



Rudolf Magnus Institute of Neuroscience

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April 2005

interview

'ADHD genes' are related to smaller brain structures

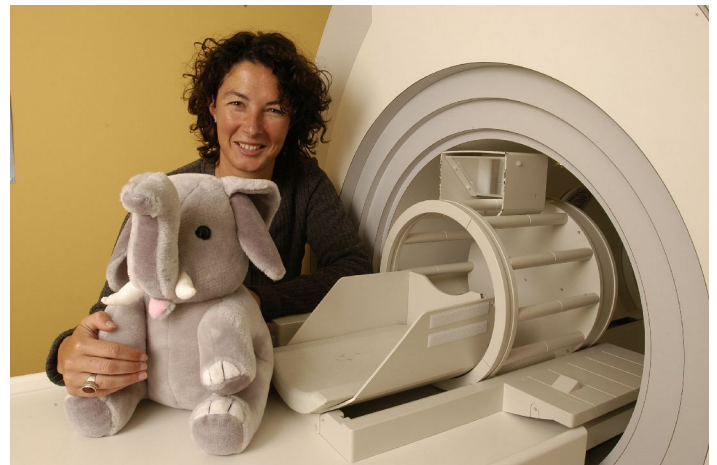
Attention Deficit Hyperactivity Disorder (ADHD) is among the most prevalent psychiatric disorders of childhood, affecting 3-5% of school age children. Sarah Durston found that two genes, of which polymorphisms are linked to ADHD, influence the volumes of two distinct areas of the human brain as measured by MRI. The DAT1 gene influences the caudate volume, whereas the DRD4 gene influences the volume of the grey matter in the prefrontal cortex. Unique findings that will be published in the next issue of *Molecular Psychiatry*.

There is growing evidence that ADHD is strongly linked to genetic traits. For instance monozygotic twins are 50-80% concordant with the disease, and siblings of ADHD patients have a 3-5 times increased risk of ADHD. On the other hand, the neuroanatomical substrate of ADHD is becoming increasingly better defined due to advances in neuroimaging. In her previous work Durston demonstrated that ADHD patients have smaller intracranial volumes and a smaller right cerebellum than controls. Therefore the obvious next step was to determine if specific genetic elements in ADHD are responsible for general or more focal changes in the volumes of the brain of affected individuals. In this study 30 male sibling pairs discordant for ADHD (children and adolescents) were studied and compared to 30 matched controls.

Guided by the results of others, two genes were selected that play a role in dopamine metabolism, and which both display polymorphisms that have been linked to ADHD. For one, the dopamine transporter gene (DAT1) that is expressed in the basal ganglia has various alleles, differing in the number of a tandemly repeated 40-nucleotide sequence. The 10R allele of this gene (i.e. with 10 repeats) has been associated with ADHD, and also with a poor response to methylphenidate (Ritalin). Durston found that the volume of the caudate nucleus of individuals who were homozygous for the 10R allele was significantly smaller than in individuals who were heterozygous or carried other variants of the gene.

The second gene of study was the dopamine D(4) receptor (DRD4), which is expressed predominantly in the prefrontal cortex and shows variant alleles differing in the number of

a tandemly repeated 48-nucleotide sequence. Different DRD4-alleles have been shown to be associated with ADHD in various studies. Durston found that the individuals carrying two 4R alleles had a significantly smaller volume of prefrontal grey matter compared to individuals heterozygous for the 4R allele or carrying combinations of other alleles.



As Durston explains, we are no where near explaining why these brain structures are smaller as a function of these particular alleles of these genes. On the one hand there is ADHD with its broad and variable spectrum of symptoms. On the other hand there are genes with a polymorphism that can be linked to ADHD. Neuroimaging provides an interesting 'intermediate phenotype', that may link these two sides of the story. The DAT1 and the DRD4 genes are highly expressed in the brain structures that are influenced in size by the observed allelic variations. Therefore, it seems that the sizes of these structures may somehow be related to the aberrant behavioural traits in ADHD.

Sarah Durston received a VENI grant from the Netherlands Organisation for Scientific Research in 2003 to pursue her quest for the genetic and neuroanatomical origins of ADHD. An intensive collaboration with BJ Casey at the Sackler Institute, New York, is one of the driving forces behind the present study. She has formed a neuroimaging group in Child- and Adolescent Psychiatry called NICHE, which closely collaborates with the imaging groups in adult psychiatry.

PhD theses

2005-10

Aggression may be predictable in 'cool kids'

April 1, 2005

Maaïke M. Kempes

The distinction between reactive and proactive aggression in children with disruptive behaviour disorders

H. Van Engeland, W. Matthys, J.A.R.A.M. Van Hooff, H. De Vries
supervisors

Maaïke Kempes experimentally measured reactive (e.g., hitting the table out of frustration) and proactive aggression ("When you do not do as I say I will hit you") in children with disruptive behaviour disorders (DBD). It appeared that she was able to predict both forms of aggression in DBD children from experimental play, but only in those DBD children who did not show elevated levels of the stress hormone, cortisol.

Kempes measured aggression experimentally in DBD and normal children during game-playing sessions with a neutral peer. Quick aggression (<3 sec.) was taken as a measure of reactive aggression and delayed aggression (>3 sec.) was taken as a measure of proactive aggression. To distinguish between the two types of aggression in the home situation Kempes developed a parent questionnaire. Aggression in the 'real life' home situation and during experimental play were related to physiological parameters such as skin conductance, heart rate, and cortisol levels.

In general, reactive and proactive aggression during play in terms of response latency did not correlate with parent-rated reactive and proactive aggression, neither in normal nor DBD children. In addition, behavioural measures of reactive and proactive aggression were not related to heart rate and skin conductance. However, in DBD children a relation between reactive aggression (in response to neutral behaviour of a peer) and parent-rated reactive aggression was found. Moreover, in DBD children reactive aggression in the experimental play session was found to be related to the difficulty in understanding the peer's intent.

The correlation between experimentally measured aggression and parent-rated 'real life' aggression was strongly dependent on the stress hormone cortisol. In DBD children, without elevated cortisol levels during play, there were good correlations between quick and delayed experimental aggression versus parent-rated reactive and proactive aggression. In DBD children with elevated cortisol levels, heart rate correlated negatively with delayed aggression, but positively with quick aggression. These correlations between heart rate and aggression were absent in DBD children without elevated cortisol levels. Thus it seems that both types of aggression can be predicted experimentally in 'cool' DBD kids (with low physiological responses to stress).

Maaïke Kempes (March 29, 1976, Amstelveen). Secondary school, 1994 (Ashram College, Alphen aan den Rijn); Biology at Leiden University, 1999. In 2000-2004 she worked at the Vosseveld clinic on the work described in her thesis. Presently

she is a postdoc (Depts of Developmental Psychology and Behavioural Biology, Utrecht University) working on the proto-moral behaviour in children and rhesus monkeys.

2005-11

April 1, 2005

A.Y. Konijnenberg

Unexplained chronic pain in children

J.L.L. Kimpfen, J.K. Buitelaar, E.R. De Graeff-Meeder, C.S.P.M. Uiterwaal
supervisors

2005-12

April 4, 2005

K. Starowicz

The interaction between melanocortins and opioids

W.H. Gispen, R. Przelocki, B. Przelocka
supervisors

2005-13

April 5, 2005

C.E. Van Meijeren

Development of an in vitro assay to assess pertussis toxin in acellular pertussis vaccines

D.J. De Wildt, C.F.M. Hendriksen, W. Vleeming
supervisors

2005-14

Operating in space

April 5, 2005

Peter W.A. Willems

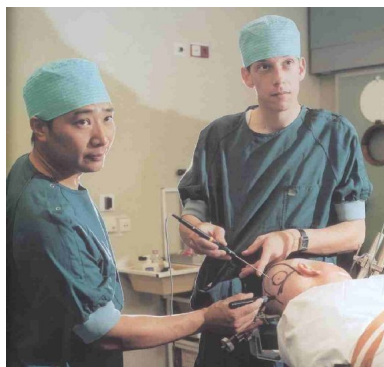
Technical and clinical assessment of neuronavigation

C.A.F. Tulleken, M.A. Viergever, J.W. Berkelbach van der Sprenkel, M.J.B. Taphoorn
supervisors

Some would argue that surgical intervention in the brain is almost as complex as the brain itself. Detailed spatial information during neurosurgery is essential to avoid unnecessary damage to brain structures and functions. Peter Willems evaluated frameless stereotactic procedures in which detailed three-dimensional (MRI) images are translated into spatial information that is used to guide the surgeon during the intervention.

Accuracy is a key feature of any successful neuronavigation system. Willems developed a phantom to study the transformation of true physical space into a digitised representation. CT-guidance was shown to be more accurate than MRI-guidance and microscope-guidance more accurate than pointer-guidance. Errors caused by the orientation of the stereotactic device were maximally 1.34 mm. Even in the most unfavourable situation the average error was shown to be below 2 mm.

Despite these accuracy figures, there is little clinical evidence to support claims regarding the added clinical value of neuronavigation. In one study Willems compared the use of frameless neuronavigation to the more classical frame-based techniques to obtain brain biopsies from patients. The robotic navigation system appeared as accurate and efficient as the frame-based system and postoperative morbidity was comparable. Thus, it seems that the more patient and surgeon friendly frameless neuronavigation in time will replace frame-based procedures for minimal invasive neurosurgery.



Peter Willems (right), neuronavigating.

To further exploit the advantages of frameless neuronavigation, Willems performed a so-far unique prospective randomised trial involving glioblastoma surgery. Though in glioblastoma surgery many previous studies have suggested a beneficial effect of gross total resection on survival, Willems' study failed to show any effect of the use of neuronavigation on radicality of resection, postoperative clinical course or survival. Since this has been the only prospective trial with regard to this subject, to date, Willems concluded that surgeons should not feel compelled to use navigation in cytoreductive surgery if tumour size or location do not suggest obvious benefit.

The most likely explanation for the failure of neuronavigation to improve either performance or benefit to the patient may lie in the occurrence of 'brain shift', i.e. the deformation of the brain during the operation. As Willems formulates it, "brain shift should be considered the Achilles-heel of neuronavigation". Neurosurgeons face the challenge to find a way to acquire and process 3D in-theatre imaging information during surgery to be able to fully exploit the advances of frameless neuronavigation.

Peter Willems (April 12, 1972, Breda). Secondary school, 1990 (Mencia de Mendoza Lyceum, Breda); Medicine at Utrecht University, 1996. In 1997-2003 he performed the work on neuronavigation as described in his thesis. Since 2003 he is a resident in Neurosurgery at the UMC Utrecht and he is expected to qualify as neurosurgeon in 2008.

2005-15

Questioning your social skills

April 14, 2005

Elias Martijn Hulstijn

Construction and validation of a social skills questionnaire for children and adolescents

P.T. Cohen-Kettenis, G.J. Mellenbergh, A. Boomsma
supervisors

Presently there are no instruments to evaluate the social skills of children and adolescents in the Netherlands. Elmar Hulstijn developed a self-assessment questionnaire to effectively measure the social skills of children and adolescents. After validation two scales emerged that can be used in research to measure social skills and allow standardised evaluation of social skills training programmes.

The model that Hulstijn build was loosely based on the MESSY-model that was developed in the 1980's in the United States. The items of the MESSY-questionnaire were redistributed into several new scales and tested for their validity, assessing children and adolescents who had never had contact with Mental Health Services and three groups with alleged social skills problems, namely children with social skills problems, adolescent with psychiatric problems and female adolescents in judicial institutions. Two of the developed scales of the questionnaire appeared particularly useful; the first scale was defined as assessing *prosocial behaviour*, the second scale could be defined as measuring *inappropriate social behaviour*.

Hulstijn developed a short, non-demanding, and easy to use questionnaire that can be used in clinical settings. It is reliable and stable, and provides insight into an individual's prosocial and inappropriate social behaviour. Each scale should be used with normative data for boys and girls separately, and for children and adolescents separately. The questionnaire is a practise-oriented instrument and an instruction manual is being prepared. The availability of the questionnaire can be a stimulus for further research into the social skills (i.e., prosocial behaviour and inappropriate social behaviour) of children and adolescents.

Elmar Hulstijn (May 1, 1959, Tiel). Secondary school, 1979 (Bogerman College, Sneek), Pedagogy and Psychology at Groningen University (diploma 1988 and 1991, respectively). Since 1999 he worked on several projects in research, health care, diagnostics, and data and information management at the UMC Utrecht. One of these projects, based on his own proposition, resulted in this thesis.

2005-16

April 28, 2005

M. Van Asselen

Neurocognition of spatial memory: Studies in patients with acquired brain damage and healthy participants

A. Postma, E.H.F. De Haan, L.J. Kappelle
supervisors

news

Rudolf Magnus Graduate School Certificates

The Director and the Research Training Committee of the Graduate School took pleasure in presenting the Certificate to the following Doctors:

Els De Schrijver (March 11, 2005)

Saskia Palmén (March 22, 2005)

Van Ree wins Prize

Jan M. Van Ree has won the Gayle A. and Richard D.Olson prize 2005 for the most meritorious behavioural research article in the journal *Peptides*, published in 2004.

Prime Minister visits Institute

Jan-Peter Balkenende, prime minister of the Netherlands, visited our Institute on Wednesday February 23rd. Balkenende visited the Utrecht University on the occasion of the official start of the 'Taskforce Innovation Region Utrecht', an innovation platform in which the Utrecht University plays a big part. As an excellent example of innovation Cees Tulleken (Professor of Neurosurgery) presented to Balkenende the revolutionary 'excimer laser-assisted non-occlusive anastomosis (ELANA) technique'. This neurosurgical technique allows bypass operations of the carotid arteries without interruption of the blood flow at any time, thus circumventing cerebral ischemia during intracranial surgery.



Jan-Peter Balkenende (left) trying to master the ELANA technique under the skilled guidance of its inventor Cees Tulleken (right)

With the complements of Rudolf Magnus!!

How do you show your gratitude towards a foreign guest who has presented an inspiring lecture? Or how do you, as a supervisor, share the happiness of a just-graduated PhD? Now it is simple; present them with the Rudolf Magnus gift-box. This box is made freely available by the Institute to hosts of lecturers and PhD supervisors to give away to guests and young Doctors, respectively.



The gift-box is freely available from the Institute's office, Jan Dekker, Stratenum, room 5-135. (photograph, J.Dekker)

And if you want to add a personal touch, a bottle of wine seems a logical choice.



agenda

April 8, Helmholtz Lecture

Shihab Shamma (University of Maryland, USA), 'Rapid plasticity in receptive fields of primary auditory cortex' 16:00-17:00, 'Rode zaal', Ruppert Building, Leuvenlaan 19, Utrecht (contact, v.maassen@fss.uu.nl)

April 25-26, Course fMRI data analysis

SPM short course: a practical and theoretical introduction into fMRI data analysis. Deadline for application, 11 April.
9:30-17:00, 25-26 April, Utrecht University, programme and registration, <http://www.rudolfmagnus.nl>. Costs 195 Euro (Rudolf Magnus and Helmholtz Institute), 260 Euro (others). Attendance at the course will be awarded by the Rudolf Magnus Graduate School by 2 credits. (contact, s.f.w.negggers@fss.uu.nl)

April 28, Special Helmholtz Symposium

'Remembering and losing things in the world: the neurocognition of space'
14:00-17:00, Museum van Speelklok tot Pierement, Steenweg 6, Utrecht (contact, v.maassen@fss.uu.nl)

June 16, 2005, Rudolf Magnus Symposium Genetics of Behaviour

Speakers will include, Jonathan Flint (Oxford), Dorret Boomsma (Amsterdam), Berry Spruijt (Utrecht), Martien Kas (Utrecht). Admittance to the symposium is free (including lunch), however registration is required.

11:00-18:00, Groene zaal, Went building, Sorbonnelaan 16, Utrecht.
Programme and registration, <http://www.rudolfmagnus.nl>.
Attendance at the symposium will be awarded by the Rudolf Magnus Graduate School by 1 credit.

September 12-13, Rudolf Magnus Summer School 2005

Conference Centre Ottone, Kromme Nieuwegracht 62, Utrecht. The programme is now available on the website, <http://www.rudolfmagnus.nl>.
Attendance including presentation at the Summer School will be awarded by the Rudolf Magnus Graduate School by 2 credits.

November 24-25, 2005, Annual Meeting PhD students

Conference Centre Woudschoten, Zeist
Information and Registration, <http://www.rudolfmagnus.nl>.
Attendance including presentation at the Annual Meeting will be awarded by the Rudolf Magnus Graduate School by 2 credits.

November 30, Rudolf Magnus Symposium 2005 and Research Award

Keynote, **Michael Gazzaniga** (Hanover NH, USA)
Programme and Nominations for the Research Award, <http://www.rudolfmagnus.nl>

November 28 – December 2, 2005, Introductory Course for PhD students

Information and Registration, <http://www.rudolfmagnus.nl>.
The course is accredited by the Rudolf Magnus Graduate School of Neuroscience and will be awarded by 5 credits.