DONDERS INSTITUTE

Newsletter 34

June 2019

Pioneering psychiatrist with endless curiosity

THE MENTOR PAR EXCELLENCE WHO LINKED ADHD AND AUTISM

From memory to gut

A CLOSE LOOK AT MEMORY, STRESS AND MICROBIOTA

Things we can do with a 'brain on a dish'

CUSTOM-MADE MEDICATION WITH CULTIVATED BRAIN CELLS

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Pioneering psychiatrist with endless curiosity

The mentor par excellence who linked ADHD and autism

An expert in autism and ADHD, skilled in the field of aggression and depression. A psychiatrist with knowledge of genetics, a clinician with fundamental curiosity. The man who wanted to know everything, and did everything, will retire this September. Jan Buitelaar is a scientific jack-of-all-trades, who will be hard to replace.

Nobody could have guessed that Jan Buitelaar would become a psychiatrist. "I found it difficult to choose a study," he says. It's characteristic of his enormous curiosity and the broadly oriented scientist he is. "It would have been more logical if I'd become an architect, like my father."

Driven by unwavering curiosity, Buitelaar has built up a solid reputation. He specialises in autism and ADHD but is also interested in aggression and depression. According to his colleague, professor of molecular psychiatry Barbara Franke, he has worked on every aspect of neurodevelopmental disorders. "From the cause to the cure, Jan is an interdisciplinary scientist. He ties things together: from genetics to imaging to treatment. That's why he's made such an important contribution to science."

EIGHT HUNDRED FAMILIES WITH ADHD

One of his biggest contributions is the NeuroIMAGE sample: brain data on 800 families in which one or more members have ADHD (plus control families). Buitelaar: "Initially, we only collected genetic and neurocognitive data from children with ADHD and their families. When we'd completed that project, we realised that we were missing brain scans. During a follow-up research project with the same cohort, we started scanning. This was pioneering at the time, around 2010. It was more common to scan within groups of no more than a few dozen subjects."

This yielded a collection of data that has been the focus of extensive research since. "We learned that there are many differences between people with ADHD. And this conclusion applies to other disorders: the larger the group of test subjects, the more heterogeneous it is." There is some overlap with his other field of research, autism, which is also far from homogeneous. The search for similarities between ADHD and autism has always fascinated Buitelaar. The disorders have similarities in the genes and in the brain, but these are not always expressed together. "For a long time, ADHD and autism were completely separate worlds in science. We started investigating the relationship and were one of the first to see that ADHD and autism may be manifestations of the same overarching developmental disorder."

ONE HUNDRED PHD STUDENTS

In the meantime, Buitelaar explored the science behind aggression and stress, made connections between psychology and biology, and broadened his methods from structured interviews to genetics. As a clinician at the Centre for Child and Adolescent Psychiatry Karakter, he also saw patients. He has built up a huge network, collaborating with dozens of researchers at all levels. His 100th PhD student graduated this year. Mentoring is one of his strongest points, says clinical neuropsychologist Nanda Rommelse, a colleague at Karakter. He is always there when you need him. "He never takes the easy path; he always looks at papers thoroughly and thinks along with you. I've never had an out-of-office reply from him. When he's on sabbatical leave, I receive more emails from him than ever."
That might be true, Buitelaar confirms. He has noticed that it's de-stressing to scan his mailbox for important emails when he's away. "I was on vacation with my family a couple of years ago and my wife sensed a feeling of unrest. One day she said: 'I think our neighbour has Wi-Fi and a laptop. Maybe you should visit him.'"

Despite the huge number of researchers who Buitelaar took under his wing, he never lost sight of details. "He always gives you constructive feedback," says psychologist and behavioural geneticist Corina Greven, who grew from a post-doc to a Principal Investigator under his care. "He provides smart, sharp comments with which you can actually do something. He strikes a good balance between a helicopter view and details. That's very impressive."

If he has to choose, Buitelaar opts for the helicopter view, which is where his passion lies. "In the end my strength is the bigger picture. I think I'm able to recognise patterns and connections quickly and that's what I find interesting." With a grin: "I have absolutely no problem with letting someone else handle the details." A conversation with Buitelaar easily switches between passion and jokes. "He often laughs the loudest at his own jokes," says Rommelse. "And really loudly too, which then makes other people laugh. As a result, it seems as if even his bad jokes are funny." This exemplifies his attitude to life: always cheerful, always in a good mood. Greven: "You hardly ever see him stressed, even when he's keeping so many balls in the air."

THINK BIGGER

According to Greven, Buitelaar is gifted in his ability to look further than others. "For me personally, he's been very helpful in thinking about the next steps. Thinking bigger." Franke agrees: "He sees so many opportunities because he's always looking ahead. Before a project is completed, he has already thought up the next questions. I owe a great deal to him. He opened up his vast network to me and gave the start of my career a boost."
Buitelaar believes it's important to support talented researchers. He became aware of this when submitting one of his first publications. An experienced editor rejected his paper and sent it back, but wrote a few sample sentences in the margin that could improve the text. "I rewrote the article based on that feedback and it was accepted after the second attempt. My writing has since improved considerably."

Buitelaar is taking a step back in September. He'll continue to do some research, but formally he will be saying goodbye. He'll be greatly missed, explains Franke: "Jan is not a five, but a six-legged sheep. Some of us can take over a leg or two, but he did it all at once."

FRANCESCO BATTAGLIA

From memory

Developmental scientist Carolina de Weerth and neuroscientist Francesco Battaglia have each been awarded major grants. With these funds, they can take the research they have been specialising in for years into a new and exciting direction. Their fields of study reflect the vast range of research carried out at the Donders Institute.

Burned into your memory

The ERC awarded Francesco Battaglia an Advanced Grant to research memory systems. He will use the €2.375 million to study the hypothesis that the Default Mode Network (DMN) is crucial for memory. Battaglia explains: "The brain is continuously active and most of its activity is spontaneous, that is, it's not provoked by external stimuli. This activity is key to our cognitive processes and is highly structured. The DMN is more active when we're sleeping or not doing anything than when we're engaged in cognitive activities."

ADVANCED OPTICAL IMAGING

"My work concentrates on neural ensemble recordings in freely behaving rodents such as rats and mice. We can record up to 100 single neurons. With our advanced optical and electrical imaging systems, we can map neural activity as the rodents travel through a closed-loop circuit in the lab. What we see is that, when these rodents are sleeping, their brain is retracing their previous experience of moving through the circuit. We believe that this replay mechanism explains how they consolidate memory."

"Memorising is a two-step process. We know that the hippocampus is the 'hub' of the memory network in the brain and, for long-term memory, information must be stored in the cerebral cortex. But how does that work? We want to observe memory replay in the brain, testing the hypothesis that the DMN is essential to transporting memory from the hippocampus to the whole cortex." The ERC grant will allow Battaglia and his team to take optical imaging a step further. "With advanced devices, we will be able to use electrodes to map a larger brain area. We also aim to study the behaviour of mice more thoroughly as they travel through a virtual circuit."

LINKING KEY CONCEPTS

Battaglia believes that he was awarded the grant because he was able to find a way to connect two key concepts in his field, namely the DMN and memory replay. "I was the first; a year later, someone else might have made a similar proposal. Even if my hypothesis is incorrect, I believe we'll be able to gather sufficient data to develop a theory of brain activity."

One of the biggest challenges Battaglia faces is processing the vast amount of data he will collect, so computational analysts will reinforce his team. "Using concepts from physics and machine learning, we hope to make better sense of this data." As to the benefits for patients: Battaglia observes that pharmacists are backing away from neurological treatments. "Developing successful treatments is extremely slow. I believe that this is partly due to a lack of fundamental knowledge. I hope my research will benefit colleagues working on memory-related illnesses such as Alzheimer's and Kleefstra Syndrome, two diseases that are intensively researched at the Donders."

to gut

Following your gut

The NWO awarded Carolina de Weerth a €1.5 million Vici grant for her research on how gut bacteria and stress shape child development. “At the beginning of this century, it became clear that there was a connection between gut microbes and development,” De Weerth explains. “It was discovered that germ-free mice had higher stress levels, worse memories, and were less social. When they were administered microbiota, stress levels went down, but only when these were provided in early life. Later in life there was no effect.”

THE IMPACT ON CHILD DEVELOPMENT

De Weerth’s previous research suggested that the development of intestinal microbiota also relates to children’s behavioural and emotional regulation. In her Vici project she will study how the gut microbiota interact with the stress system, and how they develop from birth until the age of 16 in healthy children. In randomised controlled trials with infants, she will also investigate whether stress-reducing interventions involving extra physical contact have a positive effect on gut microbiota and development.

De Weerth will also study two potential causal mechanisms through which maternal psychological stress can negatively affect infant microbial colonisation. “The first mechanism we’re looking at is the effect of maternal prenatal psychological stress on the infant’s microbiota. We want to find out whether stress influences the mother’s diet and her microbiota and in turn affects the infant’s microbiota. The second mechanism relates maternal postnatal stress to infant microbiota, specifically through breast milk composition.”

THE GUT-BRAIN CONNECTION

Whereas Battaglia says that he was lucky to get his grant application in quickly, De Weerth says she was initially too early. The ERC rejected a proposal with a similar framework some seven years earlier. “The gut-brain connection is a hot topic now. The other projects I’ve been working on have also helped to win this grant, especially the BIBO project that I started with a Vidi grant.”

In this ongoing study, she and her team will investigate how the environment interacts with individual characteristics in influencing behavioural and psychological development, as well as brain structure, brain functioning and physical health. “Thirteen years on and we’re still collecting data thanks to the great commitment of the parents. You can’t underestimate the importance of longitudinal data to the understanding of behaviour and health.”

De Weerth has always been interested in the effects of stress and anxiety on child development. She is fascinated by the idea that the gut could influence both of these factors. “Look at the number of expressions referring to the gut, such as *gut instinct*, and *I feel it in my gut.* It’s also much easier to modify the gut with diet or beneficial bacteria than to influence the brain. If modifying the gut could indirectly modify the brain, then that could be beneficial. Not just for existing patients, but also to prevent people from becoming patients.”

Vanessa Deij

CAROLINA DE WEERTH

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

Meanwhile at dondersinstitute.nl

SOME RECENT HEADLINES

- **'Pearl Award' for research programme in Food and Cognition**
  The Economic Board Arnhem-Nijmegen-Wageningen has given the Food and Cognition research programme of the Donders Institute a 'Pearl Award'. This prize is awarded in recognition of a special, innovative or sustainable initiative in the field of Food, Health and Energy.
- **Language processing brain data freely available to everyone**
  Brain researchers have provided access to brain data collected from more than 200 test subjects, who were measured while processing language. This high-quality data set has been compiled and distributed by a team of researchers from the Donders Institute and the Max Planck Institute in Nijmegen.
- **Stress hormone may improve exposure therapy for patients with PTSD**
  Exposure therapy is effective in about half of patients with post-traumatic stress disorder (PTSD). This percentage might increase with the targeted use of cortisol in the right patients. Benno Roozendaal received a TOP subsidy from ZonMw to investigate this.
- **Vici grant for research on anger and aggression**
  Dennis Schutter received a Vici grant to conduct research on anger and aggression. This grant is worth €1.5 million and he will use it to conduct research into aggression driven by blind rage.

SOME RECENT HIGH-IMPACT PUBLICATIONS

- **Associating colours with vowels? Almost all of us do!**
  Does the letter 'a' sound more green or more red? Is 'i' light or dark in colour? Even though we perceive speech and colour with different sensory organs, nearly everyone has an idea about what colours and vowels go together, explains Mark Dingemanse. Moreover, many of us have a particular system for doing so. (Behavior Research Methods)
- **How a gene called G9a regulates the energy supply for stress responses**
  In order to survive, organisms must be able to detect (threatening) changes in their environment and respond to them adequately and quickly. However, such stress responses (e.g., escaping from a predator or an immune response to an infection) consume a great deal of energy. Annette Schenck and colleagues have discovered a primary driver for this regulation process in fruit flies. (Plos Biology)
- **Who is the typical patient with ADHD?**
  Thomas Wolfers and André Marquand have shown that, biologically speaking, there is no such thing as a 'typical' patient with ADHD. Biological psychiatry heavily relies on so-called case-control comparisons. Based on this approach, a group of patients, for instance those with ADHD, is compared with a group of healthy individuals on a number of biological variables. (Psychological Medicine)

PhD defences

**Donders series number*

January 2019

- **Akkermans, S.,** *The role of the frontostriatal circuitry in impulsive and compulsive syndromes.* DS 349*
- **Van Baar, J.,** *Models of Morality in Behavior and Brain.* DS 351
- **Ter Huurne, N.,** *ADHD and the alpha rhythm. On the role of alpha oscillations in neural mechanisms underlying attention-deficit hyperactivity disorder.* DS 364
- **Te Woerd, E.,** *Feeling the beat: the neurophysiology of cueing in Parkinson's disease.* DS 357
- **Thalmeier, D.,** *Self-organization, learning & control: perspectives on complex systems.* DS 360
- **Selten, M.,** *Altered function of the inhibitory system in rodent models of neurodevelopmental disorders.* DS 362
- **Van Rhijn, J.,** *The role of FOXP2 in striatal circuitry.* DS 363
- **Mostert, P.,** *The dynamics of visual representations under top-down modulation.* DS 355
- **Markuerkiaga Olabe, I.,** *On the laminar specificity of BLOD-based cortical activation profiles.* DS 369
- **Wischnewski, M.,** *Interfering with feedback processing: Implications for decision making and learning.* DS 358
- **Schoenmakers, S.,** *Brainreading; Decoding the mental state.* DS 370

February 2019

- **Klein, M.,** *From gene to disorder in ADHD: Mapping mechanisms at different levels of complexity.* DS 365
- **Swider, K.,** *Pain perception – the power of the placebo effect and crossed hand analgesia.* DS 356
- **Lojowska, M.,** *Freeze to see: The effect of threat on detention of coarse visual features.* DS 352
- **Thielen, J.,** *Functional and neurochemical contribution of the medial prefrontal-thalamus-hippocampus network in episodic memory.* DS 372

March 2019

- **Schellevis, R.,** *The genetics of central serous chorioretinopathy.* DS 373
- **Wolfers, T.,** *Towards precision medicine in psychiatry.* DS 368
- **Meijs, E.** *Conscious perception in the predictive brain.* DS 337
- **Silva de Lima, A.,** *Quantifying Parkinson's Disease: The use of technology for objective assessment of motor symptoms.* DS 371
- **Swart, J.,** *To go or not to go. On motivational biases in decision making.* DS 359

April 2019

- **Janssen, L.,** *Attention for ADHD: Mindfulness-based stress reduction for adults with attention-deficit and hyperactivity disorders.* DS 366
- **Timmer, M.,** *Out of balance. Neurocognitive mechanisms underlying depression in Parkinson's disease.* DS 374
- **De Vos, J.,** *Naturalistic Word Learning in a Second Language.* DS 379

May 2019

- **Roelofs, R.,** *A clinical neuropsychological perspective on Noonan syndrome: From assessment to treatment.* DS 380
- **Van Vliet, J.,** *Myotonic dystrophy type 2, the challenging diagnosis of a complex disease.* DS 378

June 2019

- **Van Heck, K.,** *Probing attentional biases: The presence and presentation of individual attentional biases in relation to salient stimuli.* DS 375
- **Karssemeijer, E.,** *Brain in motion: combined cognitive and physical exercise training in people with dementia.* DS 377
- **Bussu, G.,** *Focusing on the individual infant: classification and heterogeneity of autism spectrum disorder.* DS 367

High school students battle for neuroscience prize

Who are the neuroscientists of the future? How can we stimulate interest in the brain and inspire young people to study and pursue careers in neuroscience? With this in mind, the first Dutch edition of the International Brain Bee competition for high school students was held at the Donders Institute.

On Saturday 16 March, students from several secondary schools came to Nijmegen. They came to participate in the competition, but also to explore the Brain Expo: a neuroscience fair at which PhD students from several Dutch universities presented their research. The icing on the cake was a keynote lecture by Hanneke den Ouden on human decision-making.

The competition started with a multiple choice round, followed by a workshop by Brein in Beeld. After this, participants answered challenging questions on neuroanatomy, using brain models and histology of microscopic preparations that revealed various neurological disorders.

Would you be able to recognise a brain disorder from an interview with a patient? This was the main question in the patient diagnosis round. The contestants were shown video clips and then asked to diagnose conditions such as Amyotrophic Lateral Sclerosis (ALS), Autism Spectrum Disorder, schizophrenia and Parkinson's disease. Finally, during an exciting podium finale, the top-five participants were asked tough questions by the expert judges Marloes Henckens, Tansu Celikel and Lisa Genzel.

Eighteen-year-old Myrthe Weessies from Nijmegen was announced as the winner of the very first Dutch Brain Bee. She has now been invited to compete in the finals of the International Brain Bee, in which there are more than 25,000 contestants from over 50 different countries. The finals will be held in Dague, South-Korea. With the help of crowdfunding (www.gofundme.com/hersenolympiade), the Dutch organisation aims to send her there, to compete with contestants from other countries for the title of International Brain Bee winner.

Charlotte Oomen

Donders Lecture

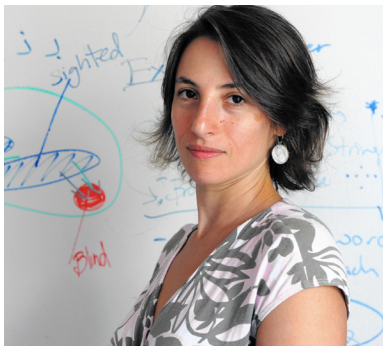
The brains of the blind

We watch, see and look with the back of our brain, which is where our visual cortex is located. What happens in that part of the brain if it lacks the expected input? If the eyes don't work, for example, as is the case with people who are blind? Then the grey matter will learn to process language, argues Dr Marina Bedny of the John Hopkins University in Baltimore. She will elaborate on this during the Donders Lecture on 24 October 2019.

Processing words and grammar is completely different from processing light that is picked up by our eyes. "We call it the visual cortex, but apparently it can do more. This contradicts the view that certain parts of the brain can do only one trick," says brain researcher and Donders Director Peter Hagoort. He will host Bedny's Donders lecture.

Bedny focuses on language, but her findings can be translated into other areas of brain science. Hagoort: "Our brain consists out of all kinds of different building blocks, but they are not equally important in terms of functionality. How does the functioning of our brain depend on the specific cell types of which our brain is built? Some cells appear to be multifunctional."

During her lecture *Nature and nurture in neurocognitive development: insights from studies of blindness*, Bedny will discuss what we can learn from this so-called neural plasticity, by researching the brains of blind people. More



and more neuroscientists now agree that this plasticity exists. Hagoort is curious how far Bedny thinks this will go. "What are the limits of that plasticity? Is it limited, or are our brain cells ultimately able to do anything?"

Roeland Segeren

THE MACHINE

Things we can do with a 'brain on a dish'

Finding custom-made medication to beat complicated disorders. That's the ultimate goal of recreating human brain cells. This brain-on-a-dish – in medical jargon: cerebral organoid – has already played a key role in the fight against ALS and the Zika virus.

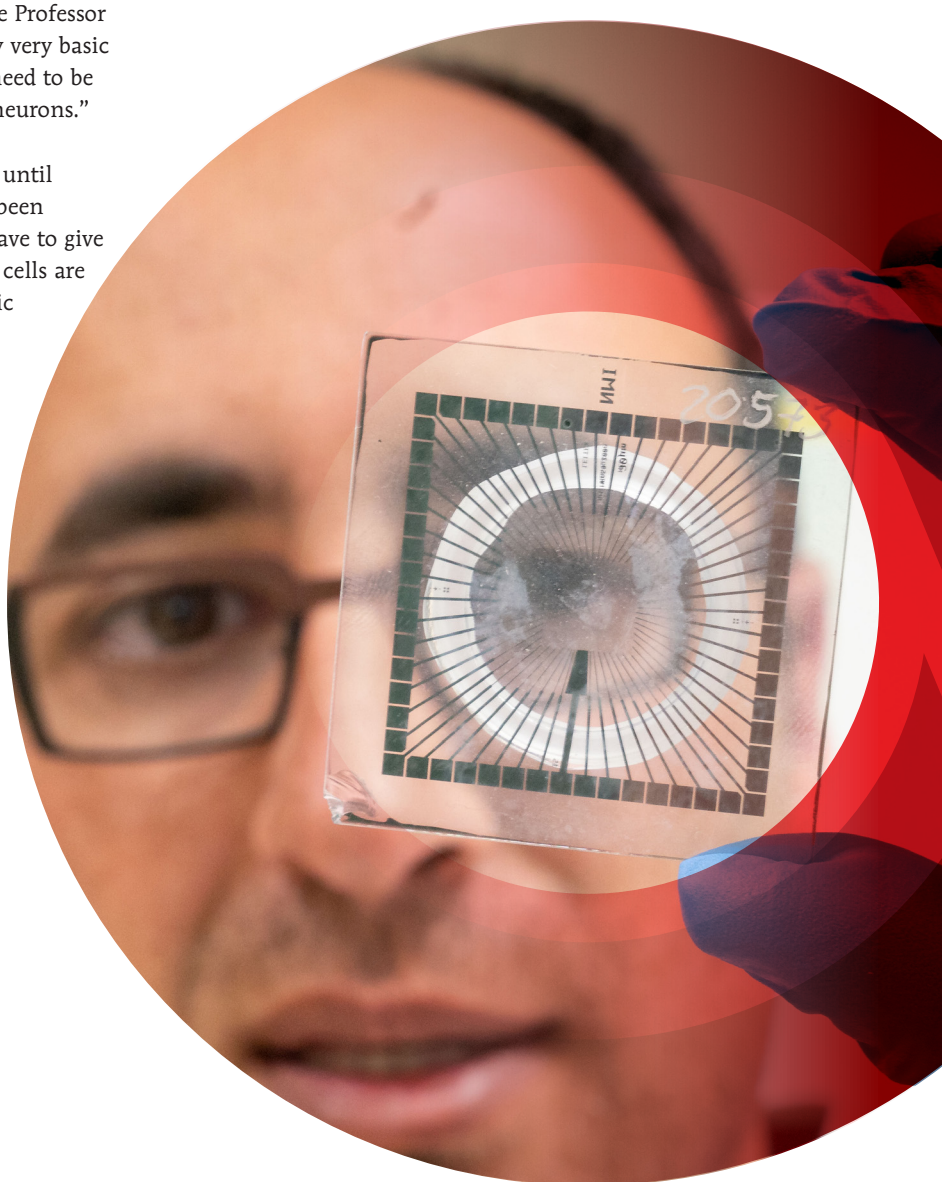
This piece of top-notch science was not invented overnight. To begin with, we need stem cells from a patient, which was still a major challenge ten years ago. Nowadays, scientists are able to make stem cells from any mature cell in the body, such as skin or blood cells. "This is a Japanese invention," says Silvia Albert, head of the Radboudumc Stem Cell Technology Center. "Since 2006 we have been able to re-programme the DNA in any cell to make the cell pluripotent. This means we can direct it to become any cell type in the body. These are called IPSCs: Induced Pluripotent Stem Cells."

When IPSCs are created, all they need is an instruction to grow into brain cells. This is done by adding specific proteins, explains Nael Nadif Kasri, Associate Professor in Molecular Neurophysiology. "It is actually very basic biology; we know which genes in our DNA need to be turned on and off to get them to grow into neurons."

After this, nature takes over. The cells divide until a few square millimetres of brain tissue has been grown. Quite unexpectedly, scientists only have to give the first cell a kick-start. Nadif Kasri: "Brain cells are self-organising. There seems to be an intrinsic programme that knows when and how to create the different cell types expressed in the brain."

These brain cells can be grown on a chip or in a dish, in order to read out their activity. With them, researchers can study genetic disorders such as microcephaly, neurodevelopmental and neuropsychiatric disorders more thoroughly than ever before. Nadif Kasri: "We now have a model with exactly the same genetic background as the patient. This helps us to better understand genetic disorders and to rationally design new therapies for each individual patient. It also has the potential to indicate which drug will work better for a specific patient. Another important application of the technique is to regenerate dysfunctional cells in the brain and implant them back into the patient, which is currently being tested clinically for Parkinson's patients."

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 field of neuroscience.

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