrenia, a gene linked to an endophenotype may also be involved in schizophrenia. The main objective of these studies was to unravel the genetic characteristics of promising endophenotypes for schizophrenia and to apply these in genetic research. In this thesis, the heritable characteristics of 13 candidate endophenotypes for schizophrenia were investigated, including neuropsychological, psychophysiological, and personality traits, in multigenerational families with multiple members affected with schizophrenia. Only five of 13 measures showed moderate within-family correlations and equivalent heritability estimates. Segregation analysis showed that a simple mode of transmission was likely for just two endophenotypes. Subsequently, it was found that both shared and distinct genetic contributions underlie these heritable endophenotypes. Intelligence strongly overlaps genetically with a known cognitive endophenotype for schizophrenia, i.e., spatial working memory and may thus be a promising endophenotype for genetic research in schizophrenia.

A genome-wide linkage scan using the heritable endophenotypes was performed to search for loci of interest. The linkage results were combined with information about biological functions of positional candidate genes and independent data of gene expression in brain tissue of schizophrenia patients, guiding us towards the NTRK3 gene as a susceptibility gene for schizophrenia. Also, linkage analysis using theta activity at occipital sites revealed several linkage peaks of interest, including the locus for DTNBP1.

These studies are an example of how phenotype analysis in pedigrees, linkage mapping, gene expression data in brain tissue, and association testing in cases and controls can be used jointly in order to study the genetic basis for complex neuropsychiatric traits.



2009-24
September 29, 2009

M. Maessen

Care and decision-making at the end of life of ALS patients

L.H. van den Berg, G. Van der Wal, J.H. Veldink, B.D. Onwuteaka-Philipsen

Supervisors
Dept. Neurology and Neurosurgery
Section Neuromuscular diseases

2009-25
October 26, 2009

N.C.C. Vulink

Feelings of incompleteness Studies on dopamine in obsessive-compulsive disorder

H.G.M. Westenberg, D.A.J.P. Denys

Supervisors
Dept. Psychiatry
Section Psychopathology of developmental disorders

Although obsessive-compulsive disorders have been subject to intense multimodal research, their pathogeneses are yet to be fully understood. However, increasing evidence from both preclinical and clinical studies support a role for dopamine in OCD. The studies in this thesis provide circumstantial evidence for the involvement of dopamine in OCD. On the one hand, first exacerbation of OCD symptoms by blocking the dopamine transporter (DAT) with bupropion in OCD patients, and second augmentation of the efficacy of citalopram by blocking the D₂ receptor with quetiapine, both confirm dopamine abnormalities in OCD. On the other hand, (1) the absence of abnormal striatal D₂ receptor binding at

baseline in a [¹¹C]raclopride PET study, (2) no differences in change in BP of [¹¹C]raclopride in the striatum after amphetamine in a [¹¹C]raclopride PET study, together with (3) similar distributions of genotypes or allele frequencies of the COMT or DRD2 receptor between responders and nonresponders to citalopram with quetiapine, challenges the evidence for dopamine alterations in OCD. However, conclusions from our PET and pharmacogenetic study are limited by small sample size. Therefore, enlargement of the sample in future studies is warranted. Heterogeneity of OCD symptoms of participants in our PET study could also be a potential confounder, since various neuroimaging studies suggest that different symptoms may be mediated by distinct neural systems.

Taken together, results from this thesis show that patients with OCD who have never been treated before, preferentially benefit from a combination of a SSRI and quetiapine, compared to monotherapy with SSRIs. Immediate augmentation increases the number of responders, though psychiatrists need to consider the increased number of dropouts due to side effects with add-on therapy. Genetic research can provide additional information which patients will respond to a combination of SSRIs and quetiapine.

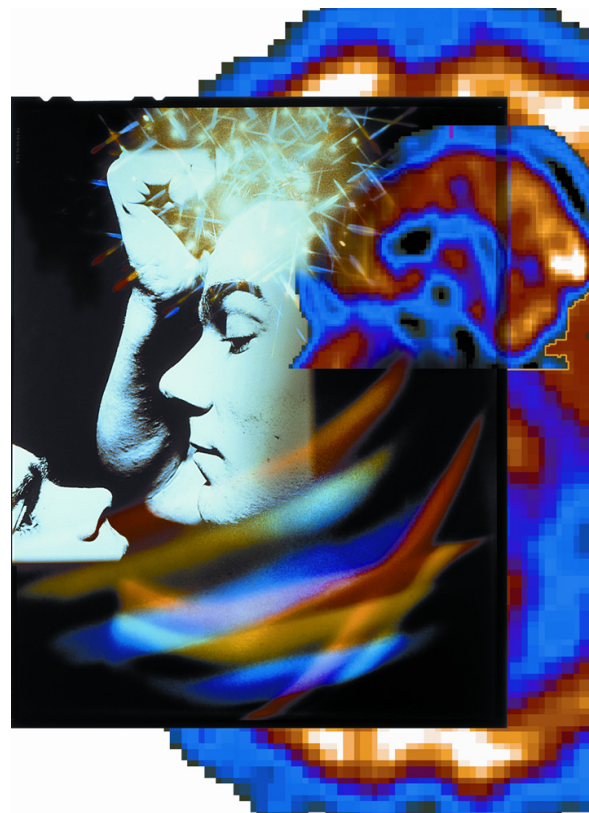


Photo by Chris Timmers

news and other things

Nature Genetics paper

Michael van Es, department of Neurology and Neurosurgery, is first author on a Nature Genetics paper entitled "Genome-wide association study identifies 19p13.3 (UNC13A) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis".

Michael van Es *et al.*, 2009, Nature Genetics 6 September 2009 Epub.

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: Martijn van den Heuvel (September 3, 2009), Esther van den Berg (September 15, 2009), Cédric Koolschijn (September 17, 2009), Nienke Vulink (October 26, 2009)

agenda and announcements

October 7, 2009 Swammerdam lecture

David McCormick (Yale University, USA)

'Cortical network dynamics'

more information: <http://www.onwa.med.vu.nl/swammerdam>

October 14, 2009 CSCA lecture

John-Dylan Haynes (Berlin, Germany)

'Decoding conscious and unconscious mental states from brain activity in humans'

Amsterdam

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

October 15, 2009 'Publieksdag Hersenstichting'

more information: <http://www.hersenstichting.nl/activiteiten/alle-activiteiten/publieksdag-2009.html>

October 28, 2009 Research lunch psychiatry

aula psychiatry, UMC Utrecht

12.00hr -13:00hr, lunch provided

more information: i.sommer@umcutrecht.nl

October 30, 2009 Swammerdam lecture

Carl Petersen (Ecole Polytechnique Fédérale de Lausanne, Switzerland)

'Synaptic mechanisms of sensory perception'

more information: <http://www.onwa.med.vu.nl/swammerdam>

November 2, 2009 Swammerdam lecture

Gilles Laurent (Caltech, Pasadena, USA)

'Dynamics and coding in an olfactory circuit'

more information: <http://www.onwa.med.vu.nl/swammerdam>

November 12, 13 2009 Symposium

International symposium on the social brain at work

Utrecht

more information: <http://socialbrain.fmri.nl/>

November 19, 2009 Swammerdam lecture

Tim Tully (Dart Neuroscience LLC, San Diego, USA)

'Enhancing memory'

more information: <http://www.onwa.med.vu.nl/swammerdam>

November 20, 2009 FC Donders Lecture

Marty Sereno (UCL/Birbeck, Londen, UK)

Donders Centre for Cognitive Imaging, Nijmegen

15.00hr-17:00hr and free drinks

more information: neuroimaging@donders.ru.nl

November 25, 2009 Research lunch psychiatry

aula psychiatry, UMC Utrecht

12.00hr -13:00hr, lunch provided

more information: i.sommer@umcutrecht.nl

November 25, 2009 RMI symposium

Green lecture hall, UMC Utrecht

13.30-18.00, drinks afterwards

More information:

http://www.umcutrecht.nl/subsite/Rudolf_Magnus_Institute

December 2, 2009 KP7 project symposium

How to build the Dopamine system

Blue lecture hall, UMC Utrecht

11.00hr -18:15hr

Presented by the EU FP7 mdDANeurodev consortium

Coordinated by Marten Smidt

more information: www.mdDANeurodev.eu, meetings

December 9, 2009 CSCA lecture

Eveline Crone (Leiden)

'Social decision-making in adolescence: changes in brain regions important for intention considerations'

Amsterdam

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

December 18-19, 2009 2009 NVP winter conference

Cognition, Brain and Behaviour

Egmond aan Zee

more information: <http://nvpcongres.eur.nl/>

