



Rudolf Magnus Institute of Neuroscience

Rudolf Magnus Bulletin 23
May 2006

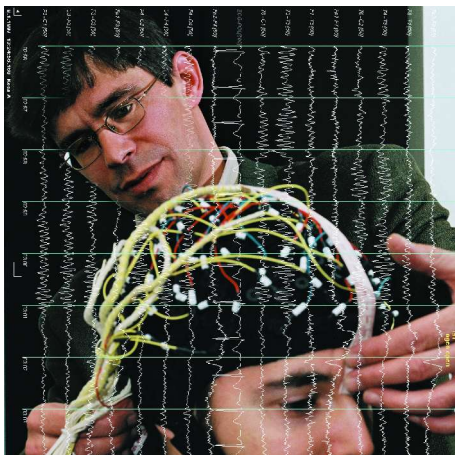
headline

Pharmacotherapy for AD/HD symposium

Attention-deficit/hyperactivity disorder (AD/HD) is a mental and behavioural condition characterized by excessive and invalidating degrees of inattention (e.g., distractibility), and/or impulsivity (e.g., premature reactions) and hyperactivity. The standard pharmaceutical treatment is Methylphenidate (MPH; Ritalin), which is effective in about 65% of AD/HD patients (as revealed during the symposium, even to the extent that they drive better). For MPH non-responders there are sometimes efficacious alternatives, such as amphetamine, atomoxetine, or modafinil. It is however very unclear what the crucial characteristics are that determine responders to MPH.

It is generally believed that this lack of clarity may very well be related to the unspecificity of the AD/HD diagnosis. To address this lack of specificity, AD/HD researchers have attempted to partition the heterogeneity in the ADHD group by specifying 'endophenotypes': 'micro-behavioural' or neurobiological characteristics that are assessed under tightly controlled experimental conditions and are relatively objective and quantifiable. Examples of endophenotypes relevant for AD/HD are the ability to suppress on-going behaviour (as objectified in the so-called stop task), and the abnormal activation of prefrontal and striatal brain regions.

Endophenotypes are considered especially promising in relation to specific genetic substrates. However, one general point that was raised during the symposium concerned the relative neglect of 'environmental endophenotypes', as exemplified by the finding that clinical AD/HD symptoms depend on the interaction between a certain gene and



perinatal conditions. A further general consensus was that the unitary diagnosis of AD/HD does in fact reflect a multitude of underlying endophenotypes, along with a multitude of associated genes and neural circuits, which also bear no obvious relation to the conventional clinical subtypes (inattentive, impulsive/ hyperactive, or combined).

Crucially, different endophenotypes may be differentially sensitive to different substances. MPH may be effective for some endophenotypes, but not for others, and therefore will benefit some patients but not others. For example, MPH seems to improve inhibition (stop task), working memory, and sustained attention, but not selective attention (Stroop task) or time estimation, all of them endophenotypes that have been implicated in at least subsets of AD/HD patients. Atomoxetine, a noradrenergic reuptake inhibitor, benefits stopping but not working memory or sustained attention, but may be relevant to time estimation, given the strong noradrenergic innervation of the cerebellum, a structure critically involved in temporal processing. Both clinical and translational models point to yet other neurotransmitter systems; for example, serotonin could be especially relevant to premature responding related to delay aversion as well as oppositional behaviour. Different neurotransmitters at least partly feed into different brain circuits, and the brain circuits involved in AD/HD-relevant phenotypes are increasingly being revealed via the advances of modern neuron-imaging. The inferior frontal gyrus, the striatum, the ventral tegmental area, the nucleus accumbens, the cerebellum, and the anterior cingulate gyrus (error monitoring) are nodes of a brain network, each of which can at least partly be specifically affected so as to result in specific AD/HD-related endophenotypes, each of which in turn involves a specific mix of neurotransmitter systems. Knowledge about the implicated structures is crucial for looping between clinical and translational experimental models in service of the ultimate aim: finding adequate treatment for each of the multiple causal factors that underlie AD/HD.

This symposium of March 31, 2006, at Utrecht University was organized by the British Embassy (Science & Innovation Unit), the Dept of Psychiatry of the University of Cambridge (UK), the Rudolf Magnus Institute of Neuroscience, and the Utrecht Institute for Pharmaceutical sciences. The speakers were Mital Mehta (Inst. of Psychiatry, London), Trevor Robbins (Univ. Cambridge), Katya Rubia (Inst. of Psychiatry, London), Barbara Sahakian (Univ. Cambridge), Edmund Sonuga-Barke (Univ. South-hampton), Sarah Durston (UMC Utrecht), Leon Kenemans (Utrecht Univ.), Katrien van Meel (Leiden Univ.), Berend Olivier (Utrecht Univ.), and Joris Verster (Utrecht Univ.).

PhD theses

2006-13

Diabetes in the brain

May 9, 2006

Sanne M. Manschot

Diabetic encephalopathy: a cerebrovascular disorder?

L.J. Kappelle, W.H. Gispen, G.J. Biessels
supervisors

Diabetes mellitus is associated with slowly progressive changes in the brain; diabetic encephalopathy. Sanne Manschot is the first to examine the role of vascular disturbances in the brain in diabetic encephalopathy. Both in diabetic rats and in diabetes patients she found that cognitive impairments are related to diabetes-related vascular disease.

Patients with type 2 diabetes mellitus (DM2) have mild to moderate impairments in attention and executive functioning, information processing speed and memory. Vascular disturbances are likely to play an important role. Manschot examined whether experimental diabetes (streptozotocin-treated diabetic rats) is associated with reduced cerebral blood flow and whether treatment with enalapril (24 mg/kg) can improve cerebral perfusion and function (blood flow and functional cerebral deficits). She found that cerebral perfusion is reduced in diabetic rats compared to controls. Treatment aimed at the vasculature can improve cerebral blood flow, deficits in Morris maze performance and long term potentiation. These findings suggest that vasculopathy plays a role in the development of cerebral dysfunction in diabetic rats. Manschot further demonstrated that long-term treatment with enalapril at a dose of 24 mg/kg can prevent peripheral and central neurophysiological deficits in streptozotocin diabetic rats, but that adverse effects, probably related to the marked hypotension at this dosage, preclude sustained treatment. Manschot: "In the rodent model cognitive impairments are associated with reduced cerebral blood flow, and improvement of blood flow by treatment with enalapril is associated with improved cognition and improvement of evoked potential latencies".



Manschot also examined associations between vascular risk factors, cognitive functioning and structural changes in the brain of patients with DM2. Therefore, she initiated a cross-sectional study involving 125 patients with DM2 and 64 matched non-diabetic controls. Manschot: "We have performed the first detailed study on the relation between

cognitive dysfunction and brain MRI changes in patients with DM2. In patients with DM2 we found more deep white matter lesions, cortical and subcortical atrophy and (silent) infarcts. Furthermore, we found an impaired overall cognitive performance, especially on the domains attention and executive function, information processing speed and memory. Within the DM2 group cognitive function was inversely related with white matter lesions, atrophy and the presence of infarcts. Risk factors for the development of diabetic encephalopathy are atherosclerotic vascular disease and to a lesser extent chronic hyperglycemia and hypertension. Longitudinal studies are needed to determine the importance of these risk factors more exactly".

Sanne Manschot (May 25, 1973, Utrecht). Secondary education (St. Thomas College, Venlo) 1991; Medicine (University Utrecht), MD 1998. During her residency in Neurology she performed the research as described in her thesis. She will qualify as neurologist in 2009.

2006-14

When blood takes a shortcut

May 16, 2006

Korné Jellema

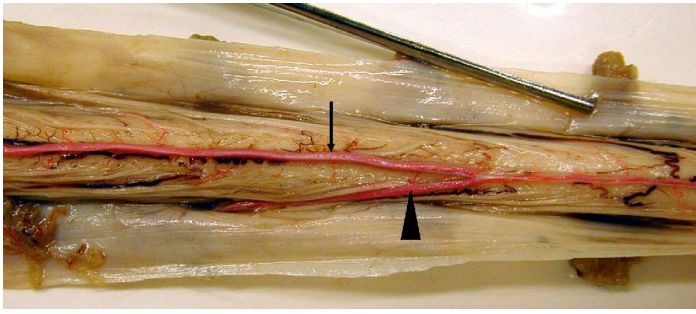
Spinal dural arteriovenous fistulas

J. Van Gijn, C.C. Tijssen
supervisors

Spinal dural arteriovenous fistulas (SDAVF) at the level of a spinal root lead to venous congestion and ischaemic damage of the spinal cord, and ultimately to severe disability. Korné Jellema found that the treatment options for SDAVF are sufficient and usually improve the condition of the patients. Yet the cause of the condition is not clear and the condition is in general under-diagnosed.

Jellema performed a retrospective analysis of the records of 80 patients who were diagnosed with a SDAVF in six hospitals over a 15 year period (1985–2001). He concluded that SDAVF is difficult to diagnose and that the delay between first symptoms and treatment is often long. In middle-aged men who present with disturbances of gait with ascending motor and sensory deficits, and who subsequently report impaired voiding or other sphincter disturbance, SDAVF is one of the first diagnoses that should spring to mind. Jellema also reviewed the intake forms of patients who had been admitted to the spinal cord injury ward of a rehabilitation centre in the period 1980–2004, to identify possible patients with an undiagnosed SDAVF, and found results suggesting that SDAVF is an under-diagnosed condition. When studying possible causes for SDAVF, Jellema found that it is unlikely that prothrombotic factors are involved in the pathogenesis. As SDAVF most often occur with a male to female of ratio 5 to 1, Jellema studied possible anatomical gender differences in human cadavers, in whom simultaneous arterial and venous araldite injection was performed with different colours. Jellema did not find significant differences in thoracic vasculature between men and women.

Jellema studied the treatment options for SDAVF; specifically whether glue-induced occlusion of the draining vein could predict permanent closure of the fistula following embolisation of spinal SDAVFs. He found that penetration of the glue into the draining vein indeed predicts permanent closure of the fistula. Jellema: "When



The thoracic and lumbar spinal cord of a 73 year old woman. Arterial araldite injection resulted in filling of the anterior spinal artery (arrow) and the arteria radicularis magna (arrowhead). (Courtesy of Korné Jellema)

penetration of the glue into the draining vein can be expected, embolisation is the preferred treatment option. In other cases operation is the treatment of choice.” Jellema assessed the long term clinical course of 44 patients treated for a SDAVF, who were re-examined after a median interval of 5.7 years after treatment, and found that most patients with a SDAVF benefit from treatment by improvement of gait and disability. Improvement of disability was independent of age, diagnostic delay or pre-treatment disability. In general, Jellema concludes, “Adequate methods exist to close the shunt by operation or via embolisation, but the causes of this condition are still poorly understood. The main challenge in preventing disability from SDAVF is to ensure that the diagnosis is made at an early stage. This can be promoted by continuing education of neurologists, even though most of them will encounter this problem only once every few years”.

Korné Jellema (November 2, 1972, Bolsward). Secondary education (Carolus Clusius College, Zwolle.), 1991; Medical Biology (Utrecht University), 1998; Medicine (Utrecht University), MD 2000. The work as described in his thesis was performed between 2002-2006 at the St. Elisabeth Hospital, Tilburg, where he is a resident in Neurology since 2002.

2006-15

Care needs further tuning

May 19, 2006

Renate C. Siebes

Processes of care in paediatric rehabilitation

A. Vermeer, L. Wijnroks, M. Ketelaar
Supervisors

A lot is being done to improve the rehabilitation process for children. Renate Siebes developed and validated questionnaires to be able to measure the quality of care in paediatric rehabilitation from the perspective of the patients, parents and care-providers. She found that the processes of care could well be evaluated, but also that a lot of work remains to optimise these processes in daily practice.

Family-centred care has become widely accepted as part of the philosophy of treatment in paediatric rehabilitation in the Netherlands. Siebes describes the validation of the Dutch versions of three measures of the family-centeredness of services: the Measure of Processes of Care (MPOC and MPOC-20; parent perspective), the Measure of Processes of Care for Service Providers (MPOC-SP; service provider perspective), and the Giving Youth a Voice Questionnaire (GYV-20; adolescent patient perspective). Using the MPOC from the parents' perspective, she

focused on the level and mode of parent involvement in the rehabilitation treatment process. Parents of children treated in paediatric rehabilitation were interviewed about their contacts with the centre, treatment aspects, and taking part in the care process. She showed that parents were involved in all stages of their child's rehabilitation process in various ways. However, none of the interviewed parents reported on full involvement in all consecutive treatment stages. According to the interviewed parents the communication between professionals and parents, parent involvement in goal setting, and parent involvement in treatment could be improved.

Since parents are not frequently present during treatment, they are not an optimal source of information for treatment process description. Therefore, Siebes also investigated the clinical implementation of the paediatric rehabilitation care process in the Netherlands, by observing the treatment process of five children with cerebral palsy and complex needs. The analyses indicated some agreement of parent identified problems, goals and activities in all subjects, but only four of the 72 treatment activities were perfectly tuned to treatment goals as well as to parent identified problems. Several options are discussed to improve the tuning and transparency of the paediatric rehabilitation process substantially. Measures (for instance, the MPOC) should be used to improve the transparency and tuning of the paediatric treatment process, and to facilitate truly family-centred care with the precise amount of involvement that parents desire.

Renate Siebes (October 8, 1973, Dordrecht) Secondary education, (Titus Brandsma College, Dordrecht) 1993; Social Sciences (Utrecht University), 1998. From 2000-2006 she worked on the dissertation as described above (Langeveld Institute, Social Sciences, University Utrecht).



(Courtesy of Renate Siebes)

2006-16

May 19, 2006

B.W.C. Zwirs

Externalizing disorders among children of different ethnic origin in the Netherlands

T.W.J. Schulpen, J.K. Buitelaar, H. Burger
supervisors

Rudolf Magnus Graduate School Certificates

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:

Frank R. Van Genderen (March 30, 2006)

Linda Van den Berg (April 27, 2006)

Floor Jansen wins Jacobus Willemsse Prize

At the Spring meeting of the Netherlands Society of Child Neurology of April 7, 2006, Floor E. Jansen received the Jacobus Willemsse Prize.



(Courtesy of Floor Jansen)

The prize is awarded to young researchers in Child Neurology and consists of a sculpture and € 2,500. Floor Jansen receives the prize for her research on epileptic source localisation in patients with tuberous sclerosis. Through newly developed imaging and neurophysiological techniques (e.g., magneto-encephalography) it appears possible to identify, among the many tubers in the tuberous sclerosis patients, the tuber causing the epilepsy. This enables epilepsy surgery in these so far inoperable patients.



May 4-5, Meeting of the Association of European Psychiatrists - Neuroimaging Section

'Neuroimaging Change over Time in Psychiatry'

Academy Building, Domplein 29, Utrecht

Programme and registration, <http://www.rudolfmagnus.nl>

May 11, Psychopharmacology Colloquium

Meg Van Bogaert (Psychopharmacology, Pharmaceutical Sciences, Utrecht) 'Role of 5-HT1a receptors in anxiety'
Room N020, Went Building, Sorbonnelaan 16, Utrecht, 12:00-13:00, contact, k.b.e.bocker@pharm.uu.nl

May 12, Neurology Seminar

Bas Bloem (UMC St. Radboud, Nijmegen)

'Parkinson Disease'

Colloquium room, C3 Oost, UMC Utrecht, 12.45-13.30

contact C.E.vanderWijngaart@umcutrecht.nl

May 18, Psychopharmacology Colloquium

Reinoud De Jongh (Psychopharmacology, Pharmaceutical Sciences, Utrecht) 'Botox for the brain: pharmacological enhancement of cognition and mood'

Room OC104, Went Building, Sorbonnelaan 16, Utrecht, 12:00-13:00, contact, k.b.e.bocker@pharm.uu.nl

June 2, Helmholtz Lecture

Masud Husain (UCL & Imperial College, London, UK)

'Space and the parietal cortex'

'Rode zaal', Ruppert Building, Leuvenlaan 19, Utrecht, 16:00-17:00

Contact, v.maassen@fss.uu.nl

June 16, Neurology Seminar

Eleonora Aronica (Neuropathology, AMC Amsterdam)

'What determines the sensitivity of epilepsy towards medication? The role of genes and multidrug transporters'

Colloquium room, C3 Oost, UMC Utrecht, 12.45-13.30

contact C.E.vanderWijngaart@umcutrecht.nl

August 28-29, Rudolf Magnus-Helmholtz Summerschool

Conference Centre Ottone, Kromme Nieuwegracht 62, Utrecht.

Programme to be announced

Check our website for updates, <http://www.rudolfmagnus.nl>

September 8-9, Brain Days

A two-days meeting with international experts on the theme, 'Brain plasticity in children'.

UMC Utrecht. Programme to be announced

Check our website for updates, <http://www.rudolfmagnus.nl>

November 8, Rudolf Magnus Symposium

Including the Rudolf Magnus Lecture 2006 by

Frans De Waal (Emory Univ. Atlanta, USA) and the announcement of the winner of the Rudolf Magnus Research Award 2006.

UMC Utrecht, 13:30-17:15. Programme to be announced

Check our website for updates, <http://www.rudolfmagnus.nl>

Contact, m.vandenadort@med.uu.nl

November 8, Rudolf Magnus Evening

A unique mixture of social and scientific events is

organised following the Rudolf Magnus Symposium.

UMC Utrecht, 18:00-21:30, programme will include diner, details to

be announced. The evening programme is only (and freely)

accessible for all members of the Rudolf Magnus Institute.

Registration is required. Contact, m.vandenadort@med.uu.nl

November 16-22, Introductory Course for PhD students in Neuroscience

Information and registration, <http://www.rudolfmagnus.nl>

November 23-24, Annual Meeting PhD students

Venue, Conference Centre Woudschoten, Zeist.

Information and registration, <http://www.rudolfmagnus.nl>