



Rudolf Magnus Institute of Neuroscience

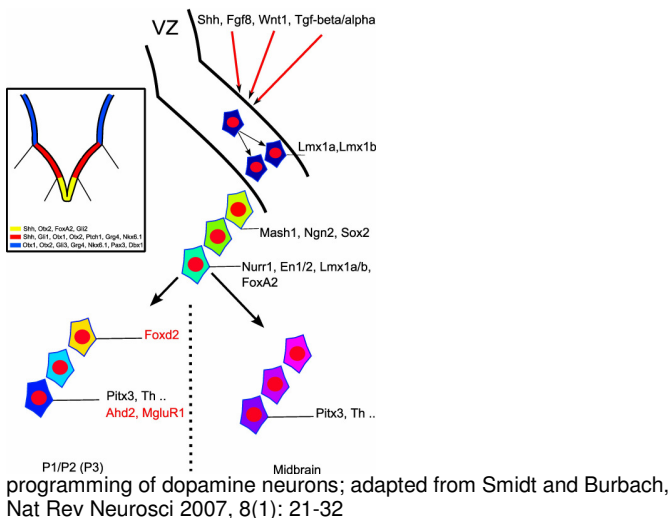
Rudolf Magnus Bulletin 40
July 2008

Marten Smidt receives large FP7 grant

In the RMI bulletin of May 2008 we announced that Marten Smidt of the department of Neuroscience and Pharmacology and the section Neurodevelopment, received funding (2.6 million Euros) of the FP7 initiative for his collaborative research project entitled: "Molecular coding and subset specification of dopamine neurons generating the meso-limbic and nigro-striatal system." In this article more details concerning this grant.

The project of the consortium led by Marten is aimed at identifying molecular and physiological mechanisms of the development and maintenance of mesodiencephalic dopaminergic neurons. The consortium will attempt to reach this aim by combining three distinct levels of research into the dopaminergic system. They will combine research into the patterning, differentiation and pathfinding of the dopaminergic neurons of the meso-limbic and nigro-striatal system.

The first area of attention in the project is the specification of the mdDA neuronal field. During development specific subsets of mdDA neurons are formed. To understand the formation of these specific subsets, the researchers will try to elucidate early specifying factors that encode parts of the ventricular zone and generate mdDA neurons that are destined to become a specific mdDA subset.



The second area concerns the differentiation of mdDA neurons. It is known that many factors play a role during early and late differentiation of the neurons. It is unknown, however, through which molecular markers these

differentiation patterns are established. To understand the relation of this specific differentiation to function and disease, in the project a focus will be on establishing the full molecular pathway from transcription factor to functional unit. The third area has a dual focus with one focus on the migration of young mdDA neurons. The researchers will try to establish the identification of the normal migration pathway of mdDA neurons and then identify the molecules essential to establish the normal migration pattern. The second focus will be axonal outgrowth and connectivity. Although the direction of initial axonal pathfinding has been characterized through the identification of several well-known molecular mechanisms in mdDA neurons, the generation of specific connectivity remains to be characterized, especially in relation to functional and molecular mdDA neuronal subsets. To be able to address the research questions of these three areas the consortium relies on a multidisciplinary genomics and molecularbiology approach.

The fundamental work in this project has a clear link to the clinic. The important link between mdDA neurons and motor, behavioral and emotional dysfunction in disorders of the human CNS has already been established and led to the intense study of this neuronal group, first in the field of pharmacology and more recently in developmental neurobiology. The mdDA neurons are affected in many neurological and psychiatric disorders, including Parkinson's disease, affective disorders such as schizophrenia and autism, and in anxiety related disorders like depression. Results of the fundamental work in this project may lead to the generation of new therapies for diseases such as schizophrenia, autism, depression and addiction.



Marten Smidt

2008-16

June 3, 2008

Mirjam Sprong

Adolescents at risk of psychosis: a comparison of the “At Risk Mental State” and Multiple Complex Developmental Disorder

H. van Engeland, H. Swaab, P.F. Schothorst
supervisors

Mirjam Sprong started her PhD in 2002 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 Psychopathology of developmental disorders.

For the last 5½ years I have been working on my dissertation entitled: “*Adolescents at Risk of Psychosis: a comparison of Multiple Complex Developmental Disorder (MCDD) and the “At Risk Mental State” (ARMS)*”. The main focus of my research was to compare potential vulnerability markers for psychosis in the abovementioned groups of adolescents (12-18 years). Psychosis is one of the core symptoms of schizophrenia. It is a severe disturbance of reality testing, which is evidenced by the conviction that delusions or hallucinations are true, or by disorganized thoughts and behavior. Adolescents diagnosed with MCDD (n=32) have clinical characteristics of autism (social impairments) and schizophrenia (thought disorder), in addition to affective dysregulation (aggression, anger, anxiety) already from early childhood. A small follow-up study has revealed that as much as 60% may develop a schizophrenia-spectrum illness in adulthood. Adolescents in the ARMS group (n=80) have subclinical psychotic symptoms that indicate that they may be in the early stages of developing a psychotic episode. Both groups had high levels of schizotypal personality traits and social difficulties, and did not differ in that respect. Moreover, 78% of the MCDD group met research criteria for ARMS, indicating that they may be in the early stages of psychosis too.

Compared to a group of healthy controls (n=82), both groups showed poorer performances on neuropsychological tasks assessing attention/working memory, psychomotor speed, and verbal output production, indicating that dysfunctions of these neurocognitive domains may represent vulnerability markers for psychosis.

The results of this study are in line with the accumulating evidence that there is considerable overlap in symptomatology and etiology of the diagnostic spectra of autism and schizophrenia, and that MCDD may best be placed right at the point of overlap.

2008-17

June 18, 2008

Jacob Vorstman

Structural genomic abnormalities in autism and schizophrenia. With a focus on the 22q11.2 deletion syndrome

H. van Engeland, R.S. Kahn, F.A. Beemer
supervisors

Jacob Vorstman started his PhD in 2002 after graduating from medical school. He performed his PhD work in the department of Psychiatry and combined his research with a residency in child and adolescent psychiatry. He completed his thesis in the section Genetic basis of developmental disorders.

About 7 years ago, when Prof. Kahn asked me whether I would be interested in doing a PhD research on the 22q11.2 Deletion Syndrome (22q11.2DS) I answered wholeheartedly “yes”. Mainly because from his explanations it was crystal clear to me that this was going to be an exciting topic with studies touching the biological basis of psychiatric disease. But, truth be told, it was also the first time I heard about this syndrome.

Prof. Kahn and van Engeland became interested in this syndrome because at that time studies showed that approximately 20-30% of patients develop schizophrenia. Several years before, Prof. Beemer, medical geneticist, had started to build an impressive database of 22q11.2DS patients. The combined interest of the three professors led to this collaborative project.

When a high proportion of individuals with a well-defined structural genomic abnormality, -in case of 22q11.2DS a piece of chromosome 22 is missing-, develop a psychiatric disease, one can hypothesize that one or more genes involved in the deletion is causally involved. This hypothesis was the central idea of the studies in the thesis. We examined all case reports on structural genomic abnormalities in autistic individuals and identified several genomic regions where multiple cases clustered, indicating the relevance of these regions to the genetic causes of autism.

Regarding 22q11DS, the most obvious psychiatric phenotype is schizophrenia; we examined the role of genetic variation in the remaining allele of genes within the deleted region and identified significant associations with this psychiatric phenotype.

We also applied the same principle to a different structural genomic abnormality; clinical and molecular genetic findings of a boy with autism and a deletion of chromosome 13q. Our result demonstrated a “double hit scenario”: the deletion was inherited from his unaffected mother, while a rare functional variant in the remaining allele of one of the genes in the deletion region, DIAPH3, was inherited from his unaffected father. In addition we demonstrated expression of DIAPH3 in specific brain areas of the mouse during embryonic development. Taken together these findings suggest that DIAPH3 is a plausible candidate gene for autism.

Maurice Magnée**Do you see what I am saying? Studies on multisensory in autism**

H. van Engeland, B. de Gelder, C. Kemner
supervisors

Maurice Magnée started his PhD in 2004 after he had finished his studies in health sciences. He performed his PhD work in the department of Psychiatry and completed his thesis in the section Brain changes in developmental disorders.

The behavior of people with autism is probably largely explained by abnormalities in the processing of visual information. They understand emotional signals, but subtle brain abnormalities prevent the proper processing. I examined thirty educated young people with autism between 16 and 28 years, using EEG. And discovered that people with autism, under the appropriate circumstances, are able to retrieve emotional information from human faces. Because of a different focus of attention during daily life, things could go wrong. Moreover, they were shown to be very sensitive to 'noise' of other, irrelevant, information. In the 'reading' of human faces, people with autism are, therefore, quickly distracted.

Another notable finding of my PhD work is that people with autism some times experienced emotions from faces stronger than healthy people. This may be explained by excessive attention to detail. Take for example the contrast between the white of the eye and the iris; when this is very large, it's frightening. People with autism might perceive normal features of the face such as these very intense, making them inclined to avoid looking at faces. People with autism are indeed able to process emotional information correctly. The study furthermore demonstrates that neither the "social brain" nor the interest in social information is defective in these individuals. The observation itself seems to be lacking.

**Peter Woerdeman****Frameless image-guided neurosurgery in motion**

C.A.F. Tulleken, J.W. Berkelbach van der Sprenkel, H.J. Noordmans, P.W.A. Willems
supervisors

Peter Woerdeman started his PhD in 2003 after he had finished his studies in medicine. He performed his PhD work in the department of Neurology and Neurosurgery and combined his research with a residency in neurology. He completed his thesis in the section Cerebrovascular disorders. After his thesis defence he will complete his training as neurosurgeon at the department.

My thesis describes three research parts. The first part concerns the application of frameless stereotaxy in the neurosurgical practice. We aimed to compare three patient-to-image registration methods in frameless stereotaxy in terms of their application accuracy. The results of this study showed that skin adhesive fiducial marker registration is the most accurate non-invasive registration method. Another objective was to quantify intra- and interobserver variability of manual fiducial localization in image space. The second part dealt with novel applications in frameless trajectory-aligned neurosurgery. We described a novel frameless stereotactic subcaudate tractotomy procedure with promising initial results in a patient suffering from intractable obsessive-compulsive disorder. We also introduced a simple modification to the free-hand frameless stereotactic placement of ventriculoperitoneal shunts in undersized ventricles. The final part was about intraoperative feedback in open image-guided neurosurgery. One of our aims was to analyze the movement of surgical instruments during frameless image-guided neurosurgical procedures. A custom-made log-mode has been implemented in the image-guidance software to file instrument coordinates intraoperatively. To mimic ordinary open neurosurgery, future neurosurgical (tele)robotic systems should at least support the instrument excursions and speeds found in our studies.

In our endeavor to enhance the use and efficacy of neuronavigation systems by improving hardware and augmenting the man-machine interface, we have shown that the field of frameless image-guided neurosurgery is still in motion. With the augmented man-machine interface, we have moved into an entirely new field of neuronavigation development, concerning the relay of the available information to the neurosurgeon. Converging multidisciplinary efforts may lead to integrating medical robotics and novel (intraoperative) direct visualization techniques with advanced neuronavigation systems.

100 years Pharmacology in the Netherlands

Rudolf Magnus, the world famous researcher whose legacy is carried on in the name of our Institute, was appointed as the first professor in pharmacology in the Netherlands on May 3, 1908. This memorable fact has been celebrated in the week of 13-16 May. The celebration took place in all university cities of the Netherlands with local activities around the theme pharmacology. The activities comprised symposia and lectures, and student activities such as laboratory site visits. The national celebration took place during two symposia, the national medicine debate and a scientific symposium, and a party in Utrecht.

The national medicine debate was a lively happening around several topics all connected to medicines or medicine use. Renowned speakers introduced the debate topics: new pills: industry or government?: drug worse than illness?: for every complaint a pill?: and pharmacy or gas station delivery? and defended two different statements related to these topics. The audience decided, via a poll, which statement was best defended and thereby the winner of the various debates. The debates gave rise to very interesting and educational discussions and clearly demonstrated the importance and the many aspects surrounding medicine development, prescription and usage.

The closure of the week was the scientific symposium: "Pharmacology in the Netherlands: Present and Future", where Dutch scientists working in the field of pharmacology and related research areas were gathered. A total of eleven speakers gave an overview of the pharmacological research done by Dutch researchers both at the academia and industry. Furthermore they presented their view on the future of pharmacology in the Netherlands for the next decades. The presentations clearly demonstrated that much has been accomplished in a relative short period, but that there is still a lot to discover.

The week has shown that pharmacology is a very active field of research involving a lot of enthusiastic people and certainly also an area of interest to the lay public and the government.



Inaugural Speech Prof Nick Ramsey

On May 19 Nick Ramsey held his inaugural speech as professor in cognitive neuroscience at the department of Neurology and Neurosurgery. He explained the nature of his research in layman's terms, and then presented his main plans for the future. He first explained what brainfunctions are and how they are measured. Current methods of choice for measuring brainfunction are electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), which allow for attributing brainregions to brainfunctions. However, to prove that those regions are important, it is essential to assess the effects of transient disruption on behavior. This can be done with virtual lesion techniques such as transcranial magnetic stimulation and direct electrical stimulation of the cortex in neurosurgery patients. The latter is not widely available, but it is at the UMC, thanks to the existence of a strong clinical epilepsy surgery program, and to an excellent collaboration between neurosurgeons, neurologists and neuroscientists. Of course such collaboration goes both ways, and the neuroscientists are developing techniques to provide neurosurgeons with presurgical maps of brainfunctions and fibertracts. Hypotheses about brainfunctions are then tested during surgery, when the surgeon stimulates areas from these maps in the awake patient while he/she performs specific tasks.

The epilepsy program also includes a rare facility, the epilepsy monitoring unit where patients are observed for a week, with electrodes implanted directly on the cortex to locate the source of seizures. One of the two core themes of Ramsey's research program is directly linked to this facility: development of Brain-Computer Interfaces, or BCI's. These BCI's read activity from the human brain and convert brainsignals to commands for a cursor in computer programs or for a wheelchair, and are designed primarily for paralyzed people. In Utrecht Ramsey's group will focus on BCI's with electrodes implanted on the cortex, and for this they work together with the epilepsy patients and their doctors. The goal is to develop a fully implantable system with electrodes positioned on specific brain areas (located with fMRI), so that patients can control a cursor by thinking about moving their hands or by other mental processes such as language or working memory.

The second core theme also deals with brainfunction, but is more fundamental. It involves uncovering the functions of specific neurotransmitter systems in humans. The coming years Ramsey's group will focus on the endogenous cannabinoid system, the system through which cannabis exerts its effects. This system appears to play a role in various symptoms of psychiatric disorders. They hope to contribute to development of new drugs for these disorders by investigating which brainfunctions are affected by cannabis.

The research program mainly deals with cognitive brainfunctions, and combines basic and applied science, with patients as the linking element.

Viviana Trezza wins pharmacology research prize

Viviana Trezza of the department of Neuroscience and Pharmacology and the section Neurobiology of behavior has won the Prize for Pharmacological Research, which is sponsored by the Italian Society of Pharmacology. This prize is meant to support Italian researchers younger than 35 who are actively involved in Pharmacological Research. The criteria of selection were based on CV, recent papers published and a research project to be done in Italy or abroad. The prize consisted of a 10.000 EUR cheque and a plate, and the ceremony was in Rome, May 27, 2008.

Ynte Ruigrok receives award of the “Amsterdamsche Neurologen Vereeniging”

Ynte Ruigrok, of the department of Neurology and Neurosurgery, section Cerebrovascular disorders, received the encouragement award of the “Amsterdamsche Neurologen Vereeniging” for her accomplishment in the field of neurological research in the last four years as young scientist. The award consists of a silver decoration.

Susanne la Fleur receives the Alan N. Epstein Award

Susanne la Fleur, of the department of Neuroscience and Pharmacology and the section Neurobiology of behavior is the 2008 winner of the Alan N. Epstein Research Award. This award honors an individual for independent research contributions that has advanced the understanding of ingestive behavior. She receives this award for her fundamental contributions to the understanding of ingestive behavior as influenced by the choice to consume palatable and rewarding fat and sugar. She has gained insight in the role of vagal and hormonal signals in the brain's response to a diet under conditions of stress and diabetes. Currently, her research focuses on obesity and the role of the central nervous system in the regulation of feeding behavior and energy balance. She is especially interested in the behavioral and metabolic effects of diets rich in fat and sugar. She is invited to speak during the Awards Symposium at the Annual Society for the Study of Ingestive Behavior (SSIB) meeting this July. At the meeting she will present an overview of her research.

Annetrude de Mooij-van Malsen received poster award at the Dutch ENP meeting

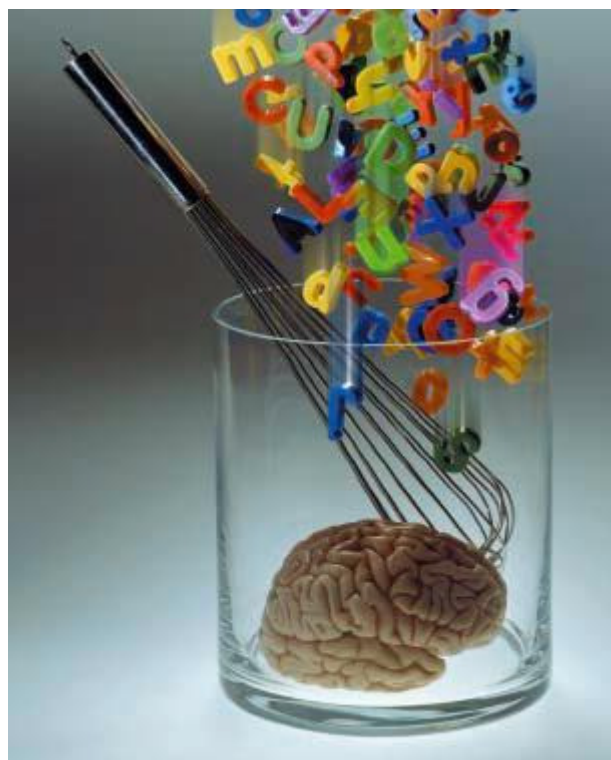
During the seventh Dutch ENP meeting in Doorwerth, June 4-6, Annetrude de Mooij-van Malsen, of the department Neuroscience and Pharmacology, section Neurobiology of behavior, was awarded with a poster award, existing of 250 euros and a commemorative certificate. The title of her poster was: “Finding genes involved in avoidance behavior and motor activity using chromosome substitution strains”.

Ewoud Smidt is granted TopTalent scholarship NWO

For the second time MSc students in their final stages of their masterprogramme could apply for a TopTalent scholarship from NWO to finance their own PhD project. Each university in the Netherlands selected a number of students; Utrecht University was allowed to nominate 17 students. These students subsequently wrote a grant proposal for the NWO TopTalent scholarship programme. The proposals were reviewed by NWO. The top students were invited to defend their proposal for a scientific committee of NWO. In the end 42 out of 131 students were granted the scholarship. Ewoud Smidt of the master Neuroscience and Cognition was selected by the Utrecht University and in the end granted with the scholarship for his project entitled: “Making up your mind: the molecular basis of dopaminergic neuronal network.” He will perform his PhD project in the group of Jeroen Pasterkamp of the department of Neuroscience and Pharmacology in the section Neurodevelopment.

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: Mirjam Sprong (June 3, 2008), Peter Woerdeman (June 19, 2008) Maurice Magnée (June 19, 2008)



agenda and announcements

July 9, 2008 Research lunch psychiatry

René Kahn

'Eufest study'

aula psychiatry, UMC Utrecht

12.00-13:00, lunch provided

more information: i.sommer@umcutrecht.nl

August 25, 2008 Summerschool

'Hersenonderzoek'

25th International Summer School of Brain Research

'Neurotherapy: Progress in Restorative Neuroscience and Neurology.'

Trippenhuis, Amsterdam

more information: www.nin.knaw.nl/summerschool.

September 10, 2008 Research lunch psychiatry

Jaap Wijkstra

'Medicamenteuze behandeling van psychotische depressie'

aula psychiatry, UMC Utrecht

12.00-13:00, lunch provided

more information: i.sommer@umcutrecht.nl

September 25, 2008 Symposium psychiatry

Lustrum symposium NVVP

Jaarbeurs & Ottone, Utrecht

more information: i.demmendaal@erasmusmc.nl.

September 26, 2008 Symposium ADHD

'Het AD(H)D-brein tussen 12 en 20! Hoe kunnen we de ontwikkeling van jongeren met AD(H)D ondersteunen en stimuleren?'

Beatrixtheater, Utrecht

more information and registration: balans@midibreda.nl

October 2, 2008 Publieksdag Hersenstichting

Topic: 'Geheugen'

more information:

<http://www.hersenstichting.nl/actueel/activiteiten/congresagenda>

October 17, 2008 Swammerdam lecture

Hannah Monyer, (University of Heidelberg, Germany)

'Molecular and functional studies of GABAergic interneurons at the cellular and network level'

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

