Donders Institute Newsletter

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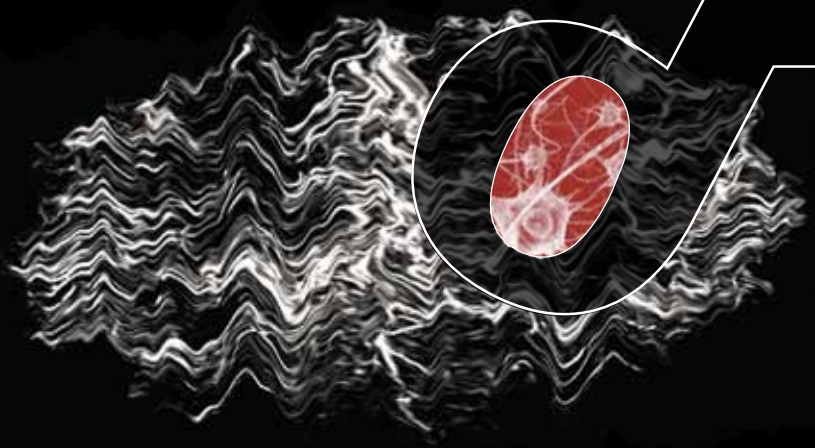
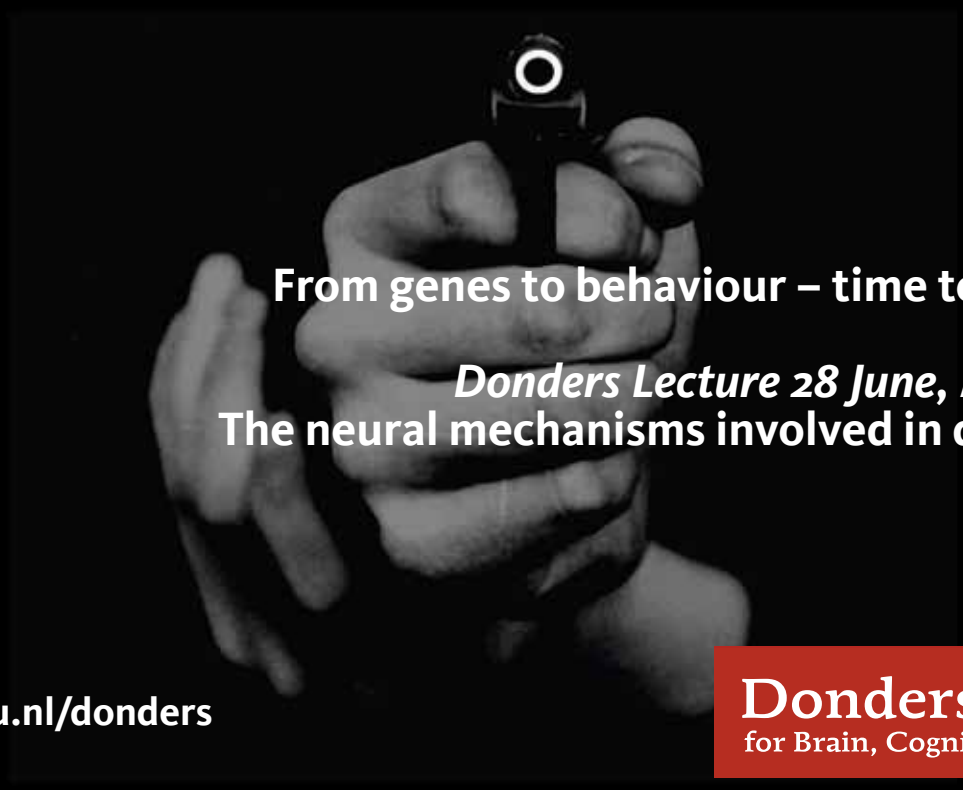
The Donders Newsletter is published three times a year by the Donders Institute for Brain, Cognition and Behaviour, which consists of research groups at Radboud University Nijmegen and the Radboud University Nijmegen Medical Centre as well as the Max Planck Institute for Psycholinguistics. Its purpose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



Guillèn Fernández
Unravelling the neurobiological underpinnings of stress



Cognomics
From genes to behaviour – time to take a big leap

Donders Lecture 28 June, Michael Shadlen
The neural mechanisms involved in decision making

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Donders Institute
for Brain, Cognition and Behaviour

Unravelling the neurobiological underpinnings of stress

When you see a gun pointing at you, your amygdala will ring like an alarm bell and a stress response will quickly prepare the body for action

By gaining insight to the brain's stress response Professor Guillén Fernández hopes to develop better clinical predictions and treatments.

'Do you remember what you were doing on 9/11?' asks Guillén Fernández. 'Very well,' I answer. 'But do you also remember what you were doing on September 11 last year?' 'No,' I say, 'I've no idea.'

'This shows that emotional events are better remembered than non-emotional events,' says Fernández. 'This may well help us to better detect potential threats in the future. One of the main reasons why we have memory at all is that it equips us with a way to make predictions about what's happening around us: Where is there food? What's dangerous here? Who is a potential partner? And making better predictions increases our chances of survival.'

Professor Guillén Fernández is Director of the Donders Center for Neuroscience, head of the Department for Cognitive Neuroscience, and Principal Investigator at the Donders Center for Cognitive Neuroimaging. He investigates the interaction between anxiety, memory and genes in an interdisciplinary context, combining cognitive neuroimaging with genetics, pharmacology and a range of clinical disciplines.

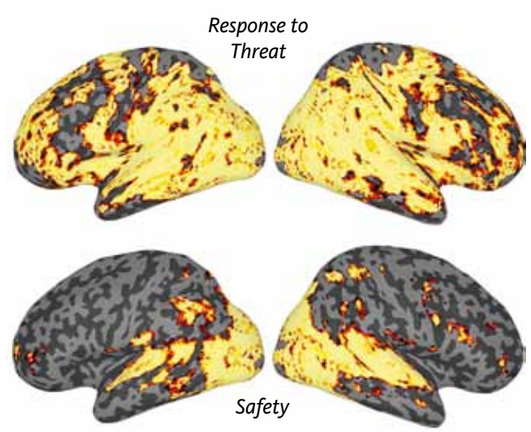
Most individual organ

'The brain is not only the most complex and variable, but also the most individual organ of the human body,' says Prof. Fernández. 'If you want to answer the question why one person is more vulnerable to stress or anxiety than another person, you need to do more than understand the general principles of the human brain. You need to understand the causes and effects of individual differences in the brain. And to understand individual brain differences, it's important to identify life-long underlying genetic differences and environmental differences.'

Together with Prof. Barbara Franke, Prof. Fernández set up the brain-imaging genetics project in order to answer the question as to how early life stress affects the brain and what role is played by the specific genetic makeup of an individual. More than two thousand subjects took part in this study. 'On the basis of their saliva, we analyze their genes,' says Fernández. 'We also make brain scans and the participants answer questionnaires about their life experiences. This is one of the new ways in which we can study individual differences in more and more detail.'

Noradrenaline vs. cortisol

When the brain perceives a dangerous situation, it's the amygdala that rings like an alarm bell. Together with the amygdala the brain makes a coordinated response to the threat: the body's motor response is activated so that it's ready for action, memory is up-regulated and vigilance is increased. All of this happens within seconds. Prof. Fernández and his team aim to unravel the precise biochemical pathways behind this response. Last year he and his collaborators discovered that it's not the stress hormone cortisol that is the driving force behind the stress response, as previously thought, but another stress hormone: noradrenaline. 'Noradrenaline up-regulates the brain response to threat, whereas cortisol actually brings this response down,' says Fernández. 'This came as a great surprise and led to a publication in *Science*.'



fMRI brain scans of people watching a movie full of threats versus a neutral movie Hermans et al. Science 2011

Happy faces

The researchers also showed that the amygdala response becomes unselective in threatening situations. Prof. Fernández: 'In a generally safe situation the amygdala responds strongly to seeing fearful and angry faces, but not to seeing happy faces. However, in a generally threatening situation, the amygdala response becomes unselective. Suddenly it responds not only strongly when people see fearful or angry faces but also when they see happy faces. In other words: the amygdala becomes hypersensitive. It would be too risky for the survival of the individual if it would respond too selectively.' Fernández and his colleagues also showed that a certain genetic makeup modulates this noradrenaline-driven response and the associated vigilance.

Soldiers under stress

Prof. Fernández also applies the insights from fundamental research to clinical questions. His team investigated the stress response of Dutch soldiers before and after a mission in Afghanistan. And in a new study Fernández will study a population of parents who have a child with cancer. The idea is that the influence of a severely stressful situation – such as having a child with cancer – might lead to a higher risk of developing a post-traumatic stress disorder (PTSD). Fernández: 'The question is whether we can predict PTSD better on the basis of brain data than with traditional questionnaires and clinical interviews.'

He not only aims to make better predictions of who will develop a post-traumatic stress disorder, he also hopes to contribute to better treatments: 'How can we more effectively help patients with an anxiety disorder? Fifty percent of anxiety patients respond well to cognitive therapy, but fifty percent do not. Here we have to realize that there are at least two basic processes that regulate anxiety and fear: one based on a mainly automatic response and another based on a mainly cognitive process. The automatic process is mediated by the brain stem, which up-regulates the amygdala, whereas cognitive processes are mediated by the prefrontal cortex, which can reduce the amygdala response via a cognitive control process. With pharmacology we can influence the automatic process in the brain stem. But the brain stem does not respond to cognitive therapy. In contrast, people whose cognitive control system is impaired may respond optimally to cognitive therapy.'

Guillén Fernández

Improved psychiatric diagnosis

Prof. Fernández' vision is to disentangle anxiety in such a way that clinicians can know which patient needs which treatment: cognitive therapy or a specific medicine. 'Psychiatry is the last clinical field where all diseases, definitions and treatments are based only on symptoms and not on underlying pathophysiology. I hope – and I believe– that we will soon be able to base psychiatry to a large extent on underlying mechanisms by using an interdisciplinary approach.'

Bennie Mols







Barbara Franke


Stan van Pelt

From genes to behaviour
time to take THE big leap

Imaging tools such as magnetoencephalography (MEG) and magnetic resonance imaging (MRI) have opened up a new field of research: Cognomics (short for Cognition genomics). World leading experts at the Radboud University Nijmegen play a central role in unravelling the links between the human genome, the brain and complex cognition and behaviour. "We try to understand the mechanisms that make people different, mapping genetic variability to cognitive individuality. Now is the perfect time to be working on this."

Society is becoming more and more personalized and increasingly dependent on tailoring education, work, and disease prevention to the talents and risks of individuals, explains Barbara Franke, Professor of Molecular Psychiatry at the Radboud University Nijmegen Medical Centre. She is the coordinator of the Cognomics programme in Nijmegen, a multidisciplinary collaboration involving leading experts in human genetics, neuroimaging and cognitive neuroscience at Nijmegen's university, Medical Centre and the Max Planck Institute for Psycholinguistics. "We currently work on neuroimaging genetics projects with cohorts of over 3,000 people. One of our studies on the genetics of brain structure – in collaboration with international colleagues – is about to be published in *Nature Genetics*."

The Cognomics "umbrella" is due to be expanded in 2013 with an even larger project known as Cognomics Resource, in which Maastricht University and the University of Twente will also participate. "We will start with three universities, but others are certainly welcome to join," Prof. Franke says. "Our ultimate goal is to establish a large resource of 10,000 participants, which we will use to trace the connections between genes, brains and cognition."

Variability between individuals

Major advances have been made in our understanding of the basic mechanisms underlying cognition and its link to brain function during the last decades. "But what we know about brain function and behaviour relates to groups. Until now, cognitive neuroscience has always ignored variability. We now want to focus on individuals, and advanced instruments, such as MEG and fMRI – and novel analytical methods – finally allow us to do so."

New way of thinking

Cognition, brain function –and even brain structure – are strongly influenced by a person's genetic endowment. And the genetic make-up of individuals also largely differs: 0.1 to 0.2% of the 3 billion base pairs of the human genome (approximately 25,000 genes) are different from one person to the next. "That really is a lot, because one individual gene consists of thousands of base pairs. We try to link this genetic variability to the variability between individuals in their behaviour, brain function and brain structure. These mappings have yet to be made."

Cognomics is a new way of thinking, Prof. Franke claims. "We try to understand the mechanisms that make us different, and want to use these mechanisms to improve society, tailoring key activities such as education more to the potential of individual children and using the knowledge we acquire for better disease prevention, as well as personalized disease treatment and rehabilitation. This is not just around the corner, sure, but now is the time to start."

Identical twins, identical gamma waves

A lot of genomic research has been conducted with identical twins, because their genome hardly differs. The Journal of Neuroscience recently published a study by researchers at the Donders Institute, in which MEG in twins revealed that gamma waves are genetically determined (i.e., highly heritable).

"Many cognitive functions are related to brain rhythms or brain waves," says Stan van Pelt, postdoc at the Donders Centre for Neuroimaging, who conducted the twin study together with Dorret Boomsma (VU Amsterdam) and Pascal Fries (Ernst Strüngmann Institute for Neuroscience in cooperation with Max Planck Society in Frankfurt, Germany). "The reason why we did this study is that previous PhD students had discovered big individual differences in gamma waves. That made us think there might be a hereditary component."

Many aspects of brain processing are intimately linked to brain rhythms, he explains. All classical brain rhythms (delta, theta, alpha, beta, and sleep waves) are heritable, but the individual differences are not substantial. Moreover, the gamma rhythm has been particularly strongly linked to cognition and it is also involved in attention, short and long-term memory, and conscious awareness.

"Twin studies represent the classic approach to looking at hereditary components, such as hair colour or IQ," he continues. "The interesting thing is that gamma rhythms are involved in all kinds of cognitive processes, especially those that make us human, such as attention, memory and perception – all higher cognitive functions. Gamma rhythms are also associated with cognitive disorders, in particular schizophrenia, Alzheimer and Parkinson's disease."

Genetically determined

Measuring gamma rhythms in the human brain is rather difficult, because they have very low amplitudes – they hardly exceed the noise level. "In humans, we can only measure them indirectly, using MEG and EEG. Pascal Fries has developed a set of stimuli that produced the high gamma waves we used in our experiments."

"By looking at identical twins only you can't conclude that traits are hereditary, because the environmental component is also very similar. We therefore included non-identical twins in our study. These were also raised in the same environment – just like the identical twins – but they differ genetically - they share just 50% of their genes. Gamma rhythms of non-identical twins appear to be much more variable than those of identical twins. This means that gamma rhythms are at least 91% genetically determined."

What can we learn from this?

"That's the big question," Van Pelt says, smiling. "We've just looked at visual perception, but our research implies that other higher cognitive functions, such as memory and attention, are also heritable. Maybe even more so, since gamma waves are thought to reflect a fundamental property of brain activity, and important for brain processing in general. In future, we'll leave the twins. Under the umbrella of Cognomics we'll look at the variability of this type of brain activity in the general population and try to associate that with genetic variability. From genes to behaviour is still a big leap."

Myrna Tinbergen

Michael Shadlen
Donders Lecture 28 June

The neural mechanisms involved in decision making

In the Donders Lecture series outstanding researchers in the field of brain and cognition present their work and ideas to an audience of scholars with a wide variety of backgrounds – from neuroscience to physics, psychology and linguistics. It's one of the ways the Donders Institute builds connections with the global scientific community.

For the upcoming Donders Lecture on June 28 Dr Luc Selen invited Prof. Michael Shadlen from the University of Washington to talk about his recent work on the neural mechanisms that are responsible for some forms of decision making.

'I don't have the seniority that is usual for a Donders Lecture host,' says Luc on the phone while winding up a music box for his baby daughter. 'But I got to know Michael Shadlen quite well while I was a postdoc in Cambridge with Professor Daniel Wolpert. Mike visited for a sabbatical year – we thought that he'd sit in a quiet office and write a book or something, but he got directly involved in our work. He was determined to establish the link between his work on decision making and ours on computational motor control. He was an excellent mentor and at the same time eager to learn from us. Last year Mike and Daniel received a HFSP grant to build a new research line based on the work he and I did together at the time.'

Together they explored the possibility of measuring the preparedness of muscles for motor action while still in the process of deciding what to do.

'As we know from single neuron recordings in monkeys, a decision is a probabilistic calculation in the brain. First you calculate your chances, than you move. But these monkeys are over-trained in a sense. They know what is coming, and they know what to do. Maybe their neuronal pathways have been modified by training. We were looking for a method that could show us how humans prepare for decisions in a more realistic setting. When you're driving a car and heading towards a zebra crossing, you prepare to brake, even if you haven't seen any pedestrians yet or judged from their behaviour whether they're about to cross the street. That preparation makes braking faster.'

This study of decision-making opens a window on the neural basis of many other higher cognitive capacities which also use information in a contingent fashion and in a flexible time frame — free from the immediacy of sensory events or the need to control a body in real time, Prof. Shadlen explains in his abstract.

'I will describe neural recordings from the parietal cortex of non-human primates that are trained to make difficult perceptual decisions. The neural responses provide insight into how decisions are made: how accuracy and speed are traded off against one another, how the brain reasons from probabilistic cues (as in predicting the weather), how prior probability affects the decision process, and how the brain assigns confidence — a degree of belief — that a decision is correct.'

'One might expect Shadlen' s talk to be more or less the same as the Donders lecture by Paul Glimcher,' Luc ads. 'But it won't be. Two researchers could hardly disagree more on a subject.'/IR

Donders Lecture, 28 June

"Believing and time: a neural mechanism for decision making"

Michael Shadlen

(MD, PhD, Professor and HHMI Investigator, Department of Physiology & Biophysics, University of Washington, Seattle, WA)

Location: on the campus of Radboud University Nijmegen in the Linnaeus Building, Heyendaalseweg 137, starting at 16:00.on Thursday 28 June.

Meanwhile at www.ru.nl/donders

Visit our website to keep up to date on our news and events.

Brain Awareness Week 2012 a great success

During Brain Awareness Week (12-18 March), the researchers at the Donders Institute for Brain, Cognition, and Behaviour intended to give the public insight into neuroscience. The extensive programme involved 26 Master classes, which were given by Donders' researchers at several high schools near Nijmegen.

However, the main event was the Open Day on 16 March at the Trigon. Around 1800 people including children, parents, and grandparents, visited the Donders research facilities. They were thrilled by the enthusiasm of people working at the Institute and enjoyed being a "researcher for a day" themselves. Dummy lab, lectures, demos and speed dates were used to inform visitors in many different ways and gave them the opportunity to listen, ask questions, and experience the atmosphere. "I felt like a real scientist and tried to figure out how the brain works", said an 11-year-old girl after visiting several lab demos. It was indeed an amazing day.

Awareness biases information processing

How does awareness influence information processing in the human brain during decision making? A new study led by Floris de Lange of the Donders Institute for Brain, Cognition and Behaviour offers new insight into this question (see the 22 November 2011 edition of the online, open-access journal *PLoS Biology*).

KNAW prize to brain researcher Peter Hagoort

Peter Hagoort, Director of the Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging and of the Max Planck Institute for Psycholinguistics, has received the Academy Professor Prize 2012, which was awarded by the Royal Netherlands Academy of Arts and Sciences (KNAW). The prize, which is worth €1 million, is intended as a lifetime achievement award for researchers who have demonstrated that they are absolute leaders in their field of expertise.

Combined knowledge for a new generation of nutrition

Companies in the food industry and research institutions will collaborate to develop test systems which will be able to predict the relationship between nutrition and the brain. These systems will help improve our understanding of perception, choice, and eating behaviour. Representing the Donders Institute, the research groups led by Prof. Roshan Cools and Dr. Alan Sanfey are closely involved. This consortium, which is investing €4 million in the project, will receive matching funding from the European Regional Development Fund (ERDF), the province of Gelderland and the Dutch government.

Science: Brain rapidly gears up for 'fight or flight' under stress

In threatening situations, the brain adapts within seconds to prepare an appropriate response. Some regions are temporarily suppressed, while others become more active and form a temporary alliance to engage in a fight or flight reaction. Noradrenaline is the driving force behind this reorganization (see also page 2 and the 25 November 2011 edition of *Science*).

The Donders Institute leads EU project on compulsivity disorders

On 1st of January 2012, the EU program TACTICS (Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndromes) started with a budget of €6,000,000. The research, led by Jan Buitelaar, cares about the background and treatment of compulsivity disorders. The project leaders for Nijmegen are Jeffrey Glennon, Barbara Franke, and Tom Heskes.

Donders Backbone

Ron Engels: 'I had 100 meters of snake at home'

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, research assistants, and administrative staff form the much needed constant, the backbone of the institute.

He was 17 and had a boring office job. So when through his father, a maintenance man at the university, Ron Engels (now 54) received an offer for a three-month job caring for Prof. Van Overbeeke's mice, he decided to take a chance. This turned into a lifelong profession. This year marks Ron's 37-year anniversary as an animal keeper. 'They asked: "Won't you get too attached to the animals? You know they are meant for research, and will ultimately be killed..." No, that's never bothered me. But of course it's my task to make their lives as comfortable as possible.'

Ron turned out to be an energetic worker and he was soon doing much more than looking after mice. The African clawed frogs (Xenopus Laevis) that are used for neuro-endocrine research came under his care. He shows them to me in the cellar of the Central Animal Laboratory (CAL), with the constant babbling of aquarium pumps in the background. 'When I started, there were fifty frogs. At their peak I had 4500 in stock. But they became obsolete for research.' For that reason he returned to the care for rodents as part of his job. They are used for behavioural experiments at the Donders Institute.

The reintroduction of these furry animals in his job resulted in a great personal sacrifice for Ron. In his early days at the mice pens he had come

Ron Engels

into contact with snake enthusiasts who would come for surplus laboratory animals to feed their snakes. Perhaps he was interested in owning a boa? Why not! Soon the lab was home to more than just one terrarium. 'I became a well-known snake hobbyist and breeder of all sorts of special colours and patterns', he shares proudly. He housed his collection in a specially converted space behind his home, which was soon augmented with other reptiles. 'At one time I had 100 meters of snake at home, if you were to lay them out.'

'When I started working with rats in the CAL, and they found out I had snakes, they immediately denied me entrance because of hygiene regulations. There was a risk of transfer of germs from the rats I fed to my snakes. I did not like having to choose between my hobby and the job I had enjoyed doing all those years. Eventually I did get rid of my snake collection. A hard pill to swallow, both for me and my son, who shared the same interest. But every cloud has a silver lining, because I became a grandfather at that time, and the thought of my grandchildren coming face-to-face with a six-meter reticulated python makes me feel relieved they're no longer around.'

IR

Diary

14-16 May 2012 **Toolkit of Cognitive Neuroscience: advanced course in functional neuroimaging data analysis** - *Donders Centre for Cognitive Neuroimaging, Kapittelweg 29, Nijmegen*

15 June 2012, 15.45 **Inaugural Lecture Pieter Medendorp** – *Radboud University Nijmegen, Aula, Comeniuslaan 2, Nijmegen*

21 June 2012, 16.00 **KNAW Academy Professor Prize award ceremony Peter Hagoort** – *KNAW, Kloveniersburgwal 29, Amsterdam*

28 June 2012, 16.00 **Donders Lecture by Michael Shadlen (University of Washington)** - *Radboud University Nijmegen, Linnaeus Building, Heyendaalseweg 137, Nijmegen*

20-24 August 2012 **Toolkit of Cognitive Neuroscience: essentials of major neuroimaging techniques (EEG, MEG, fMRI, PET, TMS)** - *Donders Centre for Cognitive Neuroimaging, Kapittelweg 29, Nijmegen*

Donders Institute Newsletter

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PhD defences

2 February 2012 – Denise van Barneveld. Integration of exteroceptive and interoceptive cues in spatial localization. Promotor: John van Opstal

3 February 2012 – Michael Helle. Artery-specific perfusion measurements in the cerebral vasculature by magnetic resonance imaging. Promotor: David Norris

15 March 2012 – Petra Spies. The reflection of Alzheimer disease in CSF. Promotor: Marcel Olde Rikkert

23 March 2012 - Lennart Verhagen. How to grasp a ripe tomato. Promotor: Albert Postma

28 March 2012 – Sven Vrins. Shaping object boundaries: contextual effects in infants and adults. Promotor: Harold Bekkering

30 March 2012 – Saskia Haegens. On the functional role of oscillatory neuronal activity in the somatosensory system. Promotor: David Norris

2 April 2012 – Johanna Egetemeir. Neural correlates of real-life joint action. Promotors: Harold Bekkering and P. Stenneken

5 April 2012 – Sascha Vermeer. Clinical and genetic characterisation of Autosomal Recessive Cerebellar Ataxias. Promotors: N.V.A.M. Knoers and H.P.H. Kremer.

12 April 2012 – Loes Janssen. Planning and execution of (bi)manual grasping. Promotors: Bert Steenbergen and Ruud Meulenbroek.

16 April 2012 – Huadong Xiang. The language networks of the brain. Promotors: Peter Hagoort and David Norris

15 mei 2012 - Lourens Nonkes. Serotonin transporter gene variance causes individual differences in rat behaviour: for better and for worse. Promotors: Stan Gielen and J. van Bokhoven

16 mei 2012 - Emanuel van den Broeke. Cortical sensory processing in experimental and clinical models of persistent pain. EEG studies in healthy volunteers and patients. Promotors: K. Vissers and G. Scheffer