DONDERS INSTITUTE

Newsletter 28

15 June 2016

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Radboud University Radboudumc

A cure for stress?

“The most nerve-wrecking moment in your life as a researcher is probably your doctoral defence. Or perhaps the moment when you present your research plan to the ERC evaluation panel,” Erno Hermans recalls with a smile. “Unfortunately, stressful situations are hard to investigate in the lab in a realistic manner. That is why I will be looking at university students during their exam weeks. That comes pretty close to daily stress.”

Erno Hermans was awarded an ERC Consolidator Grant worth €2 million in January 2016 for his research project on stress in the brain. Daily stress may perhaps sound trivial, but it is anything but. Many tiny stressors can lead to continued stress, which can eventually lead to burnout and depression. Stress-related disorders such as these cost society about the same number of effective working years as diseases like cancer or stroke.

"Basically, what I want to find out is how the brain changes under stress, and if we can influence that process. To achieve that, my research focuses on networks in the brain. I use a systems-level analysis, which means that I attempt to connect the fields of electrophysiology and molecular and cellular neuroscience to clinical psychology."

When he was a psychology student, Erno Hermans became interested in how cognitive and affective behaviour derives from brain activity. "I was one of the very first to be able to investigate such questions with neuroimaging during my training, so I seized the opportunity." And he didn't let go of the subject: Hermans is now considered one of the country's experts in affective neuroscience.

EMOTION VERSUS ATTENTION

He currently investigates the salience network: a combination of brain areas dedicated to a wide range of cognitive and affective tasks such as emotion and attention. One important area is the amygdala, which is associated with emotion. Then there is the executive control network, which is associated with attention and comprises the prefrontal cortex, among other areas. Hormones such as cortisol and neurotransmitters (e.g. noradrenaline and dopamine) control the networks and can completely flip the balance between them: from the concentrated, executive control modus to the emotional salience modus, which is activated under stress. "If we can find out what affects that balance, we might be able to use that information to predict how stress is handled in daily life," Hermans explains. "However, it's very difficult to find out how the system works exactly, because so many factors come in to play. That's why cognitive neuroscientists need to take off their blinkers. You can't add substantial information if you focus solely on your own specialization, your own expertise. You can only add something valuable by looking outside."

"One aspect of conventional 'wisdom' in neuroscience that I want to challenge is the current depersonalized approach that is taken in medicine. Especially in relation to anxiety disorders, post-traumatic stress disorder and depression. We tend to use untargeted drugs such as SSRIs (selective serotonin reuptake inhibitors, red.), for example the antidepressant Prozac. These do not take into account the specific needs of individual patients."

ERNO HERMANS

Starting off his scientific career studying psychology at Utrecht University, Erno Hermans soon became fascinated with the cognitive aspects of behaviour. He specialized in affective neuroscience during a traineeship at the Karolinska Institute in Stockholm, Sweden while preparing his PhD at Utrecht University. After working as a postdoctoral researcher in the group led by Guillén Fernández at the Donders Institute, he spent a year studying emotional memory at NYU in New York. Since 2011, he's been back at the Donders Institute, leading a group specializing in Cognitive and Affective Neuroscience.

SMARTWATCHES AND NEUROFEEDBACK

That's why Hermans and his colleagues will be using smartwatches in their upcoming project. Test subjects will wear these watches 24 hours per day, for a full week. Not once, but twice: during a test week and then during a 'normal' week, to make a fair comparison. The watches measure heart rate and heart rate variability, which are important stress indicators, as well as skin conductance, which is also used in lie detectors. The smartwatch data will be linked to MRI data indicating the balance between activity in the salience network and in the executive control network.

Previous research tells us that some people can switch between the two networks very effectively. Hermans wants to train this ability in his subjects, to help them handle stress better. "It won't be traditional training, however. It will consist of live imaging of the subject's brain activity, and asking the subject to influence that activity in real time, with minimal instructions. Remarkably, previous research has shown that this neurofeedback helps people to control their own brain activity. I want to know if it can also help people to switch more effectively between their salience and executive control networks."

"Ultimately, I want this information to find its way into our models about traumatic stress and corresponding treatments. I expect that the underlying mechanisms are roughly the same for the daily stress that we are investigating and the extreme stress that can lead to trauma. It's the order of magnitude that's different, not the model itself. Figuring this out will be a journey full of surprises and new discoveries. But it wouldn't be fun if it wasn't, right?"

Iris Kruijen

Eyes and Ears

The Radboud University Medical Center Sensory Disorders group is now part of the Donders. The institute welcomes its high-end eye and ear researchers, who will be adding a genetic and molecular angle to the Perception, Action and Control research theme. We went to see some of these new Donders scientists and hear about their plans.

No, the Donders Institute is not trying to become a Molecular Life Science Institute. "Other institutes are better equipped than we are for, let's say, studying the molecular basis of neural degeneration in Alzheimer's disease or neural inflammation in multiple sclerosis," Guillén Fernandez, director of the Donders says. "But we *are* the leading institute in system-level neuroscience that aims to understand cognition and behaviour in health and disease. And for a full understanding of how these phenomena originate from the brain, we need to expand our expertise to include genes, molecular and cellular mechanisms. With the transfer of the Radboudumc Sensory Disorders group to the Donders, we now have geneticists working on all four research themes."
Rob Collin is one of the new PIs at the Donders Institute. He's focusing on inherited retinal dystrophies and is about to clinically test a genetic therapy for Leber congenital amaurosis (LCA), a severe disease leading to blindness in the first years of life. Collin's colleagues at the hospital found out that in 15 percent of all LCA patients, something is wrong in the CEP290 gene, which encodes a transporter protein in the retina. This mistake leads to faulty processing of the RNA and thus impaired functioning of the light sensing cells in the retina. Collin has developed a method that can be used to correct RNA processing and protein synthesis, with the aim of restoring vision. One of the questions Rob Collin wants to tackle with his new Donders colleagues concerns the plasticity of blind people's brains. "How can we predict whether a person who has been blind for a long time can still

‹ *From left to right: Erwin van Wijk, Rob Collin, Hannie Kremer.*

process visual input in the brain? Animal studies have already been set up in cooperation with neurophysics people at Donders such as Paul Tiesinga and Richard van Wezel to find out."

DEAF, BLIND, OR BOTH

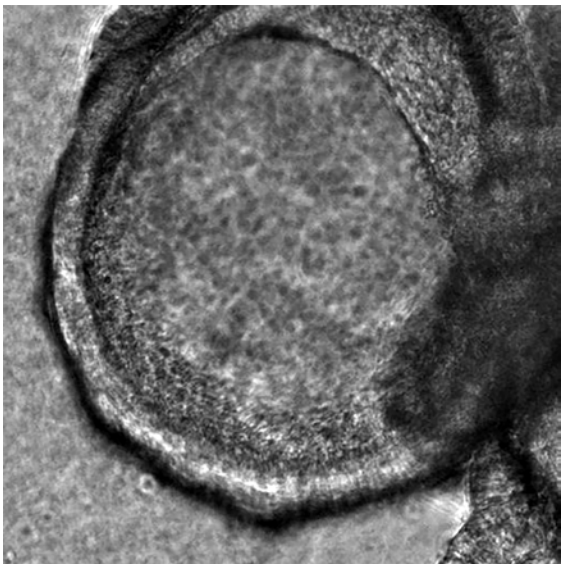
Professor Hannie Kremer specializes in hereditary deafness. As with blindness, defects in more than a hundred genes have been identified, leading to a range of failures in the auditory system. Like Collin, she expects that the sofar undetected defects are not in the coding regions of genes, but in parts of genes that are important for RNA synthesis.

"Hereditary deafness is very heterogeneous, both clinically and genetically," she says. "But we can explain sixty percent of the early onset cases of hereditary deafness now and some genetic profiles can be used to help make informed decisions on choosing the right hearing aid or implant. These are small steps that are adding up to something meaningful. But the 'eye people' are definitely ahead of us in terms of gene therapy."

"Partly that's because there's less urgency in our field," adds her young colleague Erwin van Wijk. "But deaf or hearing impaired people can often be helped by providing them with hearing aids or cochlear implants." He mainly works on Usher syndrome. Usher patients are born with hearing problems and progressively lose their sight from their early teens onwards until they become fully blind. "They often suffer from depression, which is not surprising, given the enormous stress they are under – knowing they will eventually become blind. An interesting question is whether this is a hallmark of the disease or a consequence of it. Initial clues obtained from our research in zebra fish and mouse models have revealed that the Usher genes are expressed in different regions of the brain as well. Perhaps some aspects of neurotransmission are impaired in Usher syndrome patients. I look forward to exploring this aspect with my new colleagues."

BREEDING SENSORY CELLS

The eye and ear researchers are bringing with them an interesting 'marriage gift' to the Donders: the skill to 'breed' sensory cells, even 3D eye-like structures. "First we make pluripotent stem cells from a biopsy of the patient's skin. Then we lure those stem cells into forming the kind of cells and organs we're interested in," Rob Collin explains. "It takes a few months, but then we have little eyecups in a petri dish containing cells that are genetically identical



This little lump of stem cells (sample size 400 µm) is developing into retina tissue. The researchers call them 'eyecups' and use them to test for the effects of genetic disorders in a specific patient or to test therapeutics.

to those of the patient. We can test therapeutics on them, analyse the proteins that need to be expressed, and, perhaps in the near future, we'll be able to measure their response to incoming light."

The ear people have succeeded in growing inner ear cells using the same procedure. "We want to look at RNA synthesis and the malfunctioning proteins in these cells. And, although we don't have a fully functioning organ, we hope that we can use these cells to identify what is going wrong in those hearing impaired individuals in whom current genetic analyses cannot identify a genetic defect," Hannie Kremer explains. "We think it may be possible to grow simple inner ear structures in the near future and that will open up a new realm of research opportunities."

She is curious to find out what the genetic approach will add to sound perception research and *vice versa*. "So far we haven't looked into the genetic aspects of perception impairment. We've focused on the ear as an organ, a machine that either functions well or not. But to hear well much more is needed: the sound has to be processed in the brain. It may even be that some genes for hearing impairment have a link to the language theme. I hope to discuss this with Simon Fisher, who works on language and genetics. Of course I know him and we've met a few times. But joining the Donders Institute will give us the opportunity to meet more easily and I'm sure this will stimulate fertile cross-pollination of ideas."

Iris Roggema

Go to our website to check out the latest news and events

Meanwhile at www.ru.nl/donders

SOME RECENT HEADLINES

- Emotional or stressful memories are preferentially replayed in the brain during rest; **Linda de Voogd** c.s. (NeuroImage).
- Winning nearly is more rewarding for addicts; **Guillaume Sescousse** c.s (Neuropsychopharmacology).
- How are possible changes in the environment that occur during eye movements detected? **Pieter Medendorp** c.s. (PLoS Computational Biology).
- Reading and listening to music at the same time affects how you hear the music; **Richard Kunert** c.s. (Royal Society Open Science)
- Systematic classification of some 750 genes assumed to be associated with cognitive (dys)function; **Annette Schenck** c.s. (American Journal of Human Genetics).
- Rhythmic brain waves engage and synchronize the brain regions that support integration of memories; **Christian Doeller** c.s. (Current Biology)
- Psychopaths exert reduced control over their emotional actions, testosterone plays an important role; **Karin Roelofs** c.s. (e-Neuroscience).
- Only a handful of positive learning experiences suffice to become more empathic to strangers; **Jan Engelmann** c.s. (Proc. Natl. Acad. Sci USA)
- The institute signed two collaboration agreements on research and training, one with the **Brain Mind Institute** of the **Ecole Polytechnique Fédérale de Lausanne** in Switzerland and the other with the **Brain and Mind Institute** of the **Western University in Toronto**, Canada.

PRIZES AND AWARDS

- **Harold Bekkering** was elected as a member of the Royal Netherlands Academy of Arts and Sciences (KNAW).
- **Andre Marquand** received Vidi funding for his research on statistical techniques for neuroimaging data
- **Joris Veltman** was awarded this year's King Faisal International Prize in medicine for the clinical application of next-generation genetics
- **John van Opstal** received an ERC Advanced Grant to investigate how our brains integrate audiovisual, sensory and motor information in eye-head coordination.
- **Nanda Lambregts-Rommelse** has been awarded the Kramer Pollnow Prize, a prestigious German prize for excellent clinical biological research in the field of child and adolescent psychiatry, with a focus on ADHD.
- **Bas Bloem** has received the Holst Memorial Lecture Award for his research and efforts on the innovation of medical care, particularly for Parkinson's disease.
- **Bart van de Warrenburg** and **Annette Schenck** received a Horizon 2020 E-rare grant to unravel the genetic background and molecular mechanisms of cerebellar ataxias.
- EFRO funding was obtained for a Donders project with industrial partners to develop virtual reality tests measuring cognitive development of children and their chances of becoming obese.
- Technologiestichting STW subsidized a project to develop a portable EEG system for home use involving Radboudumc and Eindhoven Technical University (TU/e).

PhD defences

**Donders series number*

- 4 March 2016, DS 211*. **Bouman Z.**, *A measure to remember: Adaptation, standardization and validation of the Dutch version of the Wechsler Memory Scale - Fourth Edition (WMS-IV-NL).*
- 4 March 2016, DS 208. **Van den Elsen, G.A.H.**, *Tetrahydrocannabinol in the treatment of neuropsychiatric symptoms in dementia.*
- 9 March 2016, DS 212. **Spronk, D.B.**, *Individual differences in the acute effects of cannabis and cocaine on cognitive control.*
- 17 March 2016, DS 214. **Ekman, M.**, *Dynamic reconfigurations of human brain networks.*
- 18 March 2016, DS 207. **Vermeij, A.**, *Cognitive plasticity in normal aging and mild cognitive impairment: Shedding light on prefrontal activation.*
- 24 March 2016, DS206. **Sarwary, A.M.E.**, *Mechanisms of interference between motor memories.*
- 26 March 2016, DS 220. **Huang, C.**, *Cortical representation of touch: from whole-cell recordings to network simulations in silico.*
- 7 April 2016, DS 223. **Hazenberg, S.J.**, *Perceptual constructions: Contextual effects on colors, shapes and scenes.*
- 13 April 2016, **Gilst, M.M. van**, *Sleep benefit in Parkinson's disease.*
- 18 April 2016, DS 213. **Müller, M.**, *Footprints of Alzheimer's disease. Exploring proteins and microRNAs as biomarkers for differential diagnosis.*
- 25 April 2016, DS 216. **Bruggink, K.**, *Amyloid-beta and amyloid associated proteins in the pathogenesis and diagnosis of Alzheimer's Disease.*
- 11 May 2016, DS 217. **Beldjoud, H.**, *Role of the amygdala in chromatin remodeling effects underlying long-term memory.*
- 17 May 2016, **Vollebregt, M.A.**, *Neuronal oscillations in children with ADHD. A journey towards the development of potential new treatments for children with ADHD.*
- 24 May 2016, DS 218. **Kostermans, E.**, *Risky decision making: individual differences and dynamic aspects of real-life risk situations.*
- 26 May 2016, DS 229. **Martens, M.**, *Emerging brain circuits in silico and in vitro.*
- 2 June 2016, **Janssen, A.M.**, *Transcranial Magnetic Stimulation. Measuring and Modeling in Health and Disease.*
- 8 June 2016, DS 222. **D'Amore, V.**, *The role of group I metabotropic glutamate receptors in absence epilepsy.*
- 9 June 2016, **Onnink, A.M.H.**, *Understanding adult ADHD. From genes to brain to behavior.*
- 9 June 2016, **Aalbers, T.**, *eHealth in the primary prevention of cognitive decline; The Brain Aging Monitor study.*
- 10 June 2016, **Brinkman, L.**, *A rhythmic view on the neurophysiological mechanisms of movement selection.*
- 10 June 2016, **Mostert, J.C.**, *A network perspective on adult ADHD.*
- 23 June 2016, **Olde Loohuis, N.F.M.**, *MicroRNAs: major regulators in neuronal development, synaptic function and neuropathology.*
- 28 June 2016, DS 230. **Szewczyk, J.**, *The mechanisms of prediction in language comprehension.*
- 29 June 2016, **Fonteyn, E.M.R.**, *Falls, physiotherapy and training in patients with cerebellar degeneration.*

DONDERS LECTURE 2 JUNE 2016

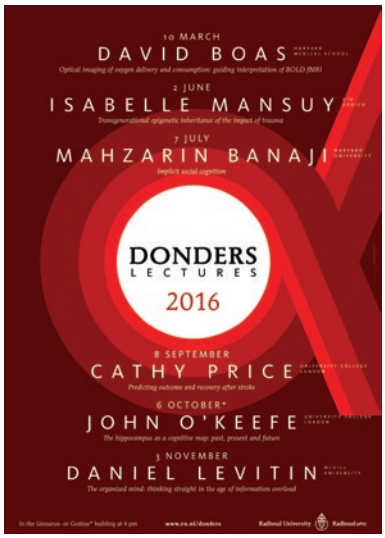
The hippocampus as a cognitive map

In October, the Donders Institute has the honour of welcoming the 2014 Nobel Prize winner in Physiology and Medicine: Professor John O'Keefe of University College London (UCL). He will address past, present and future research on the hippocampus in what promises to be a fascinating Donders Lecture.

John O'Keefe and his host Christian Doeller are no strangers to one another: Dr Doeller worked as a postdoctoral researcher at UCL, in the same department as O'Keefe. "He established a vibrant community of researchers interested in the hippocampus and memory at UCL, which is still active today. I remember being introduced to him during my first week. 'Welcome to the boat', he said to me, which made me very proud to be part of the team."

Originally from New York, John O'Keefe is now Professor of Cognitive Neuroscience at UCL, where he has spent most of his career. Furthermore, he is the co-founder and director of the Sainsbury Wellcome Centre at UCL, a new interdisciplinary research institute specializing in neural circuits and behaviour.

O'Keefe was awarded the 2014 Nobel Prize – together with May-Britt Moser and Edvard Moser – for their seminal discoveries of place and grid cells that constitute a navigational system in the brain.



John O'Keefe - *The hippocampus as a cognitive map: past, present and future*

This Donders Lecture takes place at the Grotius building on the Radboud University campus, Montessorilaan 10, Nijmegen, at 4.00 p.m. The last speaker of the 2016 series will be Daniel Levitin on November 3. He will discuss the organized mind, and how to think straight in the age of information overload.

O'Keefe was the first to observe place cells in the hippocampus which signal an animal's position in the environment. Doeller: "We are running several joint research projects with scientists in O'Keefe's department at UCL. In the future, we aim to explain how the place and grid cells interact with each other to give rise to higher-level cognition. Basically we are trying to understand the memory code of the hippocampus. Physiologists like John O'Keefe can help us crack that code."

"John is driven by curiosity, which was always the force behind his science," Doeller continues. "'Data is the route to knowledge', he used to say during team meetings. What I think is very special about him, is that he has always been looking at the big picture. His work has greatly influenced cognitive neuroscience, but also psychology. I think that should be an inspiration to all of us, to always keep an open mind. Don't restrict yourself by only looking at developments in your own field."

Iris Kruijen

Diary

- 1-5 and 8-12 August 2016, **Radboud Summer School** on brain and behaviour www.ru.nl/radboudsummerschool/
- 22-26 August 2016, **5-day toolkit course** '*Essentials of major neuroimaging techniques (EEG, MEG, fMRI, PET, TMS)*'. www.ru.nl/donders or tildie.stijns@donders.ru.nl.
- 15 September, 20 October and 17 November 2016, **Donders sessions**, designed to be of broad appeal across the themes of the DI. Trigon building, 10.30-14.30.
- 24 September 2016, **Open Day Donders Institute**. Trigon building.
- 3 November 2016, **Radboud Research Round+** "*RNA therapies for neuromuscular disease*". **Matthew Wood**, University of Oxford, Radboudumc, Tuinzaal, 16.00-17.30.
- November 2016, **Open day Research Masters in Cognitive Neuroscience**, 13:00- 17:00 pm. e.janssen@donders.ru.nl
- 1 December 2016, **Radboud Research Round+** "*Tau: Role in pathogenesis, diagnosis and treatment in neurodegeneration.*" **David Holtzman**, Washington University School of Medicine in St. Louis, Radboudumc, Tuinzaal, 16.00-17.30.
- 15 December 2016, **Donders Poster Sessions**, Radboudumc, Tuinzaal, 10.00.

Anyone who is interested is welcome.

THE MACHINE

Taking a stroll under the scanner

'If you watch people exploring Donderstown, their navigation behaviour sometimes gives you the impression that you can see them thinking.' Jacob Bellmund is a PhD candidate in the Memory and Space group led by Dr Christian Doeller at the Donders Institute. He has built a virtual city called Donderstown. The 'city' has a 'banking' district with tall buildings, an area with small houses, a market place and even a playground. Jacob: 'The great advantage of Donderstown is that it's so realistic'.

Jacob gives participants the task of searching for buildings in this virtual world, while they are in an fMRI scanner. He investigates how we form a map of our environment in our brain and how our sense of direction works. When you try to find your way through a neighbourhood, the brain forms a spatial map that represents that environment. Place and grid cells in the hippocampal formation form the basis for this internal navigation system, a discovery that was awarded with the Nobel Prize in 2014.

The mechanisms that Jacob observes in the fMRI scans when participants imagine directions are similar to the ones that guide us when we navigate. 'When we imagine directions, it's as if we were in a place in a quite literal sense.'

Virtual worlds used for navigation research are often small-scale or simplified, so the 'European-like' complexity of Donderstown's layout is unique, according to Jacob.

This is why Donderstown is currently being used for several experiments. 'It provides an opportunity to go beyond typical lab studies. We also plan to carry out a study in which people walk around freely so that we can get insight into natural navigation behaviour.' In the future, Jacob hopes to add virtual people walking around, in order to investigate how we memorise events in a setting close to our everyday experience. If you want to explore Donderstown yourself, go to: www.doellerlab.com/donderstown/

Harriëtte Koop

DONDERS INSTITUTE Newsletter

The Donders Newsletter is published twice a year by the Donders Institute for Brain, Cognition and Behaviour, which brings together research groups at Radboud University and the Radboudumc 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 neuroscience.

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Printing: DPN druk en print Nederland

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