

15 October 2009

Donders Institute for Brain, Cognition and Behaviour Newsletter



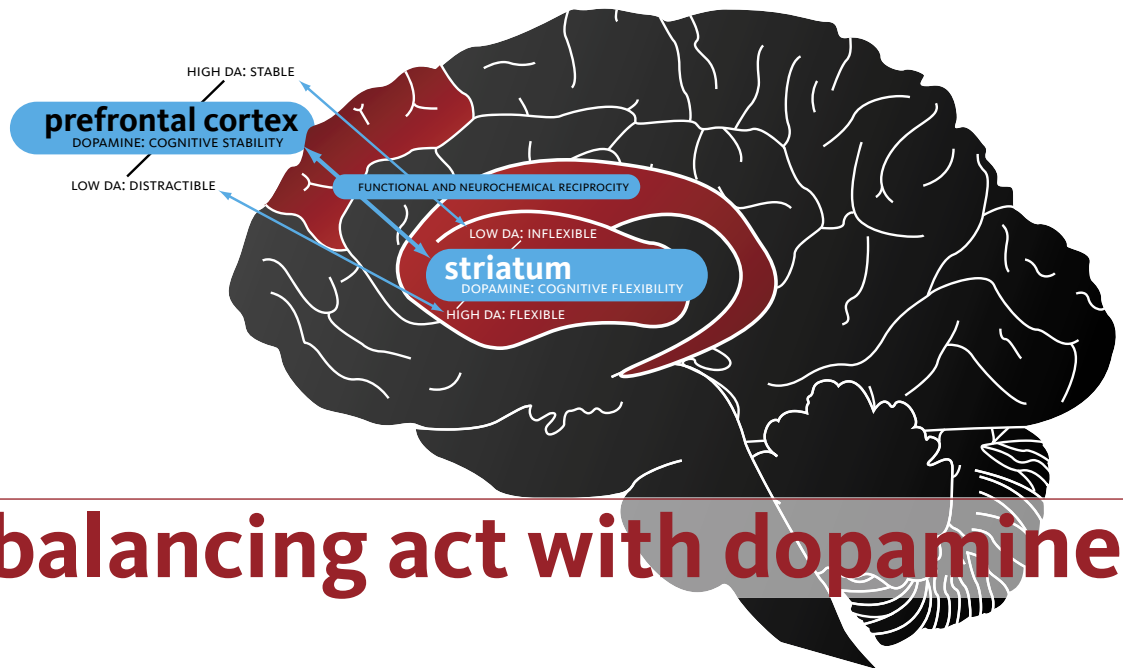
The Donders Newsletter is published three times a year by the Donders Institute for Brain, Cognition and Behaviour, which consists of research groups at Radboud University Nijmegen and the Radboud University Nijmegen Medical Centre as well as the Max Planck Institute for Psycholinguistics. Its purpose is to keep you informed of developments and important news in the field of neuroscience.

Since the Donders Institute for Brain, Cognition and Behaviour was established in September 2008, we have been remarkably successful in terms of publishing papers in top-ranking journals and obtaining grants. Recently, the Donders Graduate School for Cognitive Neuroscience was formally approved by the Netherlands Organisation for Scientific Research (NWO) and the Ministry of Education and in September we launched the new International Max-Planck Graduate School, both of which provide funding for new PhD positions. These two graduate schools offer young researchers in Nijmegen excellent training opportunities.

The activities at the Donders Institute are led by researchers with a wide range of disciplinary backgrounds, coalescing around four themes: language & communication, perception, action & control, learning, memory & plasticity, and neuronal communication. These topics reflect the unique strengths of research in Nijmegen, which includes experimental and theoretical techniques from the genetic and molecular level right up to the realm of human behaviour. Together they express our ambition to explore neurocognition from molecule to man.

With this ambition in mind, we report on novel developments within the institute. This edition presents new developments in the field of Brain-Computer Interfacing, neural and neurochemical mechanisms underlying flexible behaviour-driven by motivational and cognitive control-and novel ultrasound techniques which are used to investigate the peripheral neuromuscular system for diagnostic purposes. For us, a major source of inspiration is the amazing properties of the human brain. We hope this newsletter will convey some of our enthusiasm as you read about highlights from our work.

Prof. Stan Gielen
On behalf of the Board of Directors
Donders Institute



A balancing act with dopamine

Human beings are extremely capable of adapting to their constantly changing environment. But often we need to ignore those changes, stay as we are, and continue acting as normal. So how do we know when it's appropriate to change our behaviour and how do we balance flexibility and stability? Roshan Cools is working on the hypothesis that this is mediated by the brain substance dopamine, which regulates the dynamic interaction between two regions of the brain.

'Things developed so quickly', Cools observes, referring to her position as Principal Investigator at the Donders Institute, where she started only two years ago, soon after which she obtained a NWO Vidi grant. 'There are fourteen people in my group if I include my affiliated and Master's students,' she says. Thanks to a flourishing research programme, initial results are already coming in.

With a command of English language that reflects the time she's spent in the Anglo-Saxon world – Cools was a PhD student at St. John's College in Cambridge (UK) with Trevor W Robbins and a postdoc in Berkeley California with Mark D'Esposito – and a pace that reflects her quick mind, she explains the main hypothesis of her research project: 'It's not only the abnormal mind that has difficulty adapting. Prolonged or severe periods of stress and fatigue also make the usually healthy mind inflexible or unfocused. In our research we

aim to provide more insight into this process, with the ultimate aim of understanding the neurobiological basis of neuropsychiatric disorders such as ADHD and Parkinson's disease. One characteristic of these disorders is a neurochemical imbalance, leading to inflexibility, impulsivity and/or compulsivity. We hope that our approach will eventually lead to individualized treatment strategies that target the complex cognitive deficits associated with these conditions.'

Two interacting regions

'We appear to need both cognitive flexibility and stability. If we're too flexible, we tend to be distracted and our behaviour becomes unstable and, if we're too stable, we become inflexible. A pure form of reciprocity would imply that we need only a single mechanism that can be adjusted dynamically, depending on the task at hand. However, we often need to be both flexible and stable at the same time. That is, while we should be flexible in response to relevant changes, we should remain stable when there are irrelevant changes. To resolve this apparent paradox, it's plausible to postulate two separate mechanisms that work together. We think the prefrontal cortex – commonly associated with complex cognitive requirements – and the striatum, a deep brain subcortical structure traditionally associated only with movement control, work together. Dopamine balances this interaction.



Roshan Cools

Baseline levels

'The assumption that two separate mechanisms are involved in the balancing act is not enough to account for the paradoxical effects of dopaminergic drugs,' Cools explains. 'How can drugs that enhance dopamine improve cognitive flexibility in some individuals (e.g. those with Parkinson's) while improving cognitive stability in others (e.g. those with ADHD)? And as well as influencing the brain region that the dopaminergic drug innervates, its effects will also depend on the baseline levels of dopamine in that region. The drug will remedy brain functioning in regions with low baseline levels of dopamine, while detrimentally overdosing function in brain regions in which the baseline levels of dopamine are already optimal.'

Move or freeze?

An intriguing question is how do we know when it's appropriate to change? What kinds of clues are considered relevant? To understand this issue in the normal brain a lot of work is needed on patients with neurochemical disorders, hopefully leading to a model for cognitive flexibility. 'We also shouldn't ignore all the rodent work that's been done,' Cools says with a smile, referring to the fact that she is the daughter of Professor Lex Cools, the neuropharmacologist from Nijmegen who did so much work on dopamine-

sensitive brain areas in rats. Roshan, trained as a psychologist, advocates new behavioural studies with rodents, if only to reduce the hassle involved with using human subjects. 'Imagine one of my PhD students is doing an fMRI study on the effect of dopamine on a simple reward and punishment learning task,' she says. Her subjects have to come in four times: for a trial with a dopamine enhancer, one with a dopamine blocker, one with both drugs to control for placebo effects, and one control study with no drugs at all. 'It takes 18 months to organize this and it's very expensive.'

Roshan is about to return to Berkeley – not to accept the job they offered her (she intends to stay at Donders), but to spend a month on 'contemplative' writing alongside old colleagues and to enjoy the American can-do attitude. It's pretty addictive she admits and, suddenly putting on a Californian accent, she says: Oh, we just love what you're doing. It's so incredibly fantastic, we love you!

Explorative steps with serotonin

This year, one of the highly prestigious Human Frontiers Science Program (HFSP) grants was awarded to Roshan Cools, in collaboration with Kae Nakamura (Kansai Medical University, School of Medicine, Osaka Japan) and Nathaniel Daw (New

York University) for a multidisciplinary project on serotonin and dopamine. One third of the \$1 million plus grant will go to research at the Donders Institute. Serotonin is a brain substance that, like dopamine, has long been seen as crucial to processes that control behaviour, including decision making and reinforcement learning. However, compared to dopamine, there's much less known about the mechanisms through which serotonin affects behaviour. Cools and her colleagues will address this issue by using existing understanding of dopamine and a constellation of methods that have shed much light on the role of dopamine, integrating functional magnetic resonance imaging, psychopharmacology and neuronal recordings in monkeys and humans – all guided by computational theory.

– Iris Roggema

List of publications:

www.ru.nl/neuroimaging/staff/cognitive_control/roshan_cools/



Exploring Brain Computer Interfacing

Finding true motivation lies in bridging the gap between scientific specialisations, university and society, says Peter Desain, the director of BrainGain – a special project set up to investigate potential applications of neuroscientific research findings. He's just been celebrating the submission of a new patent application. Deciphering the neural code might be considered the holy grail of cognitive neuroscience, but this ultimate goal is not yet within reach. Many interesting detours have been identified en route, so why wait to explore them or perhaps even exploit them?

Bridge builder

At the Donders Institute at Radboud University Nijmegen it's Professor Peter Desain – head of the Artificial Intelligence department – who plays a key role in developing tools for inferring the state of cognitive processes directly from measurements of brain activity. Trained as both a technical mathematician and a psychologist, and now working as a fundamental researcher and inventor, he really enjoys bringing people together; he's the incarnation of a bridge builder.

BrainGain – a consortium of 23 research groups and companies both large and small led by Desain – translates insights from neuroscience into applications that benefit both healthy users and people suffering from autism, ADHD and ALS. The latter are progressively locked in their mind due to loss of muscle control. The communication by eye blinks they use is movingly portrayed in the film *The Diving Bell and the Butterfly*. But Brain Computer Interfacing (BCI) offers hope for a more efficient communication. BCI is a general term for any device

that picks up a specific brain signal and translates it into a computer signal, be it a cursor, a mouse or a spelling programme.

Patent on Noise

'The best ideas arise when applying technology from one field of knowledge to another, says Desain states. 'For example, broadband mobile phone signals are labelled with an individual random bit pattern that makes it possible to identify your personal call from the blurred, mixed signal of all the phones in an area.' It's exactly this idea that Desain and his colleague Farquhar apply in a newly patented BCI system.

'We watermark the stimuli with a characteristic, possibly subliminal, noise, which you can then trace back to a brain signal in the subject. So, if we present two stimuli, for example a sound on the left side and one on the right side, we can distinguish the one that the subject is paying attention to. With visual stimulation it works even better. And selective attention is often an easier and more natural task than the classic BCI task of imagined movement. Systems like this are still quite cumbersome and hard to train, both for the user and the machine'.

Another idea Desain's team is currently testing is a sort of mental juke-box. When you recall a song, it generates a specific brain signal. Imagine your favourite Christmas carol and your computer directly links this to a specific action. It's relatively easy to recall songs and the

Peter Desain



system can be tailored to your personal preferences. Though it is still quite hard to detect these reliably by computer, the example illustrate that the tasks inducing the BCI signal are vital for a quick and easy operating system. Improving BCI will to a large extent depend on developing the task side, according to Desain.

Automated conversation

'RE-phrasé' is the name of a Desain discovery that's closer to market. 'Conversations are often fairly standard. For example, helpdesks often receive the same questions and usually an answer elicits a follow-up question. So we thought: why not automate this, representing questions and answers in a huge conversation network? This works better than the usual FAQs. It's more structured and presents only relevant responses at any point in the dialogue. The method is also more interactive and learns from new input by users. As the sentences can be stored in many languages, the system can help with communication while travelling. An application called RE-phrasé Trip is now available for iPhones and iPods and the same technology is being tested for use as an electronic coach for children with autism, together with the Dr Leo Kannerhuis. This device helps to structure tasks and gives advice when flexible behaviour is needed. For a panic-stricken person with autism who, for example, has just missed a train, it can be a real benefit to have such a digital assistant.

'There's also a link to our neurocognition research as ALS patients could benefit from RE-phrasé as well. Instead of spelling letter by letter, which is quite tiresome when using a BCI we store and recycle the phrases thus entered, and make a system based on entire sentences. Users just select the phrase they need by looking at it.

Be generous

'It's not rocket science, Desain admits, 'but I'm sure that researchers can also benefit from these kinds of projects. New ideas, different views, unexpected research questions.' It's one of his reasons for stimulating business spin-offs from cognitive neuroscience. The Donders Institute is currently starting up an Innovation Lab, a business incubator. Desain is personally inspired by the attitude of Stanford University, where he enjoyed a sabbatical leave several years ago. 'The motto of their Office of Technology Transfer is: Be generous. And that's how it should be. Dare to invest. Be generous to many ideas for start ups. Most won't survive. Some will make a living. And once in a decade or so you'll have helped start a Google. I really hope we can change the mind set of our researchers. Society and research can both benefit from a more entrepreneurial attitude. I'm happy to see that these changes are now happening at our University too.'

– Iris Roggema

New road

Discriminating phonemes in an unfamiliar language you're studying, is one of the hardest things to learn. When Japanese is your mother tongue a /r/ and a /l/ simply sound the same. Intriguingly, long before we are consciously aware of the difference of these speech sounds, our brain reacts with a different signal to them. Together with Prof. McQueen from BSI, Desain' team just started working on a neuro-feedback method to speed up these learning processes. 'When you see what the perceptual processes in your brain already begin to pick up, you might be able to enhance that further.'



Van Gerven, M., Farquhar, J., Schaefer, R., Vlek, R., Geuze, J., Nijholt, A., Ramsey, N., Haselager, P., Vuurpijl, L., Gielen, S. & Desain, P. (2009). The brain-computer interface cycle. *Journal of Neural Engineering*, 6 041001 (10pp) doi: 10.1088/1741-2560/6/4/041001

Desain, P. & C. Jansen (2000). Method and System for Providing Communication via a Network. Patent PCT/NL00/00425



Sigrid Pillen makes muscle ultrasonography her life's work

‘Exploring new territory’

Sigrid Pillen (29) is a paediatrician-in-training at the Radboud University Nijmegen Medical Centre (RUNMC), where scientific work is affiliated to the Donders Centre for Neuroscience. She already has numerous scientific publications to her name, and has received various prizes for her research. At the end of May she was awarded her doctorate, cum laude, for a bulky thesis on muscle ultrasound. She has also recently given birth to a daughter, Tess. A portrait of a promising neuroscientist.

Sigrid, Nens and their two month-old daughter Tess live in a modest upstairs apartment in East Nijmegen. At least for now; because soon they will be moving to a house with a garden just 200 metres away. Tess is very well behaved during the interview, lying content on Nens' lap, beside the laptop she already seems quite familiar with.

On 26 May 2009, a few days before beginning her maternity leave, Sigrid was awarded her doctorate, cum laude, for her thesis on 'Quantitative muscle ultrasound in childhood neuromuscular disorders.' "It turned into a sort of handbook for people starting to use this diagnostic technique," says Pillen, leafing through the 254 page-thick thesis. She did her PhD research at the Department of Clinical Neurophysiology of RUNMC within the programme of the Donders Centre for Neuroscience, with Prof. Machiel Zwarts as her promoter.

Identifying muscular diseases

Muscle ultrasonography is a technique that's easy to use for making a picture of muscle thickness and structure, explains Pillen. 'In the early 1980s it was known that you could use this technique to identify neuromuscular disorders, but it was not widely applied. There were only two centres where muscle ultrasonography was used as a standard diagnostic tool, in London and in Philadelphia, but nowhere else until we started in Nijmegen. Muscle ultrasound scans are made in the same way as a pregnancy ultrasound, but seeing a muscular disorder in such a scan with the naked eye is often difficult. Qualitative, visual analysis requires a lot of experience, which is often lacking. That's why we decided to try computer-aided quantitative analysis.'

Pillen's interest in neuromuscular disorders arose while she was studying medicine at Radboud University Nijmegen. 'In my third year another student, Ralph Scholten, and I contacted the paediatric neurology department, where they were eager to try this new and non-invasive technique of muscle ultrasonography. We set it up, often working more than forty hours a week, and were given a lot of freedom. I love research: working to the limits of your intellectual capacity. Fundamental research is wonderful, but I want to discover something you can actually apply to a real-life problem. I like to take research in that direction.'

Wriggling babies

Until recently muscular disorders were diagnosed by taking biopsies, generally from the thigh muscle, with a thick needle or an operation. As a screening tool you could apply electromyography (EMG, a technique used to measure the electrical activity of muscles). "For EMG you also need to insert needles into the muscles, and then move the needle within the muscle. This causes discomfort, which is hard to explain to children. We know that in over 50% of these children no muscular disorder will be found. Which is wonderful for the child, but why should they go through a painful examination to find that out? This is why we wanted to develop a screening technique that's non-intrusive, particularly for children."

Muscular disorders can also be imaged using Magnetic Resonance Imaging (MRI), but then the subject has to lie still for 45 minutes. That's difficult, again especially for children. "For a muscle ultrasound you only need to lie still for a few seconds. That can be done even with a wriggling baby," laughs Pillen. Nowadays the pictures are analysed using simple software on a PC. "In the past the images were analyzed using the naked eye, which could only detect 70% of the muscular disorders. The missing 30% represented a big grey area. With the computer we can detect about 90% of neuromuscular diseases. Ultrasound equipment is also much more sophisticated now."

Why not 100%?

"Some muscular disorders do not show up as whiter muscles on the scan. These are the ones that result mainly in defects in energy production (rather than tissue destruction), which cannot be seen in an image of the muscle structure. White spots indicate connective tissue and fat that don't belong in healthy muscles. And in very small children it's difficult to detect muscular disorders at all. Their muscles are not yet damaged to the point that we can spot a possible disorder with an ultrasound scan."

Stretching the limits

After her training as a paediatrician, which she will complete next year, Pillen will begin training as a paediatric neurologist, possibly through a fellowship at the

medical centre. This training will take about two and a half years. At the same time, she is continuing her research on using muscle ultrasonography for better detection of neuromuscular disorders. "Many muscular disorders are incurable, but you can do so much for patients! People stretch their limits and achieve something despite their condition. That's wonderful. Many of these patients are now adults, which brings new challenges. A future goal for example is to ensure that these people have a place in Dutch society despite their limitations, and early detection can help."

In the past two years there has been more interest in using muscle ultrasonography as a basic diagnostic tool. "Now we're trying to distinguish between the different muscular disorders, and we want to develop the diagnostic technique further with adults. Muscle ultrasonography should be a standard test for every neurologist or paediatrician dealing with muscular disorders. We are organising a course to promote it in November."

As a paediatrician you have to be fairly resilient, says Pillen. "Children can be little darlings, but mainly when they are not ill. You have to be able to cope with that. As a young mother? Yes, I'm curious to see if that will make a difference when I return to work. But I'm not the type to stay at home. Changing nappies and doing housework is fun for a while, but when that's done I want to use my brain again."

– Myrna Timbergen



Sigrid Pillen

Muscular disorders: relatively rare and often hereditary

There are more than six hundred muscular or neuromuscular disorders, from those affecting the motor neuron in the spinal cord, the nerve and neuromuscular junction to the muscle itself. Most are hereditary. The best known of these is Duchenne's disease (muscular dystrophy), in which an important protein is lacking in the muscle, which therefore steadily deteriorates. Muscular disorders are almost all progressive and incurable, with the exception of inflammatory muscle diseases that are often treatable, albeit with significant side effects.

Sixty in every 100,000 children are born with a muscular disorder, so they are relatively rare. The Radboud University Nijmegen Medical centre sees thirty to forty new children each year. Curative treatments for many muscular disorders are still in their infancy.

Muscles alive: ultrasound detects fibrillations.
Pillen S, Nienhuis M, van Dijk JP, Arts IM, van Alfen N, Zwarts MJ. Clin Neurophysiol. 2009 May;120(5):932-6. Epub 2009 Apr 7.

Muscle ultrasound in neuromuscular disorders.
Pillen S, Arts IM, Zwarts MJ. Muscle Nerve. 2008 Jun;37(6):679-93. Review.



Donders Backbone

Due to its academic nature and high ambitions, staffing at the Nijmegen-based Donders Institute is extremely dynamic. Postdoctoral researchers and PhD students fly in from around the globe. Technicians, lab workers and research assistants form the

backbone of the institute. Jos Dederen is one of its vertebrae, ever since he came to work at the Department of Anatomy more than thirty years ago. For anything to do with histology, just ask Jos.

'In the old days, we built Styrofoam jigsaw models based on sections of brains in three dimensions. Nowadays computer modelling creates these in a matter of seconds.' It's not the only method Jos has seen become outdated. 'We used to study neuronal connections in living animals using tracers in the brain,' he says. 'This is not appreciated anymore, so we're currently working on post-mortem techniques. For this, you need extremely fresh brain tissue, collected as soon as possible after death. After chemically stabilizing the tissue, we show that some tracer molecules can penetrate and spread through the tissue, making it possible to visualize neuronal connections. We've done this in animal studies and we're about to make the step to human tissue.'

As one of the first qualified histological technicians, it was easy for Dederen to get an academic job back in 1975. He started working for Dr Jessie Gribnau, an embryologist in the Anatomy Department. She encouraged him to keep on developing, so he specialized in neurohistology. These days he mainly performs immunological work in which antibodies are used to detect, locate and quantify specific molecules in the brain.

Dederen demonstrates his advanced lab equipment and pulls samples out of the fridge, while muttering comments on the quality of the work done by a student



Jos Dederen

lab assistant. Standards being much higher than they used to be, an average PhD thesis on cognitive neuroscience consists of MRI studies, behavioural and genetic studies plus the histological identification of protein or neurotransmitter changes in response to illness, feeding or a particular (pathological) behaviour. This need for multidisciplinary explains why most PhD students are supported by expert technical assistants.

Dederen, who works together with researchers in and outside the Donders Institute, likes to have open scientific discussions with researchers about what's technically possible to meet their demands, especially because, when you're engaged in multidisciplinary research, a compromise in handling the tissue often has to be found.

He hopes the vacant chair in Anatomy will be granted to a real neuro-anatomist and that the research potential of the group will be restored to its former level. With his work at the Donders Institute he feels he's made a good start towards achieving this goal.

Anything more the dedicated analyst wants to add? Sure. 'I'd really like to advertise a slide series on the development of the brain from embryonic to foetal stage in Chinese hamsters, rats and rhesus monkeys. These were made in our department a long time ago. It's excellent reference material; if only people knew it was here!'

– Iris Roggema

Agenda

20 October 2009, 15:45 – **MPI Colloquium Riitta Salmelin**. Max Planck Institute (Room 1.63), Wundtlaan 1, Nijmegen

20 November 2009, 15:00 to 16:00 – **Formal Donders Colloquium Marty Sereno**. Centre for Cognitive Neuroimaging, Kapittelweg 29, Nijmegen

27 November 2009, from 15:00 to 17:00 – **Donders Lecture by Wolfgang Maass**. Linnaeusgebouw (LIN6), Heydendaalseweg 137, Nijmegen

Latest additions to the Donders Series

18. Prinz, S. (2009). *Waterbath stunning of chickens – Effects of electrical parameters on the electroencephalogram and physical reflexes of broilers*. Radboud University Nijmegen, Nijmegen, The Netherlands.

19. Knippenberg, J.M.J. (2009). *The N150 of the Auditory Evoked Potential from the rat amygdala: In search for its functional significance*. Radboud University Nijmegen, Nijmegen, The Netherlands.

20. Dumont, G.J.H. (2009). *Cognitive and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') in combination with alcohol or cannabis in humans*. Radboud University Nijmegen, Nijmegen, The Netherlands.

21. Pijnacker, J. (2010). *Defeasible inference in autism: a behavioral and electrophysiological approach*. Radboud Universiteit Nijmegen, The Netherlands.

Donders Institute Newsletter

Editors: Arjan Vink (a.vink@donders.ru.nl) and Iris Roggema (i.roggema@communicatie.ru.nl)

Editorial Board: Ellen de Bruijn (DCC), Robert Oostenveld (DCCN), Eric Roubos (DCN), Machiel Zwartz (DCN), Arjan Vink and Iris Roggema

Journalism: Iris Roggema and Myrna Tinbergen

PhD defences

2-11-2009 – **Drs. M.A.H. Steegers**, Nerve injury and chronic pain after surgery: perspectives on epidemiology and mechanisms. *Promoters: Prof. G.J. Scheffer, Prof. K.C.F. Vissers. Co-promoter: Dr. O. Wilder-Smith*

4-11-2009 – **Drs. M. Stulemeijer**, Recovery after mild traumatic brain injury. *Promoters: Prof. F.W. Kraaimaat, Prof. G.W.A.M. Padberg. Co-promoters: Dr. P.E. Vos, Dr. S.P. van der Werf*

06-11-2009 – **Drs. W.B. Groen**, Language, perception and the brain in autism. *Promoters: Prof. J.K. Buitelaar, Prof. P. Hagoort, Prof. R.J. van der Gaag. Copromoter: Dr. M.P. Zwiers*

9-11-2009 – **Drs. R. Kerkhofs**, Discourse and prosody in sentence processing: An electrophysiological investigation. *Promoters: Prof. H.J. Schriefers, Prof. W. Vonk. Copromoter: Dr. D.J. Chwilla*

30-11-2009 – **Drs. M.S. Kouzakova**, Subtle Signs of Exclusion: How lack of mimicry affects the perception of self and others. *Promoter: Prof. A. van Knippenberg, Copromoter: Dr. R. van Baaren*

21-12-2009 – **Drs. L. Hogeweg**, Word in process: On the interpretation, acquisition, and production of words. *Promoter: Prof. H. de Hoop*

5-2-2010 – **Drs. P.M. van Dam**, The shortest path to cardiac activation. *Promoter: Prof. A. van Oosterom, Copromoter: Dr. T.F. Oostendorp*

25-2-2010 – **M.L.T. Vergeer**, Perceptual visibility and appearance effects of color and form. *Promoter: Prof. Ch.M.M. de Weert, Copromoter: Dr. J. van Lier*

Translation/language editing: Michael Gould Associates

Photography: Dick van Aalst, photo archives Radboud University

Graphic design and layout: Sander Hermesen (www.sander-hermesen.nl)

Printing: Thieme Deventer

Archives: www.ru.nl/donders