Delving ever deeper into our most individual organ

Fight, flight or freeze

Network dynamics for attentional selection in the primate brain

www.ru.nl/donders
Delving ever deeper into our most individual organ

Last year the research done by the Donders Institute for Brain Cognition and Behaviour was assessed by a critical panel of internationally renowned neuroscientists. Their verdict? "Very good" to "excellent". Time to sit down and relax? Not at all. Guillén Fernández, who has chaired the Donders Board since January this year, shares his opinion on the next decade of neuroscience in Nijmegen.

Very little about the brain is understood. Should we say "only very little" or "we already know quite a bit"? Given the massive complexity of the brain and the huge differences in brain architecture among individuals, plus the relatively short time that has been spent on studying the brain system "we already know quite a bit" is probably the fairest judgment. 'The Cognitive Neuroscience Society was founded twenty years ago; that's a really short time in science,' says Guillén Fernández. 'And we have already made a lot of progress in understanding how the brain works. But the tax payer is getting impatient. A real application of cognitive neuroscience has yet to come to market; that's true.'

Prof. Fernández was trained as a medical doctor and a neurologist, before switching to full-time research. Now he's happy to take on the managerial tasks of chairing the Donders Institute at Radboud University Nijmegen and the UMC, where he came to work twelve years ago. Quite a job to combine with his research work. He tries to save time in a variety of creative ways: 'I had this standing table installed in my office in the hope that people would come to the point quicker in meetings. It does what it's meant to do.'

Personalised psychiatry and education
'I'm reluctant to give an estimate on the time needed before applications come on the market. But I'm sure that, for example, psychiatry and teaching will in due course benefit considerably. A highly individual approach to illness is certainly conceivable. A general diagnosis such as depression will be replaced by an understanding of the individual pathophysiology of such an ailment, as well as its cure. The same goes for learning; in future we may be able to tell students: “this is your personal curriculum based on the network properties of your brain.” The Donders is well positioned to make important contributions to such applications.' So far, most knowledge about the brain has been obtained from group studies, averaging out individual differences. This needs to be complemented by studies of individual differences, Prof. Fernández believes, in order to make personalised treatment and brain-steered devices possible.

Bigger projects
The most exciting projects right now involve large collections of brain and genetic data and they require interdisciplinary teams to tackle the challenging research questions that emerge. 'The Donders Institute encourages participation in large-scale studies, such as the Human Brain Project – a European Flagship consortium – and the Gravitation Grant for Language in Interaction, which we won in 2012. However, I think we can team up both within and beyond the institute more often. That might mean moving away from our PI group structure and it isn’t really compatible with the personal stardom that some people seek in science. But if we really want to push the limits of our knowledge, we need to put our heads together...'

Increase replicability
'It’s not only the public that has become more critical about how science is being done; so have we. Replicability must increase. We apply stricter statistical approaches than routinely requested. All of our PhDs are trained in rigorous statistics and we do power calculations prior to starting a study, thus proving that our experimental design matches the research questions. On the other hand – to push science further one needs to be brave sometimes and push beyond the limits. Corroborating studies will confirm whether a result is valid. For example, I published an fMRI study myself back in 1996 with data from only six subjects and an experimental design that we wouldn’t agree on nowadays. In that study we discovered the so-called subsequent memory effect: brain activity predicting whether something is remembered later on. Despite the shortcomings of the design, it turned out to be one of the most robust findings in memory research. The subsequent memory effect is so strong it sticks out a mile. So yes, we need to work hard; be reliable; keep on explaining to the public how complicated brain research is – and we need to listen to the public when they tell us what they expect from neuroscience. And now and then we need do something daring – unusual projects that change our perspective.'

Iris Roggema
In 2013, an external assessment committee of internationally recognized experts chaired by Professor Michael Gazzaniga – an eminent researcher and the founding president of the Cognitive Neuroscience Society – visited the Donders Institute. The committee rated the performance of the Institute over the past six years as excellent. The committee confirmed the Donders Institute’s international reputation by stating that it has had an important and substantial impact in the international field and that the Principal Investigators were recognized as top researchers in their field. The committee was impressed by what has been achieved in six years and observed an extraordinary spirit of cooperation: The Institute is a very stimulating environment for top researchers as well as for young talent. The four Donders themes were also assessed. Both the quality and the productivity were in each case rated as very good to excellent or excellent.
Fight or flight are the two basic reactions that people mention when they think about human stress responses. However, some years ago, stress experts started realizing that humans can also show freezing when experiencing acute stress – like a deer in the headlights. So they changed the name of the fight or flight response to the fight, flight or freeze response. The mechanisms of these basic reactions are very well known in animals but with us humans, researchers are still operating in the dark.

In some psychopathologies, the temporal regulation of fight, flight and freeze reactions (from now on referred to as FFF reactions) is disturbed. ‘We know that people with aggressive tendencies have a short freeze reaction and that they fairly quickly move on to the fight reaction’, Prof. Roelofs explains. ‘In contrast, anxious people have an elongated freeze reaction compared to normal. I want to find out how – and based on what information – people shift from the parasympathetic freeze reaction to the sympathetic fight or flight reaction.’

Freezing is a critical risk assessment stage that is characterized by bodily immobility and a lower heart rate - also called fear bradycardia. You are acutely aware of environmental cues that help you to decide whether to fight or flee. Important cues are for instance the distance between you and the predator, possibilities for escape, and your chances of winning a fight. In animals the decision to fight or flee after freezing is controlled by several subcortical structures, including the periaqueductal gray, the amygdala and the striatum. Together with members of her group, Karin Roelofs investigates the neural correlates of this decision in humans using fMRI. She also studies the temporal aspects of human freezing and the transition to fight or flight by putting test subjects on a balance platform, while wearing an EEG cap and anticipating (mild) electrodermal shocks or viewing aversive pictures. Shock anticipations and aversive cues induce freeze reactions such as reductions in body sway and heart rate. ‘When encountering a threat, we are optimally tuned to detecting danger.

We know that in animals, the freeze period can last up to thirty minutes or even longer. This might also be the case in humans. We are the first group to examine this in detail worldwide.’

From childhood to adolescence
Prof. Roelofs also investigates how FFF reactions develop during childhood and whether they might have predictive value in future psychopathology. She collaborates with members of the Nijmegen Longitudinal Study, who investigate the development and functioning of a large group of children from Nijmegen over a period of several decades. When these children were only fifteen months old, they were videotaped while sitting in a room and, all of a sudden, a toy robot walked in. A very stressful event for a small child! Karin Roelofs: ‘We inspected these videos and, already at this young age, you could see how some of the babies froze up for several seconds when they saw the robot coming their way. When these kids were fourteen, we scanned them in our fMRI and put them on the balance platform to measure their FFF reactions.’ That way, she aims to find out whether a baby’s freeze reaction at fifteen months old has predictive value for potential future problems with FFF reactions.
Prof. Roelofs also wants to find interventions for people whose reactions are disturbed. So far she has worked with Transcranial Magnetic Stimulation (TMS) and hormone administration to test whether she can alter automatic FFF tendencies directly. ‘For example, we applied a specific TMS protocol (cTBS) over the anterior prefrontal cortex to reduce activation in that brain area. Then subjects performed an approach avoidance task, requiring pulling and pushing of emotional faces using a joystick. Using this protocol, we discovered increased activity in the amygdala and problems with controlling tendencies to engage in automatic action. Now we are testing protocols in which we try the opposite: to enhance frontal control over automatic action tendencies. If this works, we will extend our research to samples of patients who have difficulty controlling their automatic FFF reactions, such as those with a social anxiety disorder.’

**Testosterone**

‘We also investigate the effects of administering testosterone to patients with social anxiety disorder, who are also known to have reduced testosterone levels. Previous studies showed that when people receive a shot of testosterone, they are more prone to pull angry faces towards them then before. Now we want to set up a study with patients with a social anxiety disorder to see if testosterone treatment can give a boost to their regular therapy. By administering testosterone you enforce the tendency to take action.’ Until now, scientists have only demonstrated this process while people were watching static images. In Prof. Roelofs’ experiments, test subjects really have to take action. They view a movie of a threatening person who gets something out of his pocket. This could either be a phone or a gun, as described in the lead of this article. The test subject then has to decide if he or she is going to shoot that person or not.

‘I see our interventions as an addition to existing therapies though. They can never fully replace them. A combination of our interventions and existing therapies might make treatment of some psychopathologies a lot more effective.’

*Iris Kruijen*

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### Stress group

Approximately every two weeks, all of the Donders researchers who are working on stress come together. People like Guillén Fernandez and Benno Roozendaal, who study the effects of stress on memory, Judith Homberg, who works at the animal laboratory and Erno Hermans, who studies how our brain enables us to survive and learn to avoid situations that threaten our physical or psychological well-being. ‘We’re combining results from our various fields of expertise and looking for cross-fertilization,’ Karin explains. ‘For instance, Judith and I are now both investigating heart-rate deceleration during threat anticipation in rats and humans, respectively. Our stress group, as we like to call it, is a nice example of the system level approach taken at the Donders Institute.’
Donders lecture 9 October 2014
Network dynamics for attentional selection in the primate brain
Professor Sabine Kastner

The Donders Lecture Series creates a forum at which important international relations of the Donders Institute can speak in Nijmegen. Sabine Kastner, who is originally from Germany, will visit this autumn to elucidate her work on spatial attention in the human and rhesus macaque brain.

‘Our research is complementary – she collects data from the primate brain which we cannot obtain ourselves, and we have the MEG expertise she needs.’ Ole Jensen, Professor of Neuronal Oscillations at the Institute, talks warmly about the cooperation that arose from their mutual research interest: how do brain waves emerge from firing neurons and what is their role in neuronal processing? ‘We started corresponding about one of her papers a few years ago. Later we met at conferences. And just last week I visited her in Princeton, where she has a chair in psychology.’

Professor Kastner made her name in animal physiology, then switched to human brain imaging and now works with animal models again, trying to figure out how the brain deals with both distraction and attention. ‘At the Donders Institute, we try to do the same thing in human network studies,’ Jensen says. ‘We aim to get an integrated understanding all the way through from neurons to networks. I expect that Prof. Kastner’s lecture will be an excellent opportunity to get a serious, thorough overview of both human and monkey research on spatial attention that will inspire new ideas.’

The two scientists team up to prove how oscillations generate network properties in the brain. ‘Right now we’re working on a new framework that will explain how the phase of the oscillation helps to encode visual information. We really need Sabine to help us test and develop that theory. By boosting or impairing brain waves we can observe their effect on performance and learn more about how oscillations relate to brain function.’

Donders lecture 9 October 2014
Professor Sabine Kastner
Network dynamics for attentional selection in the primate brain

The Donders Lectures take place on the University campus at the Linnaeus Building, Heyendaalseweg 137, Nijmegen and they start at 4.00 p.m.

More about the 2014 series at www.ru.nl/donders

Iris Roggema

Key Facts and Figures:

The Donders Institute includes researchers with 35 nationalities
TOP publication
Review on ischaemic stroke
Frank-Erik de Leeuw and colleagues published a paper in Nature Reviews Neurology. The review, which provides a critical overview of the risk factors and aetiology of ischaemic stroke in young adults, addresses its longterm prognosis, including cardiovascular risk, functional outcome and psychosocial consequences.

TOP publication
Altering emotional memories
Marijn Kroes published a study in the journal Nature Neuroscience on how emotional memories in humans can be disrupted shortly after they are recalled using electroconvulsive therapy (ECT). These findings suggest that ECT could be used to specifically induce amnesia for aversive or depressive memories. After a feature in Nature News, the results gained worldwide media attention, for instance from the Wall Street Journal and TIME Magazine.

TOP publication
Lefties for research
Left-handed people really do have different brains and genes from right-handed people. Yet left-handed people are almost never included as study subjects in scientific research. Therefore in an article in Nature Reviews Neuroscience, Roel Willems and his colleagues from the Donders Institute and Max Planck Institute in Nijmegen call for more research into left-handed people.

€12.4 million investment
Four Donders proposals for research facilities have received grants as part of a local investment scheme. The province of Gelderland, Radboud university medical center and Radboud University are spending €12.4 million on 14 projects. Regional companies are also entitled to use the new advanced medical and natural science research facilities. The Donders investments include an integrated NIRS-EEG measuring system, a motion tracking device, a set of operant touch screen cages for rodents and an upgrade for one of the 3T MRI scanners.

Radboud Excellence Initiative
Four postdoctoral researchers will join the Donders Institute as part of the Radboud Excellence Initiative, a programme through which Radboud University and Radboud university medical center invest in international partnerships between top scholars. The postdocs will stay for one or two years. See http://www.ru.nl/excellence/ for more information.

Google Research Award
Martin Dresler received a US $50,000 Research Award from Google for his project, which is entitled ‘A Memory Palace Made of Glass’. Dresler and PhD student Boris Konrad will develop and test software applications for Google Glass that will allow users to apply mnemonic strategies in everyday life. Mnemonic strategies are an effective way to learn new information.

Member of the KHMW
Peter Hagoort and Paula Fikkert have been elected to the Koninklijke Hollandsche Maatschappij der Wetenschappen (the Royal Holland Society of Sciences and Humanities). The goals of this – the oldest – learned society in the Netherlands (founded in 1752) are to advance science and to build bridges between science and society. Membership is by invitation only.

PhD thesis prize
Marloes Henckens won the 2014 Dutch Neurofederation PhD thesis prize for her thesis ‘Imaging the stressed brain’. The jury acknowledges the high quality of the studies performed by Henckens. The resulting thesis is of the highest scientific quality, and illustrates her talent for science.

Graduate School highlights in 2013
The Masters programme celebrated its 10th birthday with a one-day symposium featuring international speakers; PhD students successfully organized the 6th edition of the ‘Donders Discussions’; an international neuroscience conference for PhD students. Over 200 participants from 14 countries attended this two-day event, making it the most international so far; and the 100th PhD thesis published in the Donders Series was celebrated with an international alumni event.
OUT OF OFFICE

‘Thanks for your message. I regret that I’m unable to answer your e-mail – I’m out racing on my bike.’

The Donders Institute may be a highly ambitious international research centre, but what do staff get up to after office hours? More research, of course – clearly, it doesn’t all get done from nine to five – but lots of other things, too. This produces some fascinating out-of-office replies...

‘For me, cycling is almost a kind of meditation. The combination of the cadence of my leg movements with the whooshing sound of the bicycle allows me to completely clear my head.’ When Egbert Hartstra, who works as a postdoc on perception, action and control, talks about cycling, his eyes light up. Egbert goes cycling every Sunday with his Donders colleagues.

The bike racing group was formed about two years ago, when Egbert started working at the Donders Institute. He and his new colleagues discovered their mutual hobby at the coffee machine. Since then, they have been exploring the surroundings of Nijmegen on their racing bikes every Sunday, in round trips of about fifty kilometers. ‘We don’t really talk about work during the ride. Actually, we hardly talk at all when cycling,’ he laughs. ‘But afterwards, we always end up in a bar or on a terrace for coffee or a beer. Then we talk about all kinds of stuff, for instance possible experiments that could answer some remaining research questions.’

This summer the group plans to go cycling during the week as well, after work. ‘Just for fun; we don’t train to compete in a specific race. But we do want to climb the Alpe d’Huez this summer, so some extra training would be a good idea.’ Is there a competitive atmosphere within the group? ‘Not really; we actually try to help each other out by shifting places in our little peloton and keeping each other out of the wind. But of course it is always nice to arrive at the top of the hill first.’

The cycling team keeps growing. ‘It might be time to find ourselves a sponsor and arrange some official Donders cycling outfits,’ Egbert says with a smile. That would fit in quite well with the rest of their semi-pro gear. ‘Both Harold and René (Bekker and Scheeringa, respectively, red.) recently bought a new bike. That’s when I felt like doing the same. So for the past few weeks, I’ve been the proud owner of a new bike as well. The old one is still getting good use: another colleague who recently joined our Sunday ride is using it now.’

Iris Kruijen

Diary
2-4 June 2014, Toolkit of Cognitive Neuroscience: advanced course in functional neuroimaging data analysis
24-27 June 2014, Tool-kit of Cognitive Neuroscience: Transcranial Brain Stimulation
4 July 2014 15:45 to 17:00, Inaugural lecture Ivan Toni
7-11 July 2014, Tool-kit of Cognitive Neuroscience: essentials of major neuroimaging techniques (EEG, MEG, fMRI, PET, TMS)
11-16 August 2014, Donders Summer School: Stress and Cognition
http://www.ru.nl/donders/agenda-news/summer-school-stress/, Brain and Behaviour http://www.ru.nl/ruadobodayschool/courses/brain-behaviour/ 9 October 2014 16:00-17:00, Donders lecture Prof. Dr. Sabine Kastner (Professor of Psychology, Princeton University): Network dynamics for attentional selection in the primate brain

PhD defences
24 February, Radke, S. Acting social: Neuroendocrine and clinical modulations of approach and decision behavior. (Donders series 147)
3 March, Piai, V. Choosing our words: Lexical competition and the involvement of attention in spoken word production. (Donders series 144)
19 March. Brandmeyer, A.A. Auditory perceptual learning via decoded EEG neurofeedback: a novel paradigm. (Donders series 146)
21 March. Wester, A. Assessment of everyday memory in patients with alcohol-related cognitive disorders using the Rivermead Behavioural Memory Test. (Donders series 152)
27 March. Koenraad, K. Shifting light on cortical control of movement. (Donders series 153)
2 April. Meyer, M. (Donders series 151)
14 April. Rutten-Jacobs, L. Long-term prognosis after stroke in young adults. (Donders series 154)
25 April. Geldorp, B. van. The long and the short of memory: Neuropsychological studies on the interaction of working memory and long-term memory formation. (Donders series 150)
8 May. Boyacioglu, R. On the application of ultra-fast fMRI and high resolution multiband fMRI at high static field strengths. (Donders series 158)
12 May. Simanova, I. In search of conceptual representations in the brain: towards mind-reading. (Donders series 148)
19 May. Kleinnijenhuis, M. Imaging fibres in the brain. (Donders series 159)
21 May. Smulders, K. Cognitive control of gait and balance in patients with chronic stroke and Parkinson’s disease. (Donders series 157)
22 May. Kok, P. On the role of expectation in visual reception: A top-down view of early visual cortex. (Donders series 149)
19 June. Llera Arenas, A. Adapting brain computer interfaces for non-stationary changes. (Donders series 156)
30 June. Platonov, A. Mechanisms of binocular motion rivalry. (Donders series 161)
3 July. Massoudi R. Interaction of task-related and acoustic signals in single neurons of monkey auditory cortex. (Donders series 165)
8 July. Herbert, M. Facing uncertain diagnosis: the use of CSF biomarkers for the differential diagnosis of neurodegenerative diseases. (Donders series 155)
10 July. Schaaf, van der M. Dopaminergic modulation of reward and punishment learning. (Donders series 162)
27 July. Aerts, M. Improving diagnostic accuracy in parkinsonism. (Donders series 163)

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