



Rudolf Magnus Institute of Neuroscience

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interview

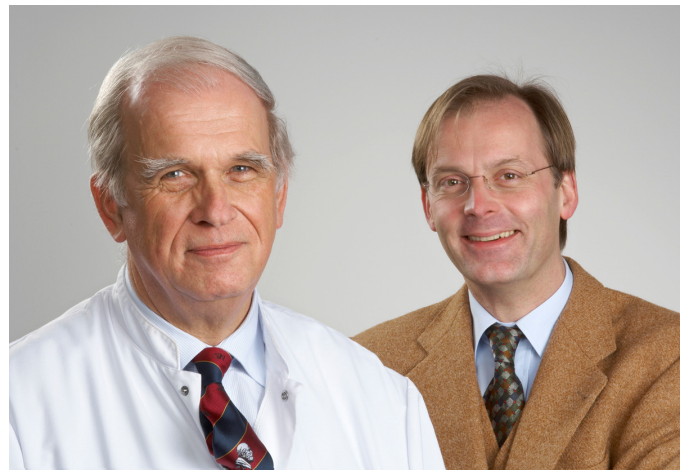
Neurological Research within the Institute

Van Gijn and Rinkel both are neurologists in the department of Neurology and Neurosurgery of the University Medical Center and both are involved in neuroscience research within the Rudolf Magnus Institute. They are considered specialists in the field of subarachnoid haemorrhage on which they published a seminar in the January 2007 issue of the Lancet.

Van Gijn studied medicine in Leiden, where he graduated in 1970. His career in the field of neurology started in 1970, with his specialty training in Rotterdam and London. In 1977 he got his PhD on 'The plantar reflex, a historical, clinical and electromyographic study'. He remained as a faculty member in Rotterdam till 1983, the year in which he was appointed head of the Neurology department of the UMCU. Rinkel started his medical career at the Utrecht University. During his medical studies he already became acquainted with the Rudolf Magnus Institute during a 6 months internship at the department of Pharmacology. After graduation in 1987, he combined his residency in neurology in Utrecht with PhD training, which he completed in 1991. He remained on the staff of the department of Neurology and Neurosurgery and was appointed professor in 2002.

A large part of their research has been devoted to subarachnoid haemorrhage. In the Lancet paper they provide a clear report on this medical condition: subarachnoid haemorrhage is not common, since only 1 in 20 strokes is caused by subarachnoid haemorrhage, corresponding with an incidence of 6-7 per 100.000 person-years. Nevertheless it is a disease which is often fatal and it strikes at a relative young age; half of the patients is younger than 55 years. The diagnosis is difficult and a real challenge for many neurologists. In the Lancet seminar van Gijn and Rinkel give an extensive overview on its pathology, current treatment, complications and current prevention. "Most cases are sporadic; on average, the prevalence of cerebral aneurysms in adults without risk factors is 2.3 %; most of these never rupture. Modifiable risk factors such as hypertension, smoking and extensive alcohol intake more or less double the risk and they account for every two out of three haemorrhages, while genetic factors only account for one in ten."

"The most characteristic symptom of the occurrence of subarachnoid haemorrhage is a sudden, terrible headache. When subarachnoid haemorrhage is suspected the preferred investigation is CT-scanning and if this is not clear a lumbar puncture is done. One of the problems after the first episode is the rebleeding, which happens in 15% of the patients in the first few hours and within 40% of the patients within the first 4 weeks after the first bleeding. Rebleeding results in a poor outcome: 80% of these patients die or remain disabled. Intervention to occlude the ruptured aneurysm through the endovascular route ('coiling') or through operation is therefore the primary aim. Besides rebleeding there are other complications that occur. These include delayed cerebral ischaemia, hydrocephalus and systematic complications such as fever, cardiac failure and hypertension. After the acute phase, there are neurological complications such as late rebleeding, epilepsy, anosmia and cognitive deficits. Of all patients only 25% report complete recovery without any complications."



Van Gijn and Rinkel

In the coming years the research focus will remain on subarachnoid haemorrhage and the complications involved. Rinkel tells that one of the main topics of his research will be to determine the risk factors for subarachnoid haemorrhage, with the aim to achieve an individualized assessment of the absolute risk for the occurrence of aneurysm rupture. Furthermore psychosocial functioning after subarachnoid haemorrhage will be studied, in collaboration with the departments of Revalidation and Neuropsychology. Van Gijn will later this year stay in the group of Rinkel as Prof emeritus. He will focus his attention mainly on the occurrence of hydrocephalus, a major complication of subarachnoid haemorrhage. This part of the research will focus on three main issues: how can we best treat the hydrocephalus?

How can we prevent infections of the ventricular catheter, the most common treatment of hydrocephalus at the moment? And finally van Gijn will study the effect of the treatment of hydrocephalus on cerebral perfusion, which is often impaired after subarachnoid haemorrhage.

PhD theses

2007-08

April 19, 2007

Jeannette Hofmeijer

Surgical decompression for space-occupying hemispheric infarction

L.J. Kappelle and H.B. van der Worp
supervisors

Jeannette Hofmeijer started her PhD in January 1999 after she finished her medical training. She works at the department of Neurology and Neurosurgery and completed her thesis in the section of Cerebrovascular Disorders.

Patients with a hemispheric infarct and massive space-occupying edema formation have a poor prognosis. Mortality rates of about 80% have been described, despite maximal medical therapy on an intensive care unit. The aim of the research presented in this thesis was to investigate the benefit of decompressive surgery in patients with middle cerebral artery (MCA) infarction who deteriorate as a result of space-occupying brain oedema. In *part 1*, experimental studies on this subject are described. In rats with space-occupying MCA infarction, perfusion improved in brain tissue surrounding the infarct after surgical decompression, indicating that secondary damage may be prevented by decompression.

In *part 2*, preparations for and preliminary results of the ongoing randomized Hemicraniectomy After MCA infarction with Life-threatening Edema Trial (HAMLET) are presented. To obtain sufficient data individual data of patients from three ongoing European randomized controlled trials treated within 48 hours after stroke onset were pooled. Ninety-three patients were included. Decompressive surgery reduced mortality and increased the probability of a good functional outcome. However, the probability of surviving in a condition requiring assistance from others also increased substantially. Moreover, the results of neuropsychological testing in a cohort of patients with space-occupying MCA infarction one year after decompressive surgery showed that in addition to the expected severe focal deficits, such as aphasia and neglect, global cognitive decline was found in the majority of patients.

It is concluded that decompressive surgery may be beneficial in some subgroups, but not in others.

2007-09

April 23, 2007

Marion Scholten

Schizophrenia and sex differences in emotional processing

R.S. Kahn, A. Aleman and J. van Honk
supervisors

Marion Scholten performed her PhD as member of staff of the department of Psychiatry. She did her PhD training at the department of Psychiatry and completed her thesis in the section of Developmental Disorders.

Patients with schizophrenia are known to be impaired in several domains of emotional processing. These deficits have been associated with impaired social functioning. Since female patients show better social skills than male patients and healthy women outperform men in emotion recognition and empathic capacity, studying sex differences in emotional processing might contribute to a better understanding of the differences between men and women in the clinical manifestation of the illness. To this end, sex differences were studied in facial emotion recognition, emotion recognition in prosody and semantics of spoken language; empathy and perception of social interaction; working memory in simultaneous and sequential processing of language and emotion; long-term memory for visual information with positive, negative and neutral content; sensitivity to threat (inhibition) and reward (activation) in relationship to heartmeasures.

The female advantage in emotion recognition, empathy and social perception was found to be preserved in schizophrenia. In addition, men but not women with schizophrenia were significantly impaired in performing a simultaneous language/emotion working memory task. These findings may explain in part the better course and outcome of female patients with schizophrenia. However, in more complex sequential or long-term processing of (emotional) stimuli, no female advantage was observed. Regarding inhibition, both male and female patients showed enhanced sensitivity to threat. Given the impaired performance in patients on all tasks involving emotional stimuli, our results confirm the accumulating evidence that schizophrenia is pre-eminently an emotional disorder.

2007-10

April 26, 2007

Sven Schiemanck

Long-term functional outcome after stroke: the impact of MRI-detected lesion characteristics

A.J.H. Prevo, M.W.M. Post en G. Kwakkel
supervisors

Sven Schiemanck started his PhD in October 1998 after he finished his medical training. He is currently employed as rehabilitation physician at the Academic Medical Center Amsterdam. He did his PhD training in collaboration with the department of Rehabilitation and Sports medicine. He completed his thesis in the section of Cerebrovascular Disorders.

For the rehabilitation physician as well as for the neurologist, a valid early prognosis of functional outcome for the individual stroke patient is required to inform patient and relatives adequately, to facilitate discharge planning, and to initiate an optimal (task-specific and goal-orientated) rehabilitation program with realistic therapeutic goals. The objective of this thesis was to gain a better understanding of the relationship between ischemic lesion characteristics (volume and localization) and long-term functional outcome of the middle cerebral artery stroke survivor.

Lesion characteristics were assessed on conventional MRI scans. Outcome was assessed at the levels of body functions, activities and participation (International Classification of Functioning, ICF) and quality of life. We evaluated if lesion-characteristics have added value in prediction of outcome alongside (clinical) patient variables. To define the impact of lesion localization, its association with long-term motor recovery of the hand and its relationship with long-term deficits in episodic memory were investigated.

Stroke volume is a reflection of damaged brain tissue. A larger infarction leads to more deterioration of body functions, more activity limitations and a lesser capacity to participate, as well as an impaired quality of life, although this relationship is only moderately strong. Besides to its volume, the location of the lesion is important, especially for the outcome of the upper paretic limb as for long-term episodic memory disorders. The strength of the correlation between lesion characteristics and functional outcome weakens after a longer follow-up period post stroke. Patient characteristics and good clinical assessment of functioning in the early phase post stroke are sufficient to predict long-term functional outcome. Neuro-imaging information does not have added predictive value compared to this clinical information. Nevertheless, imaging information is vital if the clinician is to gain a better understanding of the patient's functional deficits and insights into the recovery of body functions and activities after stroke.

news and other things

IoP-RMI exchange visit of Wiepke Cahn and Neeltje van Haren

Last January, Wiepke Cahn and Neeltje van Haren from the Rudolf Magnus Institute of Neuroscience (RMI), department of Psychiatry, visited the Institute of Psychiatry (IoP) to meet, among others, Paola Dazzan and Julia Lappin to discuss the possibilities to pool clinical, genetic and imaging data of (medication naïve) first episode psychosis patients.

Last year the RMI and the IoP decided to join forces. Both institutes have a history in both clinical and fundamental research in psychiatry and neurology. Thanks to a grant from the UMC Utrecht it is made possible to extend existing collaborative projects and to initiate new ones.

Including patients in their first psychotic episode is complicated. In clinical practice the first goal is to diminish psychotic symptoms and this is best done with antipsychotic medication. Both departments have been able to collect information before patients started on

medication and were also able to follow them for 4-6 years.

When we combine the data set we end up with almost 70 medication naïve patients that have not used antipsychotic medication before inclusion in the study. Antipsychotic medication acts on the brain and is therefore an important confounding factor when investigating the effects on psychosis on brain structure of function. MRI brain scans have been acquired as well as blood samples. In addition, clinical variables have been obtained such as symptomatology, drug use, duration of untreated psychosis, level of functioning and so on. In this first meeting we discussed how to process all the data in a uniform manner. Since we already have experience in pooling MRI data and clinically relevant information, we are confident that datasets from UMC Utrecht and the IoP can be combined. We hope to be able to report our conclusions next year.

Steven Bakker receives 'Hersenstichting' grant

Steven Bakker, department of Psychiatry, received a fellowship from the Netherlands Brain Foundation for his proposal titled "the role of schizophrenia susceptibility genes in specific psychotic symptoms".

Schizophrenia is a severe psychiatric disorder, which is characterised by false perceptions and beliefs, disorganised thought and a general loss of functioning. The disorder usually starts during adolescence or early adulthood, and affects nearly one percent of people. Specific symptoms, as well as the disease course vary widely between patients, however. The susceptibility to develop schizophrenia is largely determined by genetic factors (60-80%). Recent studies have identified several genes that are associated with the disorder, and there is evidence that certain genes predominate in groups of patients with specific symptoms.

As part of the existing collaboration between the departments of Psychiatry and Biomedical Genetics, genetic risk factors will now be related to individual symptoms in more than 1000 patients, which were diagnosed at the department of Psychiatry during the past decade. Detailed and standardised information about their symptoms is available. Patients who did not yet participate in genetic studies will be asked to cooperate and donate some blood. The combination of specific symptoms and DNA variants in several schizophrenia susceptibility genes will hopefully allow the identification of patient subgroups with a distinct clinical presentation. In the future, this information could help to refine clinical diagnosis, and to predict the course of schizophrenia in individual patients.

Jan Veldink receives 'Hersenstichting' grant

Jan Veldink, department of Neurology and Neurosurgery, received a fellowship from the Netherlands Brain Foundation for his proposal titled "copy number variation as factor determining risk and outcome in Amyotrophic Lateral Sclerosis (ALS)".

This research project will be performed as part of a close collaboration between the research groups of Leonard van den Berg (Neuromuscular Diseases) and Roel Ophoff (Neurogenetics). ALS is a fatal neurodegenerative

disease, characterized by the progressive degeneration of motor neurons in cortex, brainstem and spinal cord. Over 90% of cases are sporadic, and sporadic ALS is considered to be a complex disease caused by the combined effects of several genes and environmental factors. Genes within populations can differ with respect to their sequence (single nucleotide polymorphisms (SNPs)), or their copy numbers present in the genome (deletions and duplications). Several studies have been performed to identify susceptibility SNPs in ALS, however results were inconclusive. In his PhD thesis, Jan Veldink identified copy number variation (deletion) of the survival of motor neuron (SMN) gene as a potential genetic risk factor for ALS. Since sporadic ALS is most likely caused by several genes, the goal of the current project is to identify copy number variation in other genes that are linked to ALS. Using genome-wide genotyping techniques (Sentrix® humanHap300 genotyping beadchip (Illumina), genome wide determination of copy number variation will be performed in 500 patients with ALS and 500 healthy controls. In collaboration with the University of California, Los Angeles (UCLA) an algorithm will be developed enabling the rapid identification of copy number variation. Identified aberrations will be validated with standard PCR techniques. The identification of novel genes involved in ALS may lead to new treatment strategies in this disabling and fatal neurological disease.

Publication in Nature Genetics

Recently a research concerning the genetics of autism appeared in Nature Genetics (March 2007). The paper is a collaboration of about 150 authors, of which 7 are linked to the RMI.

Wouter Staal, child - and adolescent psychiatrist at the department of Psychiatry, comments:
Autism is an impairment which has a very high hereditary contribution, over 90%. Several linkage and association studies have been performed without consistent replication of data. The different international consortia joint forces and performed a genome-wide linkage study. At the same time copy number variations (CNV's) were mapped, these are very small changes in the amount of the hereditary material. Approximately 10% of the patients appeared to have these CNV's. This group of patients was excluded during the linkage analysis. The linkage analysis resulted in a suggestive linkage peak on the short arm of chromosome 11 (11p12-13). This area contains over 160 genes, indicating that "the gene" has not been found yet. The next step is further analysis of the CNVs in autism patients. In collaboration with Peter Burbach, the department of Pharmacology and Anatomy, and the division Medical Genetics we will now compare CNVs in autism patients to control subjects on an even higher resolution as before.

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:

Floor Jansen (March 13, 2007) and Gitte Tiesjema (March 29, 2007)

agenda and announcements

April 2, 2007 Neuroscience seminar

Tim Ryan,

'Deconstructing the synaptic vesicle',
ErasmusMC, Rotterdam, Colloquium room A
16:00, tea and coffee from 15:45
more information: <http://www.neuro.nl/>

April 11, 2007 CSCA lecture

John Duncan,

'A selective representation of task relevant knowledge in the human and monkey brain',
Doelenzaal (UB), Singel 425 Amsterdam,
16:00-17:00
more information: <http://www.cms.uva.nl/csca>

April 24, 2007 Helmholtz lecture

Michael Shadlen, (University of Washington, USA)

'A neural mechanism for Decision Making'
zaal Rood, Ruppert building, Leuvenlaan 19, Utrecht
16:00, contact, v.maassen@fss.uu.nl

April 25, 2007 Oratie

Gerda Croiset,

'Medical education with a specific emphasis on the graduate entry program'

