

# DONDERS

## INSTITUTE

### Newsletter 37

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ULTRASONIC NEUROMODULATION IS THE WAY AHEAD

# Mental health in the time of corona

NEW DEPRESSION RESEARCH AT THE DONDERS INSTITUTE

Since the outbreak of the corona virus, many of us have been staying at home in order to limit our social interactions. We do this to keep ourselves and others safe from the spread of Covid-19. Yet, there's also concern about what social distancing and anxiety generated by media reports are doing to people's mental health. Two researchers at the Donders Department of Psychiatry talk about the current situation and the grants they have received for their research on depression.



*"We have the duty to check with our patients how they are dealing with the constant bombardment of information."*

INDIRA TENDOLKAR

"Radboudumc's Department of Psychiatry has set up a National Register for Covid-19 in Psychiatry, together with the University of Utrecht and the Dutch Society for Psychiatry" explains neuroscientist Indira Tendolkar. Her research focuses on stress-related adaptation and maladaptation of the so-called declarative memory system and she is on the steering committee of this national initiative.

## STUDYING THE EFFECTS OF THE VIRUS

"Its aim is twofold. On the one hand, we're gathering information on the impact that Covid-19 has on patients already suffering from severe psychiatric diseases, of which major depression is one of the most common.

"On the other hand, we're looking into what we call 'de novo neuropsychiatric effects' of the virus itself, because we know that it affects the brain. So, it's not only that the socio-economic consequences have an

enormous impact, but it's also that we need to learn what the virus itself does to the brain. It's also important for us to look at the role the media plays in the crisis. All the media attention makes dispiriting news difficult to ignore for those who are naturally inclined to focus on the negative. It adds to their tendency to catastrophise. Depression and anxiety tend to go together. We, as professionals, have the duty to check with our patients how they are dealing with the constant bombardment of information."

## THE STIGMA OF ECT

Tendolkar also participates in collaborative research of the Donders Institute and Amsterdam UMC, with which she recently has received a €600,000 ZonMw grant. The grant is for research on electroconvulsive therapy (ECT) – a treatment for people suffering from chronic depression. ECT is also known as 'shock therapy' – a term that evokes negative connotations. "And not just among

patients and their families, but also among many caregivers," Indira explains. "The grant was awarded to discover why there's resistance to the treatment so that we can alleviate the fear and better inform people of its effectiveness. People still associate ECT with a painful form of treatment that does lasting damage to the brain and is usually given without consent. This idea is outdated. Under general anaesthesia, small electric currents in the brain change brain chemistry and induce plasticity as a way to tackle symptoms. The currents can be delivered with increasing precision. Often, a patient receives this treatment twice a week until remission of symptoms or a plateau is reached. After that, patients are put back on other forms of therapy."

## IF-ALL-ELSE-FAILS TREATMENT

"In the Netherlands, the treatment is only permitted if strict guidelines are followed. Patients get ECT when medication and at least one validated form of psychotherapy have failed. Our research, however, shows that,



*"Antidepressants can be valuable for curing people with depression."*

ERIC RUHÉ

especially for the elderly, it might be more effective if it were given sooner. In other words, we think that ECT should be an option earlier in a treatment programme. There is an extra benefit here – the fact that it's no longer being used as an if-all-else-fails treatment will help reduce fear of ECT.

"We want to develop a constantly updated decision tool that can help, for example, both GPs and children of elderly patients to decide what the best options are. My goal, in the long run, is to replace ECT with minimally invasive and targeted treatment options. But if my mother were to develop severe depression tomorrow, not eating and maybe having nihilistic delusions, and we know that this can quickly lead to very severe complications, I would ask for an ECT consultation. You could say I'm biased, but I believe that in severe cases ECT can be effective. It's now given too late and in only 1.2 per cent of patients who could potentially be helped."

## REDUCING ANTIDEPRESSANTS

Indira's colleague and psychiatrist Eric Ruhé also recently received a large ZonMw grant. His TAPER-AD study aims to answer the question how best to taper antidepressants to mitigate 'discontinuation' symptoms. "Antidepressants can be valuable for curing people with depression," Eric explains. "However, we estimate that some 30 to perhaps 60 per cent of patients have difficulty getting off the medication after recovery."

Eric and his fellow researchers at the Donders Institute and Amsterdam UMC will gradually reduce the dose of antidepressants before total discontinuation. "The discontinuation symptoms that some people have are likely related to the speed of how fast their serotonin transporter (SERT) occupancy – which is the primary target of antidepressants – is reduced. Conventional doses of drugs deliver very high levels of SERT occupancy in a curvilinear way. If you reduce the dose linearly, the lower you get, the faster the decrease of SERT occupancy.

This is why the last step in conventional reduction – from 10 milligrams to 0 mg of paroxetine – has such a large impact. What happens if we taper off the drug based on a linear decrease of SERT occupancy, based on calculations of the dose-occupancy relationship? Importantly, with the double-blind randomised design of TAPER-AD, we'll control for both placebo and nocebo effects, which is unprecedented."

He also investigates whether reducing antidepressants more smoothly will help regulate the recurrence of depressive episodes. This is connected to his other research, SMARD\*, in which he studies both the neurobiological basis of recurrent depression in the brain and smartphone interventions to reduce the risk of recurrence. "We should not underestimate the burden of recurring depression and the fear of patients for a new episode."

Vanessa Deij

\* <https://www.radboudumc.nl/trials/smard-studie>

# Get off the island,

FOUR NEWLY APPOINTED PROFESSORS EXPLAIN THE NEED FOR COOPERATION IN DEVELOPMENTAL NEUROSCIENCE

In the past, developmental neuroscience was not a field in which people from different disciplines cooperated very much. However, in recent years, the approach has been gradually changing. Four newly appointed professors at the Donders Institute – Annette Schenck, Tjitske Kleefstra, Nanda Rommelse, and Rogier Kievit – understand the importance of teaming up. Although they work in different fields of research, they are committed to working together.

In an hour-long conversation, the professors showed great team spirit and genuine interest in each other's work. According to Kievit, an expert in the development of cognitive abilities, there is an "increasingly common appreciation that we need to collaborate beyond our own labs." He feels that working together is very beneficial when it comes to sample size, generalisability and diversity of populations. "For example, collaboration makes it easier to combine insights from different countries. Ideally, we should collaborate even more in developmental neuroscience because we now focus strongly on industrialised countries."

Rommelse, a professor of neurodevelopmental disorders, pointed out that Nijmegen's developmental neuroscience research groups are known to look beyond their own discipline. "For a long time, it was fine to work on an island," she quipped. "Many developmental neuroscientists didn't see the need for collaboration. However, it's increasingly acknowledged that lifestyle, social bonding, negative life experiences, etc. are vital to fully understanding the developing brain. Vice versa, clinicians are increasingly aware of the need to be informed about progress in more fundamental research."

As a professor of Clinical Genetics and Psychopathology of Rare Syndromes, Tjitske Kleefstra had already teamed up with Rommelse and Schenck in clinical and research projects. Her association with Kievit, who recently moved to the campus, has just started. She sees herself as a lynchpin between research and clinic. "It's a huge field, and there's a lot to study, as new technologies have given us so much information, especially in the last ten years. On the biology and clinical research side, we need to make an extra effort to learn from what can be delivered by all these new genetic testing options."

Professor Schenck knows the inner workings of the brain of the fruit fly *Drosophila*. She calls it an "exotic expertise." The insect's brain has a surprising number of similarities to the human brain: the same cell types, molecules, and the way they interact. Kleefstra and Schenck work together on specific neurodevelopmental syndromes (disorders resulting from mutations in a specific gene). "We have collaborated on several disorders that Tjitske has identified, most importantly on the one that carries her name, 'Kleefstra syndrome,'" said Schenck. "In *Drosophila*, we learned a lot about the function of the affected gene and what goes wrong in the nervous system if the gene is mutated. Now, using the Vici grant that I recently received, we will search for drugs that can restore learning in the fly model of Kleefstra syndrome."

The professors thought that the fact that they started at roughly the same time was merely a coincidence, although it was clearly part of a broader move. The four chairs are part of the Radboud University's dedication to neuroscience and neurodevelopmental disorders. The coherence and complementarity of the four helps the interdisciplinary mission in Nijmegen. "If we all collect our own small sample studies, that often won't provide answers to the questions we are most interested in," Kievit says. That's why, according to the professors, the Donders Institute is such a good place to facilitate this. Despite having a wide range of backgrounds and expertise, they are literally within walking distance of each other. Schenck: "This is a strong feature of research in Nijmegen and we're all for it."

Daan Appels

# team up



**ANNETTE SCHENCK**

Annette Schenck is an expert in developmental brain disorders. At Radboudumc, she has been appointed as Professor of Translational Genomics of Neurodevelopmental Disorders. She has a close professional relationship with – and love for – the fruit fly *Drosophila*, a powerful and cost-effective genetic model. Looking into *Drosophila* brains helps us to understand how early cognitive brain disorders occur and how to treat them. Schenck studied biotechnology in Berlin, got her PhD in Strasbourg, and did her postdoc in Dresden.



**ROGIER KIEVIT**

Rogier Kievit received his PhD *cum laude* in 2014 (from the University of Amsterdam). The son of two scientists, he is Professor of Developmental Neuroscience at Radboud University. Kievit is an expert in the development of cognitive skills across the lifespan. Before joining Donders, he worked as a programme leader at the MRC Cognition and Brain Sciences Unit at Cambridge University in the UK.



**TJITSKE KLEEFSTRA**

Tjitske Kleefstra is an endowed professor of Clinical Genetics and Psychopathology of Rare Syndromes at the department of Human Genetics and set up the Vincent van Gogh Centre for Neuropsychiatry in Venray. She discovered the Kleefstra syndrome, a rare neurodevelopmental disorder with various somatic and neuropsychiatric features. As a clinical geneticist she aims to improve diagnostics and clinical management for neuro-developmental syndromes by bridging the gap between research and the clinic. Kleefstra has received several awards for her work, as well as major personal grants.



**NANDA ROMMELSE**

Nanda Rommelse is an endowed professor of Neurodevelopmental Disorders, connecting the psychiatry department of Radboudumc with 'Karakter child and adolescent psychiatry'. She is also actively engaged in patient care as a clinical neuropsychologist, thus facilitating dialogue between those involved in patient care and scientific research in the field of neurodevelopmental disorders. Her research focuses on early detection and prevention, in addition to refining and modernising diagnostics, treatment and prognosis. Rommelse has received various large research grants as well as personal awards and is within the world's top one percent of experts on autism and ADHD according to Expertscape.



A selection of recent developments

## Newsflash

- Being social requires a combination of feeling and reason**  
 Some of us are good at sensing what people feel. Others easily make many different friends. In other words: human beings are socially capable in several ways and on different levels. These capabilities build on the integration of feeling and thinking, a capacity which was presented in a recent study in *Psychological Bulletin* by Donders Researchers Matthias Schurz, Rogier Mars and colleagues.
- Brain stimulation may increase control of emotional actions**  
 To function well in society, people must be able to control their emotional reactions. This usually works, but this control can fail, resulting for example in aggressive behaviour in traffic or in people with social anxieties avoiding group meetings. Brain stimulation may help to improve control over this automatic behaviour. This is what Bob Bramson and colleagues have shown in a publication in *eLife*.
- Four Donders researchers awarded a Veni grant**  
 Kiki van der Heijden, Wim Pouw, Isabella Wagner and Elsa Eising have been awarded a Veni grant by the Dutch Research Council (NWO). Van der Heijden will study sound localisation using cutting-edge AI techniques and state-of-the-art neuroimaging. Pouw will examine the degree to which hand gestures that influence human speech are exploited in social interaction. Wagner investigates whether navigation and recognition are supported by grid-cell representations in the brain, and their potential break-down in Alzheimer's disease. Eising will study the genetics of stuttering, to discover its cause and learn about the genetic and neurobiological mechanisms underlying it.
- Koen Haak receives a Vidi grant for visual research**  
 The NWO awarded Koen Haak a Vidi grant. With this grant, he will study whether there are individual differences in how the brain compensates and/or degenerates in patients with eye disease. The Donders researcher will examine whether these differences predict the quality of functional vision, for example when we are reading or driving a car.
- Young infants have an inbuilt learning strategy**  
 Infants are probably the best learners imaginable. This is not a random process; young children select and focus on information that enables them to learn quickly and efficiently. Francesco Poli and colleagues discovered this built-in learning strategy and published their findings in *Science Advances*.

## PhD defences

\*Donders series number

- May-November 2020
- Klee, J.**, *Neural Ensemble Dynamics in the Hippocampus and medial Prefrontal Cortex during Reward Prediction.*
  - Telgte, A. ter**, *On the origin of cerebral small vessel disease.* (cum laude)
  - Zhang, W.**, *Visual motion processing in mice.*
  - Kruyt, I.J.**, *Bone Conduction Devices - Reviewing the past, evaluating the present, considerations for the future.*
  - Bielczyk, Z.N.**, *Signal detection and causal inference in functional Magnetic Resonance Imaging.*
  - Abu Bhakar, N.**, *Glycomics by mass spectrometry for the diagnosis of congenital disorders of glycosylation (CDG).*
  - Nuland, A.J.M. van**, *GMolecular, structural, and behavioral differences between tremor dominant and non-tremor Parkinson's disease.*
  - Theves, S.**, *Mapping conceptual knowledge acquisition in the hippocampal system.*
  - Quax, S.C.**, *Mechanisms of active perception, a neural network approach.*
  - Khan, M.B.**, *Genomic and transcriptomic landscape of ABCA4-associated Stargardt disease.* (cum laude)
  - Buitelaar, N.J.L.**, *ADHD and intimate Partner Violence. Impact of ADHD as a risk and a treatment factor in Intimate Partner Violence.*
  - Waalwijk van Doorn, L.J.C. van**, *Cerebrospinal fluid biomarker assays for Alzheimer's disease: standardization, validation and analysis of confounders.*
  - He, T.**, *Perceiving the future: predictive processing from the eyes to the brain.*
  - Heus, R.R.A. de**, *The ups and downs of blood pressure variation in cognitive impairment and dementia.*
  - Fritsche, M.**, *Temporal Context in Visual Perception.*
  - Sanders, M.L.**, *NeuroExercise: The effects of exercise on cognition, central and cerebral hemodynamics in mild cognitive impairment.*
  - Niehof, N.**, *Visuo-vestibular cue combination in vertical perception.*
  - Yoosefzonooz, B.**, *Computational and Learning Mechanisms in the Human Auditory System.*
  - Lugtmeijer, S.**, *Neurocognitive mechanisms of visual working memory and episodic memory in healthy aging and after stroke.*
  - Mazzetti, C.**, *On the relationship between structural and functional underpinnings of attention. Insights from clinical and non-clinical samples.*
  - Boumans, R.J.L.**, *Feasibility and effectiveness of social robots in acquiring patient reported outcomes from older adults.*
  - Peeters, D.G.A.**, *Serotonin and neurocognitive mechanisms of reactive aggression.*
  - Sharma, S.**, *Toward binaural processing in bimodal cochlear implant users.*
  - Mulders, P.C.R.**, *Current Connections: Brain patterns in electroconvulsive therapy.*
  - Thomas, J.**, *SLOW WAVES: Assessing sleep and detrimental effects of sleep disruption on brain amyloid- $\beta$  and cognitive function in shift workers.*
  - Santaella Tortós-Sala, A.**, *Tackling Parkinson's disease: a proteomic approach to biomarkers and regenerative therapy.*
  - Liu, W.**, *The dynamic nature of our memories: experimental investigations using functional Magnetic Resonance Imaging.*
  - Eidhof, I.J.M.**, *Common Biological Denominators and Mechanisms underlying Ataxia-like Motor Dysfunction: from Human to Fly.*
  - Kolk, N.M. van der**, *Towards a prescription for exercise for persons with Parkinson's disease.* (cum laude).

## NeurotechEU: a European University for brain-inspired science, innovation, and education

Sharing science with colleagues across Europe. Creating a network university that combines education and innovation. The European University of Brain and Technology – NeurotechEU – is a dream come true for neuroscientists and students.

With the vision and leadership of Donders chair Tansu Celikel, the Donders Institute has brought together eight renowned universities and more than 250 European research institutes, companies, governmental and non-governmental organisations to establish NeurotechEU. This summer, the initiative received its first external support from the European Commission: €7 million to further develop the European University over the next three years.

The mission of NeurotechEU is to improve Europe's position in brain research and engineering and to provide well-educated people to tackle future problems

in society. This is necessary, as brain disorders are a leading cause of disability and place a significant burden on society. In Europe alone, brain-related diseases – such as dementia, loss of sight and depression – account for almost a quarter of all health problems.

This European collaboration will have an impact beyond education and research. According to Tansu Celikel: “The new European University will actively work to promote diversity and a common European identity among students and researchers with multi-cultural, multilingual, international and intersectoral experiences across the European continent.”

Partner universities are Oxford University, the University of Bonn, the Karolinska Institute, Miguel Hernández University, Boğaziçi University (Istanbul), UMF Cluj-Napoca and the University of Debrecen. For more information: [www.theneurotech.eu](http://www.theneurotech.eu).

## Radboud Young Academy safeguards the future of science

Inti Brazil, Mark Dingemans, Martin Dresler, Eelke Spaak and Fleur Zeldenrust became members of the newly established Radboud Young Academy last October. Together with twelve other young professionals from Radboud University, the five Donders researchers have started building this platform to provide advice on policy, create an interdisciplinary network of early career scientists, and promote career development.

The Young Academy will address issues that are of particular importance during the early years in academia, for example safeguarding recognition and diversity to improve science as a whole. “It's a way to give a voice to young scientists”, Eelke Spaak explains. “And to debate broader topics, such as open science and crossing disciplinary boundaries.” This voice will speak solicited and unsolicited. “I think we're a sort of Red Team for the university board”, says Fleur Zeldenrust. “We have already been asked for our opinion on some topics, but we will also provide advice when we think necessary.”

The Young Academy represents researchers from postdoc to tenure track level in all fields of science at the Nijmegen campus. Mark Dingemans: “Many members are already working together all over the campus. Like me: as a linguist at the Centre for Language Studies, I maintain close ties with both the Donders and the Max Planck Institute. This offers a new platform for strengthening interdisciplinary and interfaculty initiatives.”

Many young researchers face an uncertain future. Fortunately, the dominant perspective on a scientist's work is changing. Nowadays, a researcher isn't just a publication machine. Modern scientists can also excel in teaching for example, shine in public outreach, or be an outstanding manager. “This should be accepted and recognized”, says Inti Brazil. “We hope to genuinely change the scientific culture, with its focus on research output and impact.”

## THE MACHINE

# You can't hear it, but it's there: ultrasonic neuromodulation

Brain stimulation without using electricity or a scalpel is one of the revolutionary features of ultrasound. Sound waves with an extremely high inaudible frequency are focused on a specific point in the brain with millimetre precision. By pushing the right buttons, it can help people with various brain disorders, such as epilepsy, anxiety disorder, depression and Parkinson's disease.

The high-tone speaker is curved like a cupped hand. Thanks to the curve, the sound waves are directed to a central point. Like the waves in a pool when you throw a rock in it, but the other way round. At the spot where these waves collide, a kind of mechanical thrust is created that can trigger neurons.

"With this device, we can get anywhere in the brain and stimulate brain areas that are just a few millimetres across," says Dr Lennart Verhagen of the Cognitive Neuromodulation lab. "We are still doing a lot of basic research on precisely how it works and how we can optimally control these sound waves."

Besides perfecting the technique, research must also make it crystal clear where exactly these sound waves need to go. This requires expertise from neuroscientists, psychologists, and clinicians. Verhagen: "We want to

know precisely what happens when you 'push' certain areas of the brain. To understand this, we need both theory and measurement. Intervention with these types of techniques makes the toolset complete."

Verhagen, his colleagues and Dr Inge Volman from Innovate Ideas recently won an award from Holland High Tech for developing this technique into applicable treatment methods. This opens up promising perspectives for patients, because the ultimate goal is a portable device that can be used to intervene when necessary. It's a bit like a pacemaker for the brain.

"For example, if an epileptic seizure starts, we want to intervene in a targeted way, often deep in the brain. Or, when a tremor starts in Parkinson's patients, this device could slow it down through a rapid intervention."

*Roeland Segeren*

### **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 wider field of neuroscience.

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