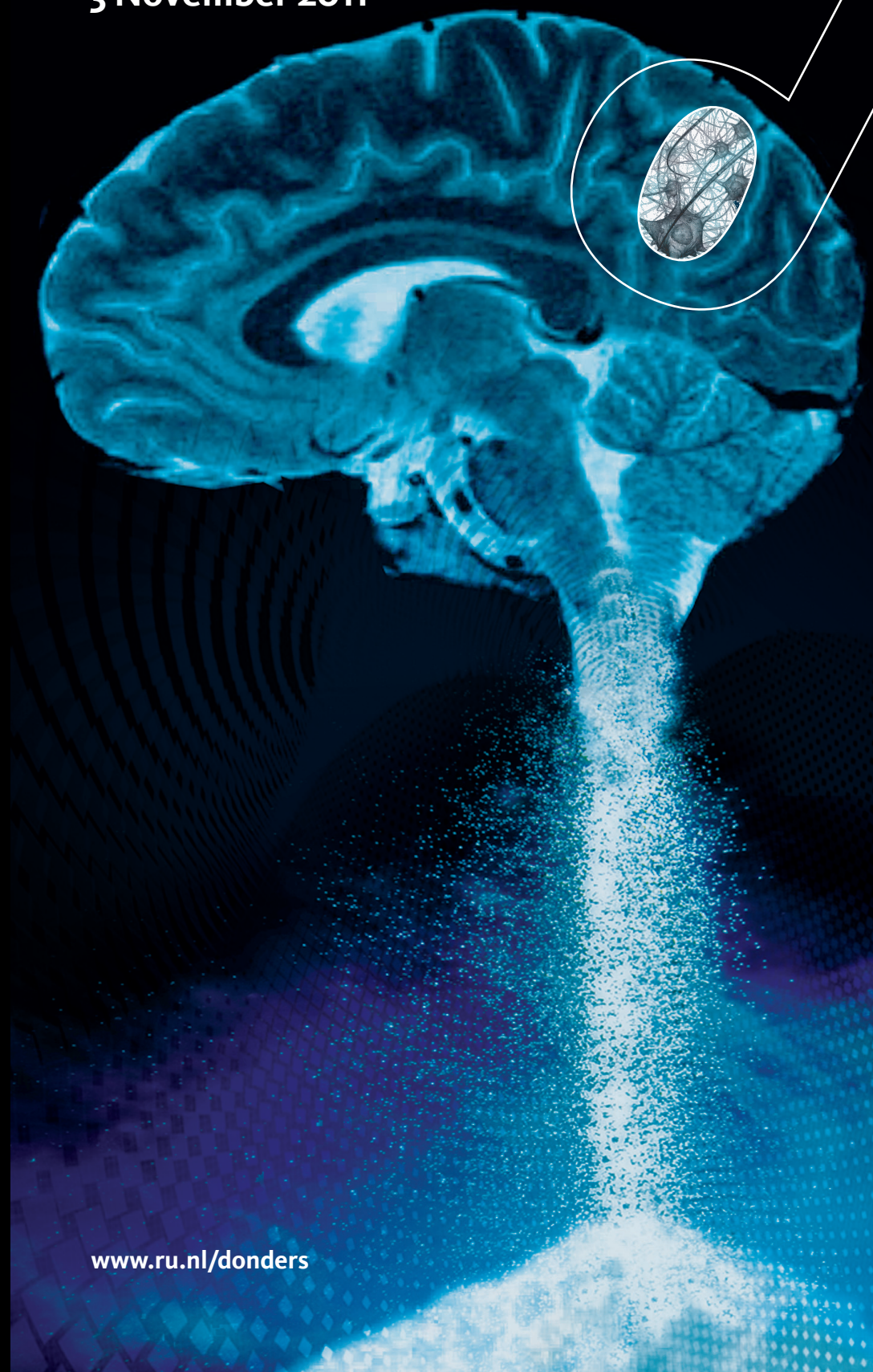
Donders Institute Newsletter

Issue 19
3 November 2011



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 in neuroscience.

An institute such as ours is always on the move. People change positions, acquire grants, new staff are appointed... Key developments include Pieter Medendorp taking over Harold Bekkering's role as director of the Donders Centre for Cognition (next year Harold will chair the Institute's Board of Directors) and Ivan Toni becoming the new speaker for the theme Perception, Action and Control, replacing Pieter. Recently NWO awarded 'Veni's' to Hanneke den Ouden, Monique Flecken and Emily Cross and ERC Starting Grants went to Pieter Medendorp and Mirjam Ernestus. A comparison of these results with the overall picture at the University confirms our position as one of the leading institutes on the campus. However, it's also important to define the values of the Institute for those of us who work in it. This will soon be specified in a 'vision' document, which will explain our commitment to equal opportunity for all, irrespective of age, race, religion or gender. We also promote the careers of minorities, who we feel are currently under-represented. We are determined to maintain an open, fair working environment in which we work for the general good of the institute, while the needs of individuals are also taken in account.

In this issue of the Newsletter the main interviews are with three members of staff: Judith Homberg, Pieter Medendorp and Henny Janssen. I hope you enjoy reading about their insights.

Peter Hagoort

Donders Institute
for Brain, Cognition and Behaviour

www.ru.nl/donders

A subject in the lab on a vestibular sled. The sled can move forward and backward, sideward, and even in a sinusoidal way

How the brain keeps us safely on track

Last July professor Pieter Medendorp received an ERC Starting Grant worth €1.5 million for his research on perception and action. On 1 October he was appointed as the new director of the Donders Centre for Cognition, one of the three research centres at the Donders Institute.

Professor Medendorp likes to run through the woods. While running, he becomes the subject of his own research. Trees pass by his eyes and the path moves under his feet. Despite these constant changes, his brain rapidly integrates the sensory information of the moving forest and the motoric information about the position of his body. His brain directs the running body along the forest path without hitting a single tree, while also avoiding low overhanging branches.

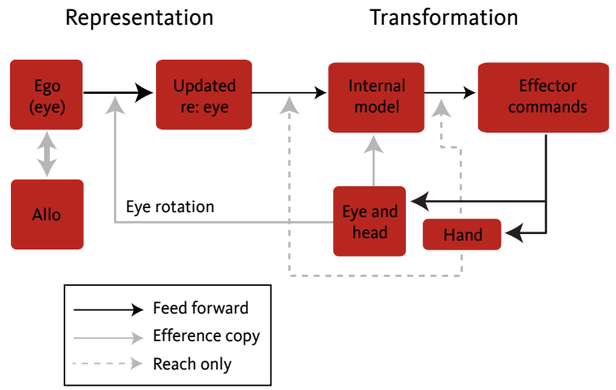
Whether we're running or walking, driving a car or riding a bicycle, our brain tries to make a stable representation of the constantly changing appearance of the outside world. It uses this representation to guide and continuously correct its movement strategies. How does the brain do this? That's the fundamental research question which Medendorp is adressing. 'Although psychologists have studied the relationship between action and perception in a dynamic environment for quite some time, relatively little was known about the neural mechanisms behind this process,' says Medendorp. 'How exactly does the brain integrate what it sees, hears and feels with how it directs the body, how it moves the arms and legs, the head and the rest of the body? We don't even know whether the brain chooses the same solution in a dynamic environment as in a stationary environment.'

Combining three approaches Medendorp, who was originally educated as a physicist, tackles this question by combining three distinct approaches: psychophysical experiments with human subjects, neuro-imaging with EEG, MEG and fMRI, and computational modelling. With computational modelling he tries to understand the integration of sensory and motoric information, not only at the qualitative but also at the quantitative level. 'It's the combination of these approaches that gives our research its strength,' he says.

Although there's a lot that researchers don't yet know, what they do know is that the brain is not just a passive machine which receives sensory input and generates motor output. It is, on the contrary, an active probability machine that constantly makes predictions about its environment and updates these predictions on the basis of new sensory information. It's this so-called Bayesian brain approach that Medendorp uses in his modelling work.

From an experimental point of view, the challenge is to devise a cleverly controlled experiment. In their laboratory Medendorp uses a vestibular sled on which subjects can move forwards and backwards, sideward, and even in a sinusoidal way. On the sled they experience various accelerations. The subjects wear EEG caps so that the researchers can record their brain activity during the experiment. The experiment takes place in a dark environment, which is only enriched with a series of small LED lights.

Medendorp: 'For the best interpretation of the EEG signal it's important to create a strictly controlled environment. We can arrange the LEDs in different patterns, so that we know that what the eyes of the subject see is only the result of the LED pattern. We also know that different EEG frequency bands are used for different brain activities. The next question is whether or not we can see in the EEG signal if the integration of sensory and motoric information leads to modulation of the expected signal.'



Egocentric target representations interact with allocentric representations. These signals are put through an inverse internal model of the eye-head-torso system to guide limb and gaze movements. Efference copies derived from the latter provide position and movement signals for the internal model and updating.

Pieter Medendorp

ERC Starting Grant

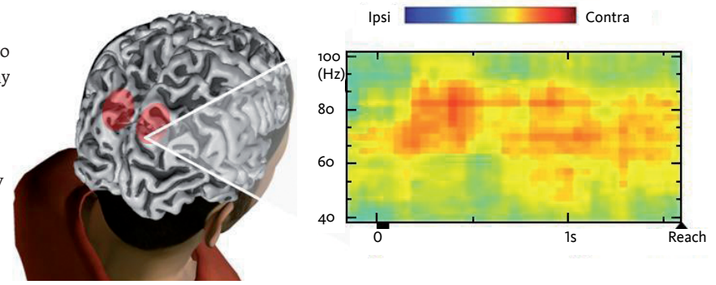
Last July Medendorp has received a €1.5 million grant from the European Research Council (ERC). He will use this money to employ two postdocs and one PhD student, and over the next five years they will together investigate how the brain controls perception and action in a dynamic environment. 'Of course five years will not be enough to solve the puzzle,' he says, 'but we should at least be able to unravel some of the basic principles.'

Medendorp plans to not only use healthy subjects, but also patients who have problems with either their sensory or motoric system. 'The question then is whether these patients adopt different sensorimotor strategies compared to healthy subjects and if they do, what the difference means,' says Medendorp. 'This is a reverse-engineering approach. From a potentially disturbed output signal we will try to work back to what it means for the underlying neural mechanisms.'

He also plans to use transcranial magnetic stimulation (TMS) to either activate or de-activate specific brain regions to determine what effect this has on sensorimotor integration in the brains of healthy subjects. 'Sensorimotor integration is a problem with many variables. TMS gives us another tool, which we can use to individually control as many variables as possible.

Integrating signals

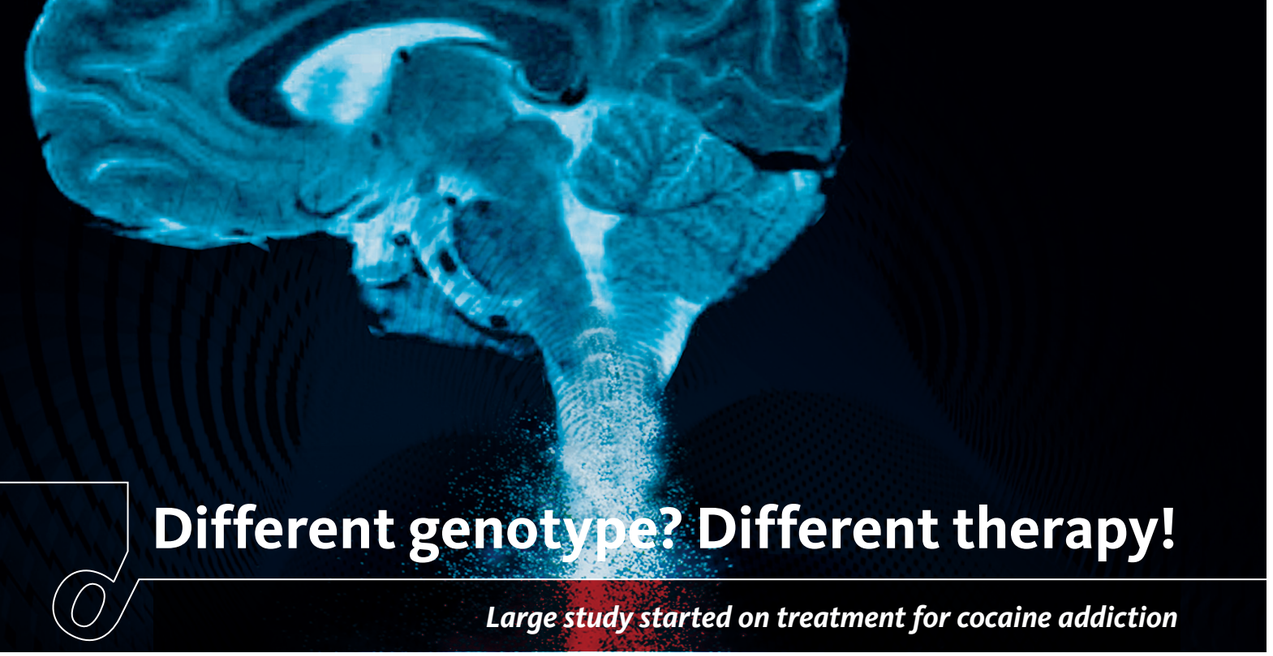
Research by Medendorp and his group has already revealed some new insights. He mentions two important, recently published results: 'We've revealed the role of the rhythmic firing of neurons in the coding of spatial representations in the human brain. A second result comes from the modelling side of our research. We've developed a statistical framework for integrating signals from the vestibular system, the position of the neck and the position of the rest of the body. The latter result, which we've been working on for about three years, will also contribute to our planned ERC research.'



Direction-selective gamma-band synchronization in human posterior parietal cortex during reach planning.

As Pieter Medendorp himself is – like all of us – in a dynamic environment most of the time, how does he get new research ideas? From his own experiences and introspection? 'Yes, sometimes. Maybe as a researcher I'm more aware of how I see what I see. And sometimes, in a flash, I get an idea. But, to be honest, the most and the best ideas arise in interactions, for example during our extremely lively weekly group meetings, where we regularly share very outspoken ideas about future direction of our research. What's more, I don't think there's a single experiment that we've done in our lab in which I haven't participated myself as a subject. It's not that I end up as an official subject in our research, but I always want to feel for myself what it's like to participate in our experiments.' *BM*

Check out: *www.sensorimotorlab.com*



Different genotype? Different therapy!

Large study started on treatment for cocaine addiction

Judith Homberg

There is an urgent need for effective therapy of cocaine addiction, but so far no suitable treatment has been found. With funding from a ZonMw Top grant Judith Homberg will try to fill in the blanks over the next four years. Her approach involves identifying the role of genetic variation in serotonin transport in the brain in relation to addiction.

Behavioural neurobiologist Judith Homberg is Principal Investigator at the Donders Centre for Neuroscience (DCN) where she studies the genetic basis of behaviour. She is steadily building up an impressive scientific track record in neurogenetics. After receiving an NWO Vidi grant last year, this year Judith Homberg was awarded a ZonMw Top grant worth €675,000 (ZonMw is the Netherlands Organisation for Health Research and Development) to study individual differences in cocaine addiction.

Conditioned stimuli

Judith explains: 'The behaviour of cocaine addicts is strongly driven by cocaine-related, conditioned cues. These elicit positive and negative emotional states and craving in cocaine addicts, and are notoriously difficult to extinguish. This may be due to reduced serotonin-mediated prefrontal cortical (PFC) top-down control over the amygdala, caused by a polymorphism in the gene that codes for the serotonin transporter (abbreviated as 5-HTTLPR).' People carrying the short version of the 5-HTTLPR allele (s-allele) make less serotonin transporters compared to those with two copies of the long version. Their prefrontal cortex has less control over the amygdala, which tends to make these individuals more sensitive to emotional stimuli like fear and drugs of abuse, and by the establishment of conditioned responses more vulnerable to anxiety and drug dependence.

The behavioural-cognitive approach that is currently used to tackle drug dependence, is exposure therapy. This involves the extinction of a cue-induced conditioned response. S/s-allele carriers respond poorly to such therapy because once acquired condioned responses are very persistent in these individuals.

Sunny side

The negative effects of the s-allele genotype also have an upside: people with the 5-HTTLPR s-allele show improved cognitive flexibility due to their capacity to acquire new conditioned responses when environmental conditions are shaped to do so.

So while high sensitivity to conditioned cues may make people susceptible to cocaine addiction, it may also provide the key to therapy.

'If our hypothesis holds true, then cocaine addiction therapy must take advantage of the learning traits belonging to this genotype,' Judith says. To test her hypothesis, Judith is setting up a unique cross-species multidisciplinary study in humans and rats.

Different angles on research

'For the human experiments we will test sixty cocaine addicts and thirty matched healthy subjects carrying the 5-HTTLPR s/s- and l/l-genotypes. 'We're working together with the Jellinek clinic in Amsterdam and the Junkiebond - an organisation of drug users - to recruit our subjects. My collaborators at the AMC in Amsterdam have special skills which enable them to handle addicts (e.g. make sure they come to appointments). We could never do that.'

'We will measure the interaction between addiction and fear extinction circuits. For this we will use various techniques: structural and functional magnetic resonance imaging and spectroscopy under basal conditions and during PFC-amygdala-dependent fear extinction. This will reveal whether s/s healthy subjects and cocaine addicts share phenotypes in the PFC-amygdala circuit.'

Furthermore, we will perform experiments with serotonin transporter knockout rats to discover whether changes in the PFC-amygdala pathway – and associated extinction failures – are pre-existing neurodevelopmental traits that pave the way for cocaine addiction. For this purpose, we will expose rats to longitudinal experimental MRI.

Therapeutic promise

In the ZonMw project Judith also studies the effects of a drug called D-cycloserine. It facilitates extinction learning.

'D-cycloserine (DCS) is a partial NMDA receptor agonist that acts in the PFC and amygdala, stimulating new learning. We will test the hypothesis that DCS strengthens extinction memory in s-allele carriers at the expense of their fear/cocaine memory.

Testing this hypothesis has a dual function: it provides further assessment of the theorized association between 5-HTTLPR-mediated changes in the brains and behaviour of cocaine addicts, and it reveals whether exposure therapy supplemented with DCS can be used as individualized therapy in s/s cocaine addicts. 'That would be the first effective medical help in the fight against addiction.' *IR*

The effect of the 5-HTTLPR s-allele in humans and rhesus macaques on positive and negative emotions and (social) cognition

From the review 'Looking on the Bright Side of Serotonin Transporter Gene Variation' (Biological Psychiatry, 2010, Judith Homberg, Klaus-Peter Lesch)

S-allele carriers are often pitied because of their vulnerability to depression and addiction. Judith Homberg opposes this bias.

'In my opinion, one shouldn't classify personality traits as overall negative or positive: it all depends on the needs in a specific context. Why would the gene be so widely spread in the population if it had no benefits? There is evidence that, some 50,000 years ago, the mutation in the gene sparked a cultural revolution and helped the people who were leaving Africa to occupy new territories. The further from Africa you go, the more s-allele you find...'

Increased emotionality
- Psychosocial stressors
- Fear conditioning
- Startle response
- Viewing happy/sad pictures
- Attentional bias for anxious words
- Autonomic reactivity
- Increased HPA axis reactivity
- Increased levels of inflammatory cytokines
- Smoking, drinking, gambling
- Excessive internet use
- Social blushing
- Social aggression
- Creative dancing
- Social support

Improved cognition
- Decision making
- Response inhibition
- Passive avoidance
- Risk aversion
- Motivationally speeded action
- Attentional set-shifting
- Reversal learning
- Delayed matching-to-sample
- Probability discounting task
- Delay discounting

Donders Lecture by Paul Glimcher

Utility, risks and rewards: the economics of our brain

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 next Donders Lecture, which takes place November the 10th, Paul Glimcher from the Center for Neural Science at New York University was invited. We asked John van Opstal, Professor of Biophysic at the Donders Institute: why Paul?

'I've known Paul for a long time; he used to do the same kind of research as I did. Not long after his PhD, he had an article published in Nature in 1992. His eye-movement research on monkeys led to predictions of monkeys' eye movements well in advance by examining the neural activity of single cells in the midbrain.'

'Later he continued to work on that kind of research. That's how he eventually got into Rational Choice Theory and the interdisciplinary field of Neuroeconomics. How can you make an optimal decision, based on uncertain and noisy data? That's also what economics is about. The brain functions according to the same principles that are used in economics by having to continuously make decisions based on uncertain (in this case sensory) information. An important aspect of the theory is: do I receive a reward for my action and, if so, how big a reward? If I get a reward, the chances are I will repeat the action. If not, I won't. It's a continuous process of weighing up the utility, risks and rewards of actions. Sometimes, the balance between these three factors is disrupted, for instance in the case of drug addiction.'

'My own research is based on the same premises as Glimcher's. The difference is that we don't vary the rewards but rather focus on how the brain integrates different kinds of information. For instance, how does the brain combine auditory and visual inputs in order to make the best possible decision – an eye movement, for instance? The outcome of this integration process always turns out to be optimal, so it seems that the brain works a lot better than the economy does. The question remains: why and how?' *SH*

Donders Lecture, 10 November

"Neuroeconomics: The neurobiology of decision"

Paul Glimcher (Center for Neural Science, New York University)

Location: on the campus of Radboud University Nijmegen in the Linnaeus Building, Heyendaalseweg 137, starting at 16:00.on Thursday 10 November.

Meanwhile at www.ru.nl/donders

Pay a regular visit to our website to keep up to date on our news and events.

Ig Nobel Prize for studying yawning tortoises

Donders Institute researcher Natalie Sebanz is one of this year's Ig Nobel Prize winners. It's popularly believed that yawning is contagious, not just in humans but also in other animals. Sebanz and her colleagues did not believe that theory and spent years studying the behaviour of tortoises. They found no evidence of contagious yawning in the red-footed tortoise.

Brains of ISAF soldier recover one year after Uruzgan

They've been back from Afghanistan for a year and the stress of being in a war zone has now dissipated. Immediately after their return, the alarm centre in the brains of the soldiers was hyperactive. According to a second study at the Donders Institute in Nijmegen the brains of the soldiers who took part in the ISAF mission in Uruzgan have recovered (publication in *Molecular Psychiatry*).

Speaking and listening share much of the brain

Which areas of the brain are involved in the linguistic processes underlying speech and listening and are there large differences between them? Neuroscientists from the Donders Institute at Radboud University Nijmegen are the first to have successfully investigated this question using fMRI. They have established that there is a large degree of overlap between the areas involved. This conclusion will surprise many scientists (publication in *Psychological Science*).

Stereo vision helps us distinguish objects from their backgrounds

The main function of stereo vision is to distinguish objects from their backgrounds and not so much to see depth or estimate distance, as is claimed in text books. This is not only true for people, but also for owls, as has been shown in a study involving trained barn owls, wearing small 3D glasses. 'Evolution's had enough time to equip us with a perfect system for seeing depth,' says Rob van der Willigen of the Donders Institute. The fact that we don't have it suggests that the primary advantage of stereo vision is the ability to recognizing objects in relation to the background' (publication in *Journal of Neuroscience*).

Foxp2 helps wiring of neurons in developing brain

Foxp2, a gene involved in speech and language, helps regulate the wiring of neurons in the brain, according to a study led by Sonja C. Vernes and Simon E. Fisher of the Wellcome Trust Centre for Human Genetics in Oxford and the Max Planck Institute in Nijmegen. The study was published on 7 July in the open-access journal *PLoS Genetics*. The researchers identified this functional link by first revealing the role of genetic programmes downstream of Foxp2 in developing brain tissue and then analysing its effect on neurons.

Roshan Cools wins 2011 Radboud Science Award

Roshan Cools was one of three researchers who were awarded a Radboud Science Award on 14 September 2011. This award is presented annually by the university's science cluster (wetenschapsknooppunt) to encourage collaboration with primary schools, in order to stimulate interest in science among pupils. The collaboration will lead to the development of teaching materials for primary schools based on Cools' research on punishment and reward.

Donders researchers receive Stichting Koningsheide Award for psychopathy research

Katinka von Borries and Inti Brazil, PhD students at the UMC St Radboud, Pompestichting and the Donders Institute for Brain, Cognition and Behaviour, received the Stichting Koningsheide Award 2011. The award is given for the best article in the field of forensic psychiatry published between 2009 and 2011. The articles on which this decision was based focus on performance monitoring in criminal psychopaths.

Betto Deelmanprijs awarded to Roy Kessels

The Dutch Foundation for Neuropsychology (Stichting Neuropsychologie Nederland) has awarded the Betto Deelmanprijs to Roy Kessels, who leads a research group on Neuropsychology and Rehabilitation Psychology at the Donders Institute.

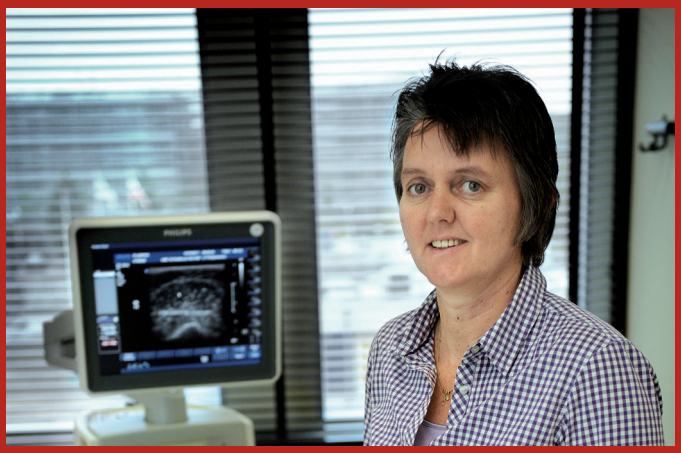
Prestigious ERC grant goes to Mirjam Ernestus

The European Research Council has awarded Mirjam Ernestus with a Starting Grant worth €1.5 million. Mirjam Ernestus received the grant for a research project on how foreign language listeners process the reduced pronunciation variants that are very common in everyday conversations, such as ptiku for English particular, psip for Dutch principe, and plous for French pelouse. Previous research has shown that these pronunciations variants represent a real challenge for adult learners of a language.

Donders Backbone

Henny Janssen: dietician becomes lab technician

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 much needed constant, the backbone of the institute.



Henny Janssen

It was 'sheer coincidence' that Henny Janssen (47) started at the clinical neurophysiology department (KNF) at UMC St Radboud, 25 years ago. It was 1986 and she had just graduated as a dietician, but she soon had second thoughts about motivating people who were often reluctant to follow a strict diet. Having decided to find a different job, she started a three-year professional training as a laboratory technician and became an apprentice at KNF. A choice she has never regretted.

'The clinical research we do here is fascinating, really top notch. I assist physicians and PhD students from the Donders Institute with their clinical tests on patients: mainly muscular echography, high-density EMG (electromyography) and TMS (transcranial magnetic stimulation). People often think I work in a laboratory doing research on blood cells, but that's not the case.'

'At secondary school, my favourite subjects were physics and mathematics, so this technical job suits me just fine. I'm precise, accurate and efficient – essential qualities for a lab technician. I love working with patients, trying to find out what complex syndromes they suffer from. Here, you don't need to motivate people; patients are always grateful for any help you can give them. But it's often daunting, because the patients we examine are usually very ill. It's shocking to see how handicapped people can become in a very short time. The hardest thing is meeting children with dreadful metabolic disorders. Through our research, we hope to contribute to improving their treatment.'

'The problems we have to solve are always very complex. We do a lot of research for patients who suffer from ALS (amyotrophic lateral sclerosis), which is a severe and lethal muscular disease. There are three centres for ALS patients in the Netherlands and Nijmegen is one of them. I like to assist researchers as well. I've been a paranymph three times, all of them for Donders PhD students who I assisted during their research. Together, we aim to produce the best results.'

'When I'm at home, I love being outside, walking and gardening. I'm not a city dweller; I prefer living in the countryside, probably because I was born on a farm. The things I see in my work are often so terrible that I need some relaxation. It brings home the importance of being healthy...'/MT

Diary

10 November 2011, 16:00
Donders Lecture by Paul Glimcher (New York University, Center for Neural Science) - *Linnaeusgebouw, Heyendaalseweg 137, Nijmegen*

12 January 2012, 16:00
Donders Lecture by Jesse Snedeker (Harvard University) –*Linnaeusgebouw, Heyendaalseweg 137, Nijmegen*

20 January 2012, 15:45
Inaugural Lecture Karin Roelofs - *Aula, Comeniuslaan 2, Nijmegen*

27 January 2012, 15:45
Inaugural Lecture Roshan Cools – *Aula, Comeniuslaan 2, Nijmegen*

1 March 2012, 16:00
Donders Lecture by Andreas Meyer-Lindenberg (Central Institute of Mental Health, Mannheim) – *Linnaeusgebouw, Heyendaalseweg 137, Nijmegen*

Donders Institute Newsletter

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Translation/language editing: Michael Gould Associates BV
Photography: Dick van Aalst, Bert Beelen, Erik van 't Hullenaar, Donders Institute, Peter Pearson, Sander Hermsen
Graphic design and layout: Sander Hermsen (www.sander-hermsen.nl)
Printing: JP Offset, Duiven

PhD defences

1 September 2011 – Rebecca Schaefer. Measuring the mind's ear: EEG of music imagery. Promoter: Peter Desain.

30 September 2011 – Miriam Reelick. One step at a time. Disentangling the complexity of preventing falls in frail older persons. Promoters: Marcel Olde Rikkert, Roy Kessels.

18 October 2011 – Arnt Schellekens. Gene-environment interaction and intermediate phenotypes in alcohol dependence. Promoters: Jan Buitelaar, Cor de Jong

25 October 2011 – Andreas Mädebach. Lexical access in speaking: Studies on lexical selection and cascading activation. Promoter: Herbert Schriefers.

1 November 2011 – Geert Poelmans. Genes and protein networks for neurodevelopmental disorders. Promoter: Jan Buitelaar.

2 November 2011 – Pieter Buur. Imaging in motion. Applications of multi-echo fMRI. Promoter: David Norris.

29 November 2011 – Karlijn de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Promoters: Bas Bloem, David Norris

30 November 2011 – Anouk Van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Promoter: Bas Bloem

12 December 2011 – Lu Xu. The non-preganglionic Edinger-Westphal nucleus: an integration center for energy balance and stress adaptation. Promoter: Eric Roubos

19 December 2011 – Eric Jansen. New insights into V-ATPase functioning: the role of its accessory subunit Ac45 and a novel brain-specific Ac45 paralog. Promoter: Gerard Martens