Rudolf Magnus
Institute of Neuroscience

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PhD program RMI updated

The Rudolf Magnus Institute was among the first graduate schools in Neurosciences in The Netherlands. Recently the RMI has restructured its PhD program, to bring it as close as possible to the daily work and interest of its students.

In 1994, the PhD training program of the Rudolf Magnus Institute was first accredited by the Royal Netherlands Academy of Arts and Sciences. Providing an optimal training program for its PhD students has ever since been one of the major goals of the institute. Nowadays the institute harbors on average 180 PhD students at any time. Most of these are enrolled in the RMI PhD program in Clinical and Experimental Neuroscience. This program also forms one of the tracks of the Utrecht Graduate School of Life Sciences (UGS-LS).

The recent definition of the UGS-LS regulations as well as the change in directorship of the RMI in spring was seen as an excellent opportunity to renew the program. Leading principle is that at the end of their PhD period students not only have a thesis of excellent quality but also have all the knowledge and skills to independently perform Clinical and Experimental neuroscientific research at an internationally competitive level. Training should be practical in every sense of the word, i.e. close to the interest and requirements of the students, and provided during clear time-slots in the year.

RMI symposium

A good example of this policy is the range of skill courses that will be offered to students of the program. All courses have a similar format, in which a topic is addressed in a plenary workshop, after which students independently work on an assignment and receive personal feedback from the tutor. For instance, the making of an effective (oral) scientific presentation will start with a plenary session in which the do's and don'ts will be highlighted. Subsequently, each student who has participated in the workshop can send his/her first presentation for feedback to the tutor and receive constructive comments and advise. This format will be used for many diverse subjects, including statistics, time management and English writing. Needless to say, students who look for more in-depth training can enroll in more extensive courses.

All workshops are offered twice yearly: during the RMI retreat in April and early in September. The workshops run in three parallel tracks, i.e. one for starting PhD students, the second for those that are in the middle of their project and the third for students that are close to completing their training. The latter set encompasses e.g. a workshop on grant writing, but also one that supplies professional support in career orientation.

RMI retreat

Apart from these skill workshops, the PhD program aims to provide students with thorough background knowledge in Clinical and Experimental Neuroscience. Students can subscribe to any number of the topical PhD courses which are collectively offered by the Graduate School Neurosciences Amsterdam Rotterdam and the Rudolf Magnus Institute. This collaboration ensures that students both from Amsterdam / Rotterdam and from Utrecht have a wide array of courses to choose from. Within this program, the RMI will take responsibility for subjects that are at the heart of its scientific work. For instance, the RMI provides a biennial course in Neurodevelopment, one of the spearheads of its research activities. New is the annual course on Current Issues in Clinical Neuroscience. This course will give a comprehensive overview of the state of affairs in selected areas of Clinical Neuroscience, alternating between the field of Neurology, of Psychiatry or subjects that are linked to both fields. World experts on the subject will contribute

to the courses, making the program attractive not only to PhD students but also to research-oriented neurologists or psychiatrists in The Netherlands. In 2011 the course will address the latest insights in 'prediction models and risk assessment in complex multifactorial disorders'. As of old, the RMI also participates in the organization of the biennial course in Neuropsychopharmacology.

In addition to these in-depth courses, the PhD period is perfectly suited to broaden one's view. Therefore, students of the RMI program are expected to also engage in events that extend beyond their own area of expertise. Such events with a broader scope include (among other possibilities) the annual RMI symposium in fall and the Neuroscience & Cognition Utrecht research-day early in September.

Apart from these obligatory elements, there is a large degree of freedom for students in composing the rest of the program. Participating in other Dutch PhD programs in neuroscience, in international conferences, journal clubs or clinical training can all be part of the overall program. A special place is reserved for international training, outside of The Netherlands. In this respect the current standing collaboration with the Institute of Psychiatry in London and a soon-to-be-started collaboration with a limited number of other European partners are worth mentioning.
An effective and stimulating PhD program is one of the cornerstones of a research institution. The Rudolf Magnus Institute regards its program in Clinical & Experimental Neuroscience as such and hopes that its students will see the program as a worthy finishing touch to their education.

PhD theses

Over the past months, 8 RMI PhD students have defended their thesis. For a regular update, please check News on: http://www.umcutrecht.nl/subsite/Rudolf_Magnus_Institute/

M.J. Mulder (June 3, 2010) Cognitive Control and Decision Making in ADHD. Supervisors H. van Engeland, S. Durston, dept. Psychiatry

Mw. M.W.A. de Backer (June 3, 2010) Optimization of viral vector technology to study gene function in the hypothalamus. Supervisor R.A.H. Adan, dept. Neuroscience and Pharmacology

D. Steenbeek (June 15, 2010) Coal Attainment Scaling in Paediatric Rehabilitation Practice: a useful outcome measure. Supervisors E. Lindeman, M. Ketelaar, J.W. Gorter, dept. Rehabilitation, Nursing science and Sport

T.P.C. van Doormaal (June 24, 2010) Evaluation and further development of the Excimer Laser Assisted Non-occlusive Anastomosis (ELENA) technique. Supervisors L.P.E. Regli, A. van der Zwan, dept. Neurology and Neurosurgery

Tristan started his study medicine at the 'Limburgs Universitair Centrum' in Diepenbeek, Belgium for 2 years. In 2000, he continued his medical training at the Radboud University in Nijmegen, The Netherlands. In 2002, as student assessor, he was a full-time member of the research and educational board of the University Medical Center (UMC) St. Radboud, Nijmegen, The Netherlands. In 2007 he became part of the ELANA research team as PhD student at the UMC Utrecht, The Netherlands (supervisors prof. dr. C.A.F. Tulleken, dr. A. van der Zwan, dr. B.H. Verweij and prof. dr. L. Regli), and was trained in microsurgical techniques. In the upcoming years, Tristan will be trained as neurosurgeon in the UMC Utrecht (supervisor: Dr. J.W. Berkelbach van der Sprenkel). He will continue his research in vascular neurosurgery by supervising new PhD students which work in the specially designed ELANA laboratories.
Tristan describes in his thesis the work he has done to develop and optimize the ELANA technique. The ELANA technique is a method to construct a bypass to the brain without the need to temporarily occlude a brain artery. The ELANA technique was originally invented in the UMC Utrecht by Prof.dr. C.A.F. Tulleken. The research described in the thesis had 2 main goals. The first goal was to evaluate the results of the ELANA technique in various patient subgroups. The results showed that the ELANA technique is safe and effective, but that it can be technically challenging. Therefore the second goal of the research was to make the technique easier and faster, i.e. even less invasive to the brain. The result was a new 'sutureless' ELANA or 'SELANA' technique. Short and long term in-vivo results were very promising. Currently a pilot study in patients is prepared.
The research resulted in 6 families of patents over the past 3 years (all currently pending). During these years, van Doormaal, together with the other members of the ELANA team in Utrecht, trained 50 neurosurgeons from 20 different countries in the ELANA technique. The main result of his research until now is the SELANA anastomosis, which is designed to make a safe anastomosis in the brain to treat otherwise untreatable aneurysms, arterial occlusions and brain tumors. In September 2010 a pilot study will start in the UMC Utrecht to assess the technique for the first time in patients. Together with Dr J.W. Berkelbach, he recieved an NWO grant to build a dedicated laboratory in which reperfused human corpses can be operated. In this laboratory, which is nearly finished, new operative techniques can be developed and a wide range of neurosurgical procedures can be trained.

H.C. Stronks (June 29, 2010) Interaction of electrically and acoustically evoked responses in the cochlea of the guinea pig. Supervisors W. Grolman, S.F.L. Klis, dept. EN&T

Mw. A.H.B. van Langeveld (July 8, 2010) The Spinal Cord Injury- Interventions Classification System (SCI-ICS). Supervisors E. Lindeman, M.W.M. Post, dept. Rehabilitation, Nursing science and Sport

Mw. E.V.S. Hessel (September 23, 2010) Identification of febrile seizure susceptibility genes. Studies in mouse chromosome substitution strains and temporal lobe epilepsy patients. Supervisors J.P.H. Burbach, O. van Nieuwenhuizen, P.N.E. de Graan, M.J.H. Kas, dept. Neuroscience and Pharmacology

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T.B. Ziermans (September 30, 2010) In transition: A longitudinal exploration of the adolescent brain at risk for psychosis. Supervisors H. van Engeland, C. Kemner, S. Durston, P.F. Schothorst, dept. Psychiatry

Publications

Over 60 papers have been published by investigators from the Rudolf Magnus Institute in the months July, August and September. A selection of these papers, which appeared in the top 10% journals, are highlighted below. For a regular update, please check News on: http://www.umcutrecht.nl/subsite/Rudolf_Magnus_Institute/

Human Brain Mapping 2010 Aug;31(8):1117-27.
Reduced functional coupling in the default-mode network during self-referential
processing.
Van Buuren M, Gladwin TE, Zandbelt BB, Kahn RS, Vink M.
Dept. Psychiatry

Activity within the default-mode network (DMN) is thought to be related to self-referential processing. Although the DMN is generally considered to function as a network, evidence accumulates suggesting that areas of the DMN are each specialized for different subfunctions of self-referential processing. The results in this article provide an indication for such functional specialization within the DMN.

Human Molecular Genetics. 2010 Aug 4. [Epub ahead of print]
A large genome scan for rare CNVs in amyotrophic lateral sclerosis.
Blauw HM, Al-Chalabi A, Andersen PM, van Vught PW, Diekstra FP, et al.
Dept of Neurology and Neurosurgery

Recent genome-wide association studies have identified several common variants which increase disease susceptibility. In contrast, rare copy-number variants (CNVs), which have been associated with several neuropsychiatric traits, have not been studied for ALS in well-powered study populations. The results of this study show, that although two loci are indicated for more thorough investigation, rare CNVs with high effect size do not play a major role in ALS pathogenesis.

Proceedings of the National Academy of Science USA. 2010 Aug 10;107(32):14449-54
Karst H, Berger S, Erdmann G, Schütz G, Joëls M.
Dept. Neuroscience and Pharmacology

The authors of the article describe a rapid mineralocorticoid receptor-dependent enhancement of glutamatergic transmission in basolateral amygdala neurons. Contrary to the hippocampus, this rapid enhancement is long-lasting, potentially allowing an extended window for encoding of emotional aspects during stressful events. Renewed exposure to corticosterone rapidly suppresses glutamate transmission. Responses of basolateral amygdala neurons to the stress hormone corticosterone can thus switch from excitatory to inhibitory, depending on the recent stress history of the organism.

Progress in Neurobiology 2010 Jul 15. [Epub ahead of print]
Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia.
Bossong MG, Niesink RJ.
Dept. Neurology and Neurosurgery

This review reports the results of a literature search comprising various neurobiological disciplines, ultimately converging into a model that might explain the neurobiology of cannabis-induced schizophrenia.

Schizophrenia Bulletin 2010 Jul;36(4):778-87.
Tract-based analysis of magnetization transfer ratio and diffusion tensor imaging of the frontal and frontotemporal connections in schizophrenia.
Mandl RC, Schnack HG, Luigjes J, van den Heuvel MP, Cahn W, et al.
Dept. Psychiatry

In the pathophysiology of schizophrenia, aberrant connectivity between brain regions may be a central feature. Imaging studies have shown altered fractional anisotropy (FA) in white brain matter in schizophrenia. Focal reductions in myelin have been suggested in patients but to what extent is still unknown. In this article the authors show that decreased FA in the left uncinate fasciculus may be more prominent in patients with longer illness duration. A compensatory role for myelin in uncinate fasciculus fibers could reflect or possibly represent aberrant frontotemporal connectivity.

Stroke 2010 Aug;41(8):1736-42.
Cost-effectiveness of magnetic resonance angiography versus intra-arterial digital subtraction angiography to follow-up patients with coiled intracranial aneurysms.
Schaafsma JD, Koffijberg H, Buskens E, Velthuis BK, van der Graaf Y, et al.
Dept. Neurology and Neurosurgery

To follow up patients with coiled intracranial aneurysms, magnetic resonance angiography (MRA) is a promising noninvasive alternative to current standard intra-arterial digital subtraction angiography (IA-DSA). MRA test results do not always concord with those of IA-DSA, and the impact of discrepancies on health benefits and costs is unknown. The authors show that MRA provides equivalent health benefits as IA-DSA and is cost-saving. MRA dominates and should replace routine IA-DSA to follow-up patients with coiled aneurysms.

Trends in Cell Biology 2010 Sep;20(9):568-76
Semaphorin signaling: molecular switches at the midline.
Derijck AA, Van Erp S, Pasterkamp RJ.
Dept. Neuroscience and Pharmacology.

This review reports on recent breakthroughs in our understanding of the extrinsic signals and molecular processes that control growth cone responses to class 3 semaphorins (Sema3s) at a well-characterized intermediate target, the spinal cord midline.

Trends in Pharmacological Sciences 2010 Oct;31(10):463-9
The pleasures of play: pharmacological insights into social reward mechanisms.
Trezza V, Baarendse PJ, Vanderschuren LJ.
Dept. Neuroscience and Pharmacology

The authors address in this review the notion that social play is rewarding, and discuss recent developments in the neuropharmacology of this behavior. This provides a framework to understand how the brain processes social emotions, to make young individuals enjoy social play.

Stroke 2010 Oct;41(10):2391-5
Definition of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage as an Outcome Event in Clinical Trials and Observational Studies. Proposal of a Multidisciplinary Research Group.
Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF et al.
Dept. Neurology and Neurosurgery

This paper deals with the problem of inconsistencies in the use of definitions to describe delayed cerebral ischemia (DCI). The authors propose two main outcome measures for clinical trails and observational studies which aim to investigate strategies to prevent DCI.

Int J Obes 2010 Aug 24. [Epub ahead of print]
Melanocortin receptor-mediated effects on obesity are distributed over specific hypothalamic regions.
De Backer MW, la Fleur SE, Brans MA, van Rozen AJ, Luijendijk MC et al.
Dept. Neuroscience and Pharmacology

That reduction of melanocortin signaling results in obesity is known, however, where in the brain this effect takes place is poorly understood. The authors describe in this paper the knockdown of the melanocortin signaling pathway using virus mediated silencing. They show the effects of the knockdown and conclude that AgRP and NPY have complementary roles in energy balance.

Diabetes Care 2010 Jun;33(6):1309-14.
Progression of cerebral atrophy and white matter hyperintensities in patients with type 2 diabetes.
De Bresser J, Tiehuis AM, van den Berg E, Reijmer YD, Jongen C et al.
Dept. Neurology and Neurosurgery

The authors address in this paper the association between type 2 diabetes with a moderate degree of cerebral atrophy and a higher white matter hyperintensity volume. They describe the follow up study over 4 years of type 2 diabetes and control patients. The conclusion of the authors is that there is a greater increase in lateral ventricular volume in type 2 diabetes patients, which associates with a slow increase in cerebral atrophy.

Schizophr Bull 2010 Sep 23. [Epub ahead of print]
Kraepelin Was Right: A Latent Class Analysis of Symptom Dimensions in Patients and Controls.
Derks EM, Allardyce J, Boks MP, Vermunt JK, Hijman R et al
Dept. Psychiatry

The authors address in this paper the reason why genetic variants contributing to schizophrenia risk explain only a fraction of the heritability. They argue that phenotypic heterogeneity within patients might be the reason why. Using combined factor analysis and latent class analysis the authors show that reduction of phenoptypic heterogeneity within psychosis patients and controls might facilitate etiological research.

J Neurosci 2010 Sep 22;30(38):12725-32.
Time-dependent effects of corticosteroids on human amygdala processing.
Henckens MJ, van Wingen GA, Joëls M, Fernández G.
Dept. Neuroscience and Pharmacology

This paper deals with the association of acute stress with a sensitized amygdala. The authors investigate the effects of corticosteroids on amygdale processing, by scanning healthy male subjects who are exposed to faces with different expressions. The results of the study indicate that there is a fine tuned mechanism in the brain that is critical for avoiding amygdale overshoot during stress and enabling adequate recovery after stress.

J Am Geriatr Soc 2010 Jul;58(7):1318-21.
Glycemia and levels of cerebrospinal fluid amyloid and tau in patients attending a memory clinic.
Exalto LG, van der Flier WM, Scheltens P, Biessels GJ.
Dept. Neurology and Neurosurgery

Whether or not there is an association between markers of glycemia and cerebrospinal fluid amyloid beta 1-42 and tau levels in patients visiting a memory clinic is the objective of the authors of this paper. The authors show that their data do not support the hypothesis of an association between dysglycemia and impaired cognitive functioning through aberrant amyloid or tau metabolism.

Grants

Several grants were obtained by researchers from the institute. These vary form prestigious national, European to American grants. Two of the recipients are highlighted. For a regular update, please check News on: http://www.umcutrecht.nl/subsite/Rudolf_Magnus_Institute/

Four investigators were involved in grants awarded through the Programmes of Excellence, as part of the NWO 'Brain and Cognition: an integrated approach': **Hilleke Hulshof Poll** (dept. Pychiatry) as main applicant, **Marian Joëls** (dept. Neuroscience and Pharmacology) as co-applicant, **Sarah Durston** (dept. Psychiatry) and **Frans Leijten** (dept. Neurology and Neurosurgery) both as collaborators.

Hilleke Hulshoff Pol is appointed as professor in Psychiatric disorders at the UMC Utrecht. She is the head of the neuro-imaging research group of the department of Psychiatry. Hulshof Poll received her masters in psychophysiology at Utrecht University. She transferred for an internship in neuropsychology to the University of California in San Diego to return to Utrecht for her doctorate research at the Rudolf Magnus Institute. In 1995 she has been appointed member of staff of the department of Psychiatry at the UMC Utrecht and started the research group structural neuro-imaging. Hulshoff Pol uses magnetic resonance imaging to do research into structural and functional plasticity of the human brain, as well of psychiatric patients (mainly schizophrenic patients) as of healthy persons. She received a VIDI from NWO and a high-potential grant from the Utrecht University.

The grant she received in the Programmes of Excellence focuses on intellectual ability and the role of the functional brain network herein. During adolescence the structure of the human cortex changes considerably. These plastic changes are associated with intellectual ability. Intellectual ability is strongly associated with global efficiency of functional brain networks. Functional brain networks are influenced by genes. However, it is presently unknown if and how functional brain network plasticity changes and if these changes differ with intellectual ability. Also, it is unknown if such plastic properties of functional brain networks are heritable or due to environmental experiences. Indeed, does functional brain network efficiency improve with age for optimal transition from childhood to adulthood?

In a unique longitudinal setup, using the extended twin design, a total number of 200 monozygotic and dizygotic twins scanned at the age of 12 years, and their siblings, will be followed up 3 years later at age 15. Changes in (resting-state) fMRI, DTI, cortical thickness, cognitive function, and gonadal hormone levels will be measured. This longitudinal twin-study will disentangle genetic and environmental patterns of functional neural network maturation during adolescence. By joining efforts of the Department of Biological Psychology at the VU Amsterdam and the Neuroscience division at the UMC Utrecht, and additional scientific input from Experimental Neurology at the VU Amsterdam and McGill University Montreal, a strong added value is added to this project because of combined expertise in twin research, cognition with imaging research including functional neural networks expertise in a unique longitudinal setup in twins. This is the first developmental-genetic study of plasticity in functional neural networks and its relation to cognition. Findings from this study will not only provide insight in normal cognitive brain development during adolescence but also aid study into psychiatric diseases that are accompanied by cognitive problems and often show their first symptoms during adolescence, such as schizophrenia and depression.

Roger Adan (dept. Neuroscience and Pharmacology) participates in three frame work 7 projects of the European Union. The projects are entitled:

Neurofast: The Integrated Neurobiology of Food Intake, addiction and Stress.

Full4Health: Understanding food-gut-brain mechanisms across the lifespan in the regulation of hunger and satiety for health.

I-Family: Determinants of eating behaviour in European children, adolescents and their parents.

Viviana Trezza (dept. Neuroscience and Pharmacology), was awarded an NWO VENI grant.
Over the past 5 years, Viviana's research focused on two main themes: 1. the role of endocannabinoid signalling in the modulation of emotions and cognition; 2. the neurobiology of social behavior.

The endocannabinoid system is a unique neuromodulatory system in mammalian physiology. It consists of cannabinoid receptors, their endogenous lipid ligands (endocannabinoids) and the enzymatic machinery for their synthesis and degradation.

In the brain, the ability of endocannabinoids to modulate synaptic efficacy has a wide range of functional consequences and provides unique therapeutic possibilities. The research she performed during her PhD at the University of Rome "Sapienza" showed that endocannabinoid neurotransmission plays an important role in the control of emotionality and in consolidation of emotional memories, and that manipulating the

endocannabinoid system during development induces long-lasting consequences on cognitive performance and emotionality in rats.

She followed up on these studies at the Department of Neuroscience and Pharmacology of the Rudolf Magnus Institute of Neuroscience, where she moved in 2005 to work in the laboratory of Louk Vanderschuren, who has established a scientific program to understand the neurobiology of social behavior, impulsivity and drug addiction. They investigated the role of endocannabinoid neurotransmission in social behavior by focusing on social play behavior, that is the most characteristic social activity displayed by young mammals. It is highly rewarding and essential for proper cognitive and social development. Their studies revealed a novel role for endocannabinoid neurotransmission in the modulation of social play behavior in adolescent rats, in concert with opioid and dopaminergic systems. Furthermore, they revealed the neural mechanisms underlying the effects of methylphenidate, nicotine and ethanol on social play, and developed new behavioral paradigms to investigate the rewarding, motivational and cognitive aspects of social play.

Altogether, these studies provided the foundations for her VENI proposal, titled “Neurobiology of social behavior in adolescent rats: towards novel pharmaco-therapies for social dysfunctions”. By combining intracerebral drug administration, immunohistochemistry and neurochemical experiments, they will aim at identifying the neural substrates of social play. Furthermore, they will combine classical ethological analysis of social behavior with Pavlovian and instrumental conditioning tasks to dissociate the hedonic, motivational and cognitive aspects of social play. This will help them to understand how separate, but interacting neural circuits produce an integrated sequence of social behaviors. Last, they will test the possibility that pharmacological manipulation of social play might be clinically relevant, by investigating the effects of drugs that increase social play in rat models of abnormal social behavior. This might open new therapeutic opportunities to treat social dysfunctions. Given the high prevalence of neuropsychiatric diseases with specific impairments in social behavior, the development of such therapies is of the utmost importance.

Marjolein Ketelaar (dept. Rehabilitation, Nurse Science and Sport) received a research grant from the Innovation Program Rehabilitation. This grant has been given to implement guidelines for diagnosis and treatment of children with cerebral palsy.

Marco Boks, Rene Kahn and Roel Ophoff (dept. Psychiatry) received a large grant from the American NIH for their project entitled: “Genomic Studies of Bipolar Disorder in a Large Cohort from The Netherlands”.

Bart van der Worp (dept. Neurology and Neurosurgery) received a large grant from the Dutch Heart Foundation for his project entitled: “Surface cooling for acute ischaemic stroke”.

Martien Kas (dept. Neuroscience and Pharmacology) received a grant from the Swiss Anorexia Foundation.

Sanne Dorhout Mees and Gabriël Rinkel (dept Neurology and Neurosurgery) received a grant from the Dutch Brain Foundation for the study:
'Relation between cerebral autoregulation and secundairy ischemia after stroke'

agenda and announcements

Award

Martijn van den Heuvel (dept. Psychiatry) has been awarded the 2010 prize by the ‘Provinciaal Utrechts Genootschap van kunsten en wetenschap’.

October 27, 2010 RMI Symposium

Brain connections, genes and disease
14:.00-18:00 UMC Utrecht, lecture hall Pink
More information: Krista Poel, k.poel@umcutrecht.nl