Amsterdam Neuroscience MAGAZINE

Connecting the people, the science and the brain

Word from the directors

Arjen Brussaard (top)
Diederik van de Beek (bottom)

Prior to the outbreak of the COVID-19 pandemic, we had already selected our 2020 theme: team science. Team science is of great importance to us and it is imperative for the mission and vision of our institute. Which is why we always aim to build teams around important subjects in neuroscience, to enhance our knowledge, develop new treatments and make a difference for patients. In the current COVID-19 era, and with social distancing being so prevalent, the team science theme turned out to be spot-on. Not only is it an essential story line for many of our colleagues within Amsterdam Neuroscience, it is also a prerequisite for meaningful and curiosity-driven academic endeavors and translational medicine. Also, in these times, it is essential for keeping up the good work within the neuroscience field.

In the second edition of Amsterdam Neuroscience MAGAZINE you will read about how team science is being embraced – there are in-depth interviews with three prominent teams (written by Marieke Buijs) and six shorter profiles of researchers who have paired up (interviewed by Naomi Vorstermans). The good-spirited way in which these teams present themselves in these interviews reflects both the resilience and the can-do attitude that seems to be an increasingly essential driving force of how science is done these days. Hence also a good argument for our motto: **Amsterdam Neuroscience: connecting the people, the science and the brain.**

Arjen Brussaard, *director*
Diederik van de Beek, *co-director*

On the ball

How do you create a group that is able to quickly shift its focus from one devastating illness with unpredictable outcomes to another, almost overnight? For Diederik van de Beek, it's by nurturing social cohesion and creating an environment where innovative ideas get a chance to flourish – often over a game of foosball.

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A unique perspective

When treating their patients, child psychiatrist Hilgo Bruining and his team step away from the standard 'one size fits all' practices of diagnosis and protocol. Not only does this personalized approach bring surprising and welcome results to all involved, it also brings Bruining and his colleagues to the forefront of precision psychiatry.

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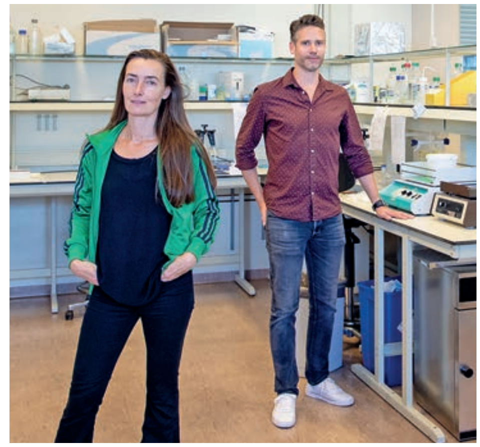

A gift of a job

Thanks to a large Gravitation grant for the BRAINSCAPES project, leading researcher Daniella Posthuma and her team of 21 scientists are using their revolutionary approaches to make a connection between Complex Trait Genetics and neuroscience.

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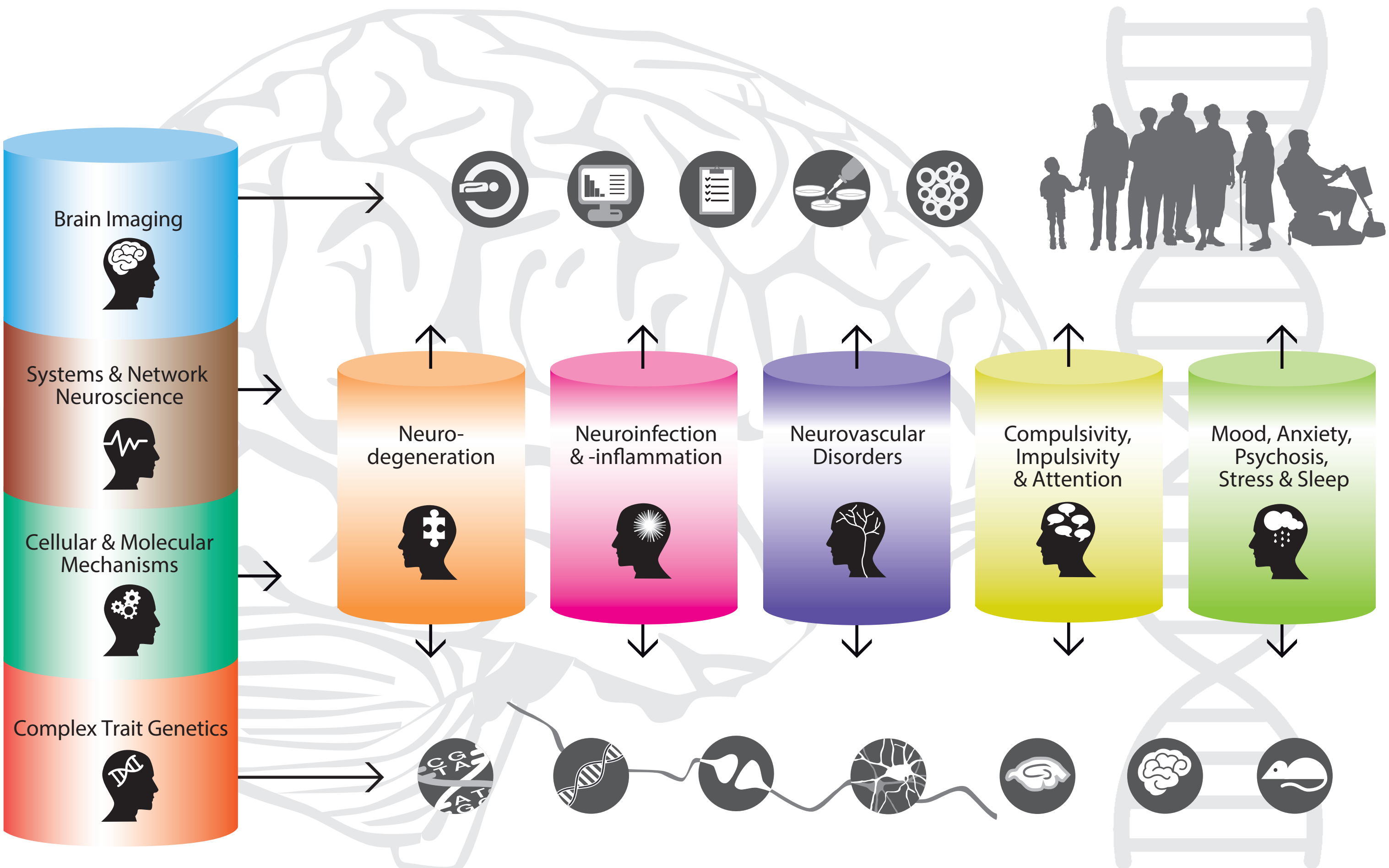

Amsterdam Neuroscience

Amsterdam Neuroscience
An interdisciplinary research institute

Amsterdam Neuroscience is the research institute for neuroscience of Amsterdam UMC and the science faculties of Vrije Universiteit Amsterdam and the University of Amsterdam. Researchers and clinicians from these three institutions join forces in the field of fundamental, translational and clinical brain research. This collaboration strengthens the scientific excellence in this area, making Amsterdam Neuroscience one of the largest neuroscience communities in Europe.

Translational medicine is at the heart of Amsterdam Neuroscience: we aim at making seminal contributions in understanding the functioning of the human brain and the peripheral nervous system, and their disorders. To enable translational neuroscience research, we develop and translate neuroscience knowledge into applications for patients. Amsterdam Neuroscience focuses on scientific excellence, young talent and innovation in four cross-disciplinary research programs. In addition, there are five clinical research programs that focus on both existing and new treatments for a number of brain and nervous system diseases, including neurological, neurovascular and psychiatric disorders.

Amsterdam Neuroscience's overall mission is to broaden the fundamental knowledge of the human brain and nervous system, and to translate this into effective therapies and treatments for the individual patient.

With a focus on both fundamental and translational neuroscience, we work on the primary function of the brain and the underlying cellular and molecular mechanisms. In addition, however, we also identify relevant biomarkers, drug targets and new molecular structures for the purpose of interventions for brain disorders. Through clinical trials on patients, we validate new diagnostic tests, therapies and interventions. The clinical research often focuses on the prevention of brain and nerve disorders, or the recovery thereof. We do this both by investor generated research and through collaborations with external parties such as biotechnology or pharmaceutical companies. Cooperation with industrial partners can, in turn, help accelerate clinical development and validation of new methods and interventions. And all of this while putting the interests of the patient first.

Through scientific excellence and high clinical standards, we provide the best breeding ground for the next generation of neuroscientists, neurologists and psychiatrists. Team science and communication are important core values that make Amsterdam Neuroscience THE connecting research institute, where principal researchers contribute to a good infrastructure with partnerships, suitable financing and valorization opportunities.

On the Ball

Social cohesion is crucial in Diederik van de Beek's research group, where the researchers can often be found bonding over a game of foosball. In dire times, it is this communal bond that allows the bacterial meningitis researchers to shift their collective attention to the coronavirus currently ravaging the world.

CV Diederik van de Beek

2016 - present	Scientific Director of Amsterdam Neuroscience, Amsterdam UMC
2012 - present	Full professor of Neurology, Amsterdam UMC – location AMC
2007 - present	Neurologist, Amsterdam UMC – location AMC
2006 - 2007	Neurologist, Mayo Clinic, Rochester, Minnesota, USA

It's a Tuesday morning in March 2020. Room number 175 is buzzing with energy. The lab is about eight square meters in size and contains the same number of people. Four scientists are huddled around two microscopes, others are working under a fume hood, and every now and then people pop in to fetch samples from the freezers. What's bringing everyone here is the presence of some particularly interesting creatures: zebrafish. German PhD student Nina Teske is lining the sedated animals – all facing to the left – neatly on a grid under the microscope. Visiting researcher Emma Wall, from the Francis Crick Institute in London, watches her in awe.

In fact, it is actually zebrafish larvae that Teske is working with. They're about 1.5mm each; so small that she uses an eyelash, attached to a pipette tip, to handle them. "It's one of mine," she explains without taking her eyes from the microscope. "I removed it this morning. You can buy expensive utensils for the task, but this works just fine." It's a little trick she learned from one of her colleagues and that she is now sharing with Wall.

Because the zebrafish research is a critical step in the expansive project that approximately 30 scientists are involved in together, the lab is a popular hangout. The researchers form the group working under neurologists Diederik van de Beek and Matthijs Brouwer, and together they try to figure out why it is that some people have the misfortune to contract bacterial meningitis, while others do not. And why, for some, the outcome is severe, even fatal, while for others the disease has a milder trajectory. It is research that could help save millions of lives worldwide. So how do you create a group environment where innovative ideas get a chance to flourish? A group that – if needed – is able to quickly shift its focus to another illness that has unpredictable outcomes: COVID-19?

While Teske and Wall huddle around the microscope, COVID-19 is ravaging Wuhan, Iran and Italy, and is gradually making its way to

> "I get a lot of solace from the COVID-19 research. It feels good to be able to contribute in such a dire situation."

Amsterdam UMC. Weeks earlier, Van de Beek saw the first images from China, where officers were cleaning the streets with disinfectant. As he looked at them, he wondered: 'Are we, as doctors, prepared for what's to come? And how can we, as scientists, help defuse the deadly virus? Is there anything we have learned from our meningitis research that could be relevant in alleviating the suffering from COVID-19?'

But for now, all seems fine. Teske chats about her day. She set her alarm at 6 am to make sure she started her experiments by 7.30 am. "We have lunch together at noon," she explains. "I cherish those moments, when we can catch up. So I plan my experiments accordingly." As she comes from Munich, Teske's fellow PhD students have become more than just colleagues; they're her social network too. "We have dinner parties, go to the movies and hang out in bars together," she says.

As the head of the lab, Van de Beek encourages the communal activities that take place. "I believe it's important for people to feel at ease with each other because it creates an atmosphere that breeds good collaboration." In order to contribute to the camaraderie, Van de Beek had a foosball table installed in one of the communal rooms. The researchers track their efforts with academic rigor, and present the developments at their latest lab meeting. And when they aren't busy, the PhD students spend many an hour kicking a tiny ball back and forth with the help of little men connected through a metal pole.

Of course the group's main focus is not lunch or table foosball but their research topic: bacterial meningitis. Humans carry billions of bacteria in their throat. Most of them are harmless but every once in a while some might travel, invading the bloodstream, crossing the blood brain barrier and settling in the meninges where they cause an infection. Fever and headache ensue and in about 20 percent of cases, the disease even has a fatal outcome.

Van de Beek and his team receive clinical data, blood, cerebrospinal fluid and bacteria samples of meningitis patients from hospitals across the Netherlands. This has resulted in the largest meningitis dataset worldwide. The team of doctors and scientific researchers addresses fundamental questions in a bid to understand what is happening to these patients. Why do they get sick while their partners, who carry the same bacteria, are fine? And why is bacterial meningitis fatal in some patients while others recover after a few weeks? The group suspects that an unfortunate interaction between the genetic makeup of the bacterium and the host is the driving force behind this diversity in outcomes.

To find answers, Van de Beek and his team use a range of research techniques. They perform genome-wide association and deep sequencing studies to identify risk genes in both the host and pathogen. Subsequently, they search for interaction effects between these genes. As with many types of genetic research, the real challenge is in making sense of the identified risk genes. What is their role in the pathway of infection? What makes them relevant?

This is where the zebrafish under Teske's microscope come into play. As a model organism that breeds rapidly and is not too remote from humans in their immune response, it is the ideal specimen to shed light on the function that the identified genes fulfill in the cell.

After their communal lunch, during which the PhD students discuss the likelihood of the pandemic-in-the-making interfering with their planned ski vacation, people fetch coffee or tea and gather in a windowless room to listen to visiting researcher

These events show how a variety of perspectives, combined with the freedom to think outside the box, results in unorthodox research that might lead to valuable new insights about a devastating illness.

Wall. The lights are dimmed and Wall elaborates on her meningitis research in Malawi. The 20-or-so researchers present listen intently. Afterwards there's a discussion about the research's technicalities in response to questions from Brouwer and postdoc Philip Kremer. The discussion ends, the lights go back on and people gather in small groups in the hallway to discuss next steps and explore options for collaboration.

"That was a rather tame gathering," says pathologist JooYeon Lee. "We generally refer to this meeting as 'The Roast' because of the tough questioning." Officially, Lee will start her postdoc in a few weeks but she's already spending all her time planning her next study. "I cannot wait to start," she explains.

Despite the intense scrutiny at The Roast, Lee describes the research group as a safe environment. "It's good preparation for an academic career. It is much better to get criticism or tough questioning here, from the colleagues you know, than during a presentation at a conference or PhD Thesis Defense. We all know that's the purpose of these interactions. They help us develop as scientists; we really feel like a team."

This team spirit is tested only weeks later, when COVID-19 (and attempts to minimize its spread) begin to dictate life in the Netherlands and none of the regular meningitis research can continue. Van de Beek considers his role as a scientist in the crisis further and decides to set up two projects. The first is to test whether patients hospitalized with COVID-19 could benefit from medication that impacts the activity of the complement system, a crucial component of the immune response in the blood. The second is even grander: to gather as much information as possible from the patients admitted to the ICU of Amsterdam UMC in an expansive COVID-19 biobank.

And so it comes about, almost overnight, that members of the research team find themselves working at odd hours to process incoming samples of blood, faeces and urine to document the disease that is destroying societies worldwide. The biobank they create allows for different types of research on the virus, and they receive requests for samples from research groups around the world.

Five months down the line, Van de Beek reflects how they were able to make this swift shift "thanks to our sense of togetherness," he says. "If you ask people to abandon their regular work and to help create this biobank and a randomized clinical trial instead, they might refuse because, for example, they may be scared of the virus or just wonder what is in it for them. But there was no hesitation; I was delighted to see that people just dove right in." Being able to make that transition was a soothing experience for Van de Beek. "During those hectic and uncertain weeks in spring, my wife pointed out that I get a lot of solace from the COVID-19 research and she's right. It feels good to be able to contribute in such a dire situation."

In her office, Lee has a picture hanging on the wall above her computer. It is one of those photographs of stained cells that researchers get excited about, while to outsiders they appear pretty obscure. The image shows a bunch of red fluorescent circles among a mass of blue blobs. It's a testimony to one of her projects from her time as a PhD student. And for her, it is evidence of the safety and freedom she experiences in the research group.

While tinkering with a staining method, Lee stumbled on pneumococci bacteria in the brain tissue of pneumococcal meningitis patients who had been treated with antibiotics. This was surprising, because scientific consensus holds that the bacteria do not survive antibiotic treatment. "The thought struck me that these bacteria we found might be one of the explanations for the relapse some people experience after treatment," Lee says. "This went against the scientific consensus and Diederik and Matthijs had little faith in my suggestion. However, I'm a very stubborn person and I wanted to find out what the presence of those bacteria means. Despite their skepticism, Diederik and Matthijs allowed me to pursue the idea." Further scrutiny showed the bacteria to be beautifully intact. "But we don't know yet whether they are alive, mummified or hibernating. My suspicion is the latter; that they reside in tissue of treated patients and perhaps under specific circumstances spring back to life, causing new problems." Based on his clinical observations, Brouwer does not share this thought. However, these events do show how a variety of perspectives, combined with the freedom to think outside the box, results in unorthodox research that might lead to valuable new insights about a devastating illness.

Discussing the importance of safety in a research group, Van de Beek pauses to consider. "There's a sentiment that people should always be pushed beyond their comfort zone in order to perform, but I don't share that perspective. Of course I want to stimulate the young researchers in my group and will push them to some extent. But I don't see reasons to push people too far. They have their comfort zone for a reason; it is where they feel at best and that allows them to express themselves and flourish."

And as for Lee, she has come up with another rebellious plan. "Currently I am really interested in the way the arteries are involved in meningitis." True to her nature, she has chosen a bold approach for this research question. "Mice and zebrafish are useless in this regard; their arteries don't resemble those of humans. But pig brains have arteries similar to human counterparts. So I thought, 'What if I visit a slaughterhouse, pick up a pig's brain and attach that to a heart-lung machine? Would it be a novel suitable set-up for studying vascular inflammation involved in meningitis?'" It sounds like the start of an exciting new research chapter.

Amsterdam Neuroscience Governance

Management team

Arjen Brussaard (director)	Amsterdam UMC – location VUmc
Diederik van de Beek (co-director)	Amsterdam UMC – location AMC
Susanne la Fleur	Amsterdam UMC – location AMC
Paul Lucassen	University of Amsterdam
Brenda Penninx	Amsterdam UMC – location VUmc
Yolande Pijnenburg	Amsterdam UMC – location VUmc
Guus Smit	Vrije Universiteit Amsterdam
Taco de Vries	Amsterdam UMC – location VUmc
Guido van Wingen	Amsterdam UMC – location AMC

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Liesbeth Reneman	Amsterdam UMC – location AMC
Huibert Mansvelder	Vrije Universiteit Amsterdam
Helmut Kessels	University of Amsterdam
Matthijs Verhage	Vrije Universiteit Amsterdam
Susanne la Fleur	Amsterdam UMC – location AMC
Danielle Posthuma	Vrije Universiteit Amsterdam
Frank Jacobs	University of Amsterdam
Wiesje van der Flier	Amsterdam UMC – location VUmc
Rob de Bie	Amsterdam UMC – location AMC
Joep Killestein	Amsterdam UMC – location VUmc
Matthijs Brouwer	Amsterdam UMC – location AMC
Peter Vandertop	Amsterdam UMC – location VUmc
Jonathan Coutinho	Amsterdam UMC – location AMC
Odile van den Heuvel	Amsterdam UMC – location VUmc
Judy Luigjes	Amsterdam UMC – location AMC
Sabine Spijker	Vrije Universiteit Amsterdam
Christiaan Vinkers	Amsterdam UMC – location VUmc

Two Sides to One Story

Neuroscientist Hanneke Hulst and neurologist Brigit de Jong bring the worlds of scientific research and clinical patient care together in a bid to find out more about cognitive impairment in people with multiple sclerosis. And with their unique expertise center for cognition at the MS Center Amsterdam, they have introduced a multidisciplinary approach that is of value to patients and the medical world alike.

Hanneke Hulst
- Assistant Professor at the Department of Anatomy and Neuroscience, Amsterdam UMC – location VUmc, MS Center Amsterdam

Brigit de Jong
- Neurologist at the Department of Neurology, Amsterdam UMC – location VUmc, MS Center Amsterdam

Hanneke Hulst and Brigit de Jong work together at the MS Center Amsterdam on cognitive impairment in people with multiple sclerosis (MS). As a neuroscientist and neurologist (respectively), they want to understand the underlying biological mechanisms of cognitive decline and emphasize the importance of paying attention to cognitive deficits in MS patient care. Both are investigating novel interventions to improve cognitive functioning and the quality of life of patients suffering from this debilitating symptom. They are a dedicated and enthusiastic couple who have a solid understanding of how you can combine scientific research and patient care in one multidisciplinary team.

When Hulst and De Jong describe their days at Amsterdam UMC it becomes clear that they work together intensively. On a daily basis, before COVID-19, Hulst's pedometer tracked around 7,000 steps, which illustrates just how much she was on the move between buildings, from her office in the O2 building to the outpatient clinic, the hospital and medical faculty. "Meetings with colleagues, brainstorms about new research projects, teaching, or working together with clinicians such as Brigit: it is never boring, interacting with so many different disciplines and trying to speak the same language," she says. And De Jong can also be found in many departments: "Neurology, rehabilitation, or giving lectures in the medical faculty... I regularly bump into Hanneke in many of these places."

De Jong and Hulst have joined forces on numerous different projects, in both a scientific and clinical context. “All our joint projects focus (in)directly on MS and cognition,” explains Hulst. “Cognitive decline is just one of the symptoms of MS, affecting up to 70% of the (young) people with MS. But in my opinion, it’s among the most debilitating complaints – just imagine the impact cognitive deficits would have on yourself, your work, family and friends. Therefore, we need to gain a better understanding of why some MS sufferers develop cognitive decline, while others do not. What is the role of neurodegeneration and the brain’s structural and functional network functioning in cognitive performance of patients with MS? We are continuously trying to translate observations in the clinical setting (i.e. the patient) to research, and vice versa, for example by using innovative outcomes in a clinical setting. An excellent example of this crossing of disciplines – where scientific research and clinical care are continuously interacting – is our Second Opinion MS and Cognition (SOMSCOG) outpatient clinic, of which we are incredibly proud. It was initially established by Bernard Uitdehaag and Jeroen Geurts in 2015, after which Brigit and I developed it into its current form. Several other departments are involved in the SOMSCOG, including neurophysiology, clinical chemistry, radiology, neuropsychology, ophthalmology and rehabilitation medicine, so it’s the perfect exemplification of team science.”

“With the SOMSCOG clinic we want to provide people with MS who are experiencing cognitive decline the best possible care and support. We do so by combining research and care under one roof, which is unique as you won’t find this anywhere else in the world,” De Jong explains proudly. “People from all over the country who suffer from MS and cognitive complaints are welcome at SOMSCOG for a screening day. The patient will receive questionnaires that they need to complete in advance to help identify factors – such as fatigue, depression and anxiety – that might be associated with their perceived cognitive problems. On the day of their visit to the MS Center we carry out all several examinations, including extensive neuropsychological screening, structural and functional MRI of the brain, magnetoencephalography (MEG), optical coherence tomography, blood tests, a lumbar puncture and a neurological examination. A week later, all the different disciplines involved in SOMSCOG meet to discuss and integrate the patient’s examination results. We aim to answer questions such as: ‘Why is this person experiencing cognitive decline?’ ‘Can the complaints be objectified or are there other factors involved?’ and, most importantly, ‘What does this patient need in order to feel better?’. Our ultimate goal is to provide each individual patient with their own personalised (treatment) advice.”

“As a neuroscientist, it is not that common to be actively involved in such multidisciplinary patient meetings, but at the SOMSCOG clinic we deliberately choose to do so,” Hulst continues. “The real-life examples from the clinical cases are inspiring; they help us enrich our scientific research and formulate relevant research questions as the results can sometimes point us in a direction that we would not have even imagined or considered as a scientist. And vice versa, we are able to use new markers from scientific research in the clinical evaluation. We’ve already seen nearly 150 people and accumulated a lot of new ideas and research questions. The first multidisciplinary papers are currently being written and we recently submitted a joint research proposal.”

Hulst emphasizes that starting an expertise center for cognition was a brave thing to undertake. “We are investing a lot of time in something we believe in, something that we are convinced to be of benefit to the patients,” she explains. “By just getting started we hope to obtain structural funding for projects such as SOMSCOG. It is now up to us to convince health insurance companies that our multidisciplinary approach is of value for the patient’s quality of life and functioning in daily life.” “We’ve noticed that the people visiting us are grateful that we took the time to listen and that their complaints were taken seriously,” De Jong adds.

“Working closely together with Brigit and other colleagues involved in SOMSCOG really enriches my view on the problems we are facing,” says Hulst. “We work as one team, with a clear mission: To provide the MS patient with the best cognitive care. This joint mission makes me feel valued as a researcher.” De Jong agrees: “After each team meeting, I feel fully energised and eager to continue what we are doing. It is a great synergy.”

Two Minds Think Alike

When it comes to effectively applying endovascular treatment for a stroke, time is of the essence. And with just a few hospitals capable of performing it, ambulance staff need to know immediately where to take their patients. Thanks to neurologist Jonathan Coutinho and technical physician Wouter Potters, a new simple device can now help the paramedics make that life-saving call.

“For years there was no acute treatment for people suffering a stroke,” says neurologist Jonathan Coutinho. “However, during the nineties this changed with the rise of thrombolytic therapy. This treatment uses clot-busting drugs to help dissolve blood clots that cause early acute ischemic stroke. In 2015, an enormous breakthrough – in which the MR CLEAN trial and the work of, among others, Professor Yvo Roos of location AMC was of great importance – was added to the list of treatments for patients with large vessel occlusion [LVO] strokes. The new endovascular treatment [EVT] turned out to be highly effective, but only if applied in a timely manner. Due to the complexity and need of specific knowledge and tools, only a minority of hospitals are capable of performing this EVT, where a catheter is inserted via a groin puncture to remove the blood clot.”

Coutinho and Wouter Potters started their working careers on the staff of the neurology department at location AMC in 2015 and 2016 respectively. And it is here that Coutinho experienced this period in which the EVT treatment became more and more advanced. “It was a revolution,” he says, “but it also introduced a problem since half of EVT-eligible stroke patients are initially admitted by ambulance paramedics to hospitals that do not provide this therapy. On average, this delays the initiation of treatment by about one hour, which substantially decreases the patient’s chances of a successful clinical recovery. This led to the question: What’s the quickest way we can we bring those patients in need of EVT (which amounts to around 10-20% of all patients with a stroke) to a hospital providing EVT? For that, we need reliable prehospital screening methods to identify stroke patients eligible for EVT in the ambulance. After a while I considered the potential of electroencephalography (EEG), which brought me to Wouter and his expertise in intraoperative neuromonitoring. We already knew each other, but had not collaborated together yet.”

Potters, who works as a technical physician and combines clinical tasks and research, is an expert in the field of EEG and gets his motivation from innovating healthcare and improving processes in the hospital with technology. “EEG has become an important, non-invasive and easy-to-use neuroimaging technique. When oxygen supplies drop, the EEG signals of the brain immediately change, which makes it straightforward to measure. At the time Jonathan contacted me, I had just learned about dry electrodes. Normally, EEG preparation takes around fifteen minutes, but these dry electrodes drastically reduce the time of the montage and the measurement to less than five minutes. When we combined the new development of the dry electrode EEG-cap with the diagnostic potential, we had the bright idea of studying EEG as a suitable tool for prehospital stroke screening.”

In October 2018, Coutinho and Potters started their close collaboration with a study called ELECTRA-STROKE. Thanks to a crowdfunding innovation grant from Dutch Heart Foundation, as well as having won the 2018 Amsterdam Science & Innovation Award, they had enough of a budget to start developing and testing the prototype. “Endlessly trying to perfect it,” Coutinho says. “We also spoke multiple times with the ambulance paramedics who can be seen as the end-user of our product. Which criteria should be met? How can we contain good test characteristics in a small, quick and easy-to-use product?” Potters adds: “In that time, we kicked off with testing the dry electrode EEG-caps on healthy subjects, followed by patients at the brain care unit, and then acute stroke patients at the emergency department of location AMC. This all resulted in the product we have today: a small, portable suitcase that can directly be used by the ambulance paramedics at the patient’s home or in the ambulance. What’s more, all the data that is collected with the EEG-cap is sent over a secure connection to Amsterdam UMC and is no longer stored in the ambulance, which is important from a privacy perspective.”

It 's great example of a collaboration, not only by Coutinho and Potters, but also between the researchers, clinicians and ambulance paramedics. Coutinho wants to highlight the enthusiasm of Ambulance Amsterdam. “The ambulance teams made

Wouter Potters
- Technical Physician at the Department of Neurology and Clinical Neurophysiology, Amsterdam UMC – location AMC

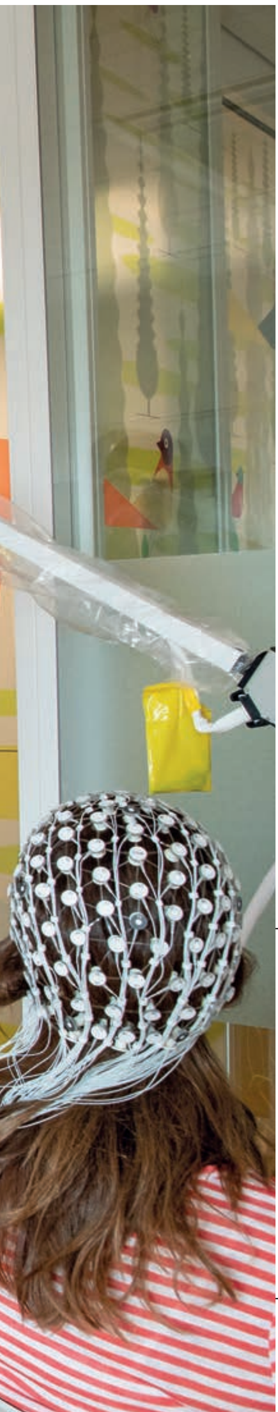
Jonathan Coutinho
- Neurologist at the Department of Neurology and member of the Neurovascular Disorders group, Amsterdam UMC – location AMC
- Research program leader of Neurovascular Disorder, Amsterdam Neuroscience

it clear from the start: ‘Don’t turn us into neurologists, keep it simple.’ After a year and a half of testing and modulating, training the paramedics, and having to deal with the COVID-19 pandemic too, the first six ambulances have now started the data collection for our study in Amsterdam.” In the forthcoming year around 220 suspected stroke patients will be included with the goal of developing an EEG algorithm for LVO strokes. “With the subsidy of Health~Holland, and the partnership with Nico.lab and ANT Neuro, we will develop an artificial intelligence decision support system,” Potters explains. “We need lots of data to develop our perfect algorithm; one that is reliable to autonomously give a decision on which stroke patients should be treated in which hospital.” “We first have to see the results,” Coutinho adds in a pragmatic way. “The proof of the pudding is in the eating.”

The two researchers say they will continue their collaboration over the following years with pleasure. “I think we complement each other well,” says Coutinho. “From our first meeting I noticed that Wouter is specialized in the technology and data part, something I do not know much about and have subsequently learnt from him.” On his part Potters is proud of the final product and how Coutinho manages the contact-side of things with the clinicians and paramedics. “We both have our own specialization, which helps us to accelerate and move forward with a product of service that suits the ambulance staff and improves the acute treatment of people suffering a stroke.”

A Unique Perspective

For every patient child psychiatrist Hilgo Bruining and his team see, they try to establish what specific problems he or she faces and how they might be able to bring relief. Stepping away from the standard practices of diagnosis and protocol, they are at the forefront of precision psychiatry. To get this transition going, the team relies on a wealth of science and expertise.



"Max is a really good kid!" says nurse specialist Cathalijn Gerver as she talks affectionately about a boy with blond curls and a broad smile who she and her team have been treating for the past year and a half. Max was not doing well when Gerver first met him. He is very sensitive, his mother explained in an interview filmed by Gerver's colleagues. He is acutely aware of everything that is happening around him and he wants to respond to it. It causes aggravation. He has temper tantrums and is often exhausted. His previous doctors diagnosed him as autistic, and so he received stimulant medication, was looked after by the neighbourhood care team, and received counseling from the remedial teacher at school. Additionally, his mother received psychoeducation about autism on how to interact with her son, but none of this brought any solace.

Currently, registered treatments suppress symptoms rather than target underlying mechanisms. Long-term effects are uncertain and they often cause serious side effects.

Now Max is a patient of child psychiatrist Hilgo Bruining and his team at VKC (Vrouw Kind Centrum) of the Emma Children's Hospital, Amsterdam UMC. For them, the question is not what diagnosis Max should be given and which medication does the protocol prescribe, but rather: What difficulties does Max face? What is going awry in his brain? And how might we be able to help him with a personalized intervention?

After assessing Max, the team concluded that 'autism' does not accurately describe what he is dealing with. "We think putting this severe psychiatric label on such a relatively healthy kid is not helpful," Bruining remarks. Instead, the team suspects that Max processes sensory information differently than other children do. They switched his medication to bumetanide, which is commonly used as a diuretic but can also influence the neural processing of stimuli. "The change that followed is hard to put into words," Max' mother recalls. "It felt like I had an entirely new child at home. He was much more relaxed, he understood if I explained something to him. It was as if we were on the same wavelength for the very first time."

Bruining and his team help Max and many other children with severe developmental

CV Hilgo Bruining

2019-current	Associate Professor, Department of Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam UMC/Levvel – location AMC
2018- 2019	Associate Professor, Department of Psychiatry, UMC Utrecht Brain Center
2014- 2018	Assistant Professor, PI of the Sensory Processing Program, UMC Utrecht Brain Center
2011	PhD, "Genetic dissection of behavioral phenotypes. Lost and found in translation", UMC Utrecht
2000-2010	Clinical specialty training in pediatrics and child psychiatry, UMC Utrecht and Amsterdam UMC – location AMC

problems by applying a radically new approach to psychiatric treatment and research that puts them at the forefront of the development of precision psychiatry. Rather than starting with a diagnosis, such as autism or ADHD, and following the associated protocol – as is standard practice in psychiatry – they try to understand the specific problem of every child that visits them. In order to do so, they integrate a lot of information regarding neural and cognitive functioning, medical and family history, genetic mutations, perinatal events such as a preterm birth, and previous responses to medication in order to determine the most promising treatment for the child.

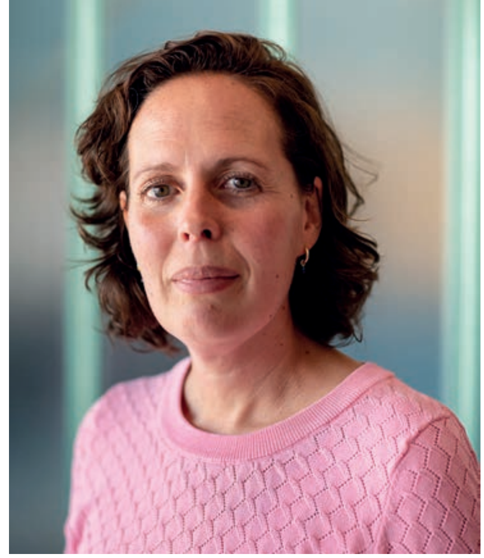
After arriving at an appropriate intervention, the team keeps a close eye on how the child is doing. In this subsequent monitoring and evaluation, they use an entirely different statistical method to determine effectiveness of treatment. And their efforts have not gone unnoticed. In 2018 Bruining and his team received a large consortium grant from the Dutch Research Council (NWO) to further develop their approach to precision psychiatry.

The motivation for these efforts is the frustrating lack of therapeutic success in psychiatry, explains Matthijs Verhage, professor in functional genomics and a collaborator on the project. Currently, registered treatments suppress symptoms rather than target underlying mechanisms. Long-term effects are uncertain and they often cause serious side effects. Novel treatment options are tested in conventional randomized controlled trials whereby a certain medication is compared to a placebo in a large group of patients with a particular diagnosis. "But within that group of patients there is probably such heterogeneity in underlying pathology that on average the new drug does not seem effective," Verhage explains. Both he and Bruining suspect that this average negative result obscures a possible positive effect in a subgroup of people who actually do benefit from the medication. "So within this average, we are trying to distinguish what type of medication might be beneficial for a specific child," Verhage says.

Turning the entire psychiatric approach upside down in a responsible manner is something that, not surprisingly, involves an unbelievable amount of work. Behind every aspect of their approach to precision psychiatry lies a wealth of expertise and science. "We don't just work as a team of doctors, nurses, psychologists and occupational therapists; we also strive to constantly embed scientific innovations such as the improved EEG analyses and decision support systems of Klaus Linkenkaer-Hansen and his group into our practices," says Bruining.

"The professionals taking care of our kids lean on the research of many others. Once a month everyone gets together, and the clinicians and scientists interact to cross barriers in their language and align their expertise to improve the outcomes for individual patients. For instance, we discuss stem-cell techniques to grow brain cells of known patients, but also novel ways to monitor patient-relevant symptoms in everyday life. These meetings fuel the team science spirit and create focus for everyone's expertise."





For many of the children Bruining and his team see, the problems are related to disturbances in the ability to select and process sounds, images and social and learning stimuli. But the way in which this system is affected differs from one child to the next. The network may be overactive, it may not be responsive enough, or it may exhibit other deviations.

Many of the research questions underpinning the clinical approach focus on the neural systems for processing stimuli. For example: Which aspects from electroencephalogram (EEG) signals are most informative for determining possible disturbances in the balance between excitatory and inhibitory neural inputs? How can we use this information together with other sources to predict the most suitable treatment? Other relevant research questions include: Which registered medication influences which aspect of stimulus processing and might be beneficial to specific patients? And how can we measure cognitive functioning in an integrated manner that is also pleasant for the child? Can we build a self-learning model that can predict the most promising treatment based on all available information?

In tackling these questions, the synergy between clinicians and scientists in Bruining's, Verhage's and Linkenkaer-Hansen's groups offer a beacon of hope for children who often spend years going from one specialist to another looking for help. "This is such a shame," Gerver says. "These are precious years in childhood where our kids do not get the chance to learn and develop to the best of their potential. Many of our patients are not welcome in schools, not even in special education, because they are considered too difficult. They spend their days at home. It's frustrating for them and places a heavy burden on the parents."

Since joining Bruining's team, Gerver has overseen the intake of about 400 patients with autism or ADHD. "No two are the same," she says. "Child psychiatrists have to give a certain diagnosis because that is standard practice and is necessary when it comes to getting the treatment paid for by insurance companies, but that diagnosis does not say much about the child." Bruining adds: "Current neurodevelopmental diagnoses are not well substantiated, neither in the way the disorder manifests itself nor in the underlying mechanisms."

In order to illustrate the diversity of behaviors falling within the same diagnostic categories, the team describes Mia, a 16-year-old girl who has been with them for several years and, like Max, was 'labeled' as autistic. Whereas Max could have animated conversations while making eye contact, gesturing and producing facial expressions, Mia was withdrawn. She sat hunched over and did not look at Gerver. Mia suffered from severe anxiety and would not speak a word, a rare phenomenon called selective mutism. "We could not interact with her at all," Gerver recalls. "All communication went through her parents." Furthermore, Mia was often exhausted, had a limited attention span and memory function, and a history of epileptic seizures.

The team compiled all their information about Mia in an overview, referred to as 'the dashboard', and got together to weigh in on the results. PhD student and medical doctor Lisa Geertjens explained how Mia performed on the tests for attention and memory. Postdoc Jennifer Ramautar, who coordinates the clinical EEG lab, had measured Mia's EEG and described how this can be interpreted for clinical decision-making. Furthermore, the team discussed Mia's two notable genetic aberrations on the dashboard: one of these resulted in an extra X-chromosome; the other caused a disturbance in the sodium channels of her neurons.

As a first step, they critically evaluated the anti-epileptic drug Mia had been taking for years. "Children are often kept on medication and it remains crucial to keep asking whether it is still necessary," Bruining remarks. Mia stopped taking the pills and her energy levels rose. In addition, the team decided on treatment against anxiety. "From previous research, we know that people with this genetic mutation on the X-chromosome generally respond well to anxiety medication that inhibits the reuptake of the neurotransmitter serotonin." Along with the medication, Mia started cognitive behavioural therapy to help her critically evaluate the anxious thoughts she was having.

The team was surprised when Mia came in for a follow-up study. "Cathalijn [Gerver] had warned me that it might be difficult to perform the EEG follow-up on Mia because of her fear," Geertjens says, smiling. "But we had no problem whatsoever; she cooperated and it went just fine." Even more surprising, Gerver adds, is that, "She spoke! We could talk about the examination taking place. She admitted that she indeed found it a bit frightening. I was amazed at the fact that she could voice that emotion, she had gone through an enormous transformation."

The next step in Mia's treatment is to see whether the team can adjust the way she processes sensory input, which might help reduce her sensitivity to stimuli and enhance her ability for memory and learning. "Based on animal models, we know bumetanide can help restore the neural balance between excitatory and inhibitory signals when this mutation in sodium channels is at play," Bruining explains.

The team will closely monitor Mia's response to the new treatment. They use information from their previous group trials to estimate treatment success in individual cases with the help from the statistical expertise of postdoc Bas Stunnenberg. In the team's novel analytical approach, called an 'N-of-1-trial', Mia and Max will form their own little sample. "In short, the patient is its own control, meaning that repeated measurements of different treatment and placebo blocks are compared within the same patient," Bruining explains. Throughout the process the team keeps track of developments the patient finds important. For example, for Mia tolerating noise in the classroom is crucial as well as being able to get on the school bus. "Only when we listen to the patient and the parents, measure the outcomes that are most significant to them and relate these to mechanistic readouts, can we truly establish success for a potential treatment," says Bruining.

Currently, Bruining, Gerver, Ramautar and Geertjens discuss the dashboards of each of their patients in order to arrive at the treatment option they deem most promising. Part of this information integration will be outsourced to a learning algorithm. That way, they are no longer tied to the boundaries of human capacity to assess information and relate it to relevant prior data, so treatment decisions can be based on many more variables than a single group of experts can oversee.

In the near future, their approach to precision psychiatry will be expanded even further. "Ideally we would take some brain tissue to study what brain cells are doing and how they respond to certain treatment," says Bruining. But the human

> The synergy between clinicians and scientists in Bruining's, Verhage's and Linkenkaer-Hansen's groups offer a beacon of hope for children who often spend years going from one specialist to another looking for help.

body found a way to protect this precious organ with a thick layer of bone, so that is not an option. Instead, both Mia and Max have allowed the team to collect a little bit of their skin tissue. These skin cells are brought to Verhage's lab, where he and his technicians perform a trick that almost seems like magic: they turn the skin cells back into stem cells and then have these develop into little networks of brain cells.

For each patient, Verhage ends up with a large array of networks of brain cells in a petri dish. Using this unique network, containing the specific genetic blueprint of the child, Verhage and his colleagues measure as many variables as they can. How the neurons communicate with one another, which genes are expressed, which proteins are present and how stable the network is; how much input it takes before the network gets overstimulated.

Furthermore, the team can test bumetanide and other registered medications that act on the balance of excitation and inhibition on these little networks. How do the synaptic components in brain cells of this specific child respond to the drug? "Based on those measurements, we can let Hilgo know which medications might be beneficial for that specific patient," Verhage explains. He expects to be able to give the first recommendations based on these analyses later this year. "And at a later stage, we can even use this approach to develop new medication in specific subgroups of patients."

But even in the current, preliminary form, patients already benefit from Bruining's precision psychiatry approach. "It is not perfect yet," he says. "But both children and parents feel a shift in dynamics. They sense that we take their problems seriously and they feel involved with the study. I have patients who travel all the way from Groningen to take part in the study and receive treatment because we provide them with a perspective they do not experience anywhere else."

Two are Better than One

Experienced researcher Wiesje van der Flier and postdoc researcher Ingrid van Maurik work closely together on research projects to further develop and validate the individualized risk-prediction modelling of Alzheimer's. What's more, they also share their knowledge and research method with other departments so that it can be adopted and applied in other disease fields.

Alzheimer Center Amsterdam, which celebrates its 20th anniversary this year, has countless team science stories to its name. "Collaboration is what makes our work so enjoyable," says Wiesje van der Flier, who has been associated with the Alzheimer Center for more than 15 years. "We have approximately a hundred people working together in our center, with different backgrounds in, for instance, patient care, research and fundraising, among others. This is team science par excellence."

Ingrid van Maurik was recently awarded her doctoral degree (cum laude), with Van der Flier acting as her promoter for her work on the Alzheimer's Biomarkers in Daily Practice (ABIDE) project. She is currently working as a postdoc on the European follow-up, called the Alzheimer's Disease Data Driven Insights on Individual Outcomes (ADDITION) project. Van Maurik and Van der Flier work closely together on these research projects, and this is illustrated by their shared drive. "The ABIDE project was originally designed to translate diagnostic tests in Alzheimer's disease (AD) and their related biomarkers' values to daily practice in local memory clinics," says Van Maurik. "We initially intended to translate the scientific knowledge on biomarkers to local memory clinics," adds Van der Flier, "but it soon became clear that our results were also of interest to numerous academic memory clinics in other European countries. To support clinicians the world over, we developed the ADappt tool that can be used by professionals to interpret and discuss AD diagnostics test results with their patients and caregivers. It functions as a conversation starter and decision-making tool."

What's really noteworthy, as Van der Flier explains, is that "the breakthrough with the ABIDE project is that biomarker-based risk prediction models allow the application of biomarker-knowledge on an individual patient level. This is an unprecedented step in the AD field." The collaboration in the ABIDE project did not go unnoticed, and ZonMw rewarded the team with the prestigious ZonMw Pearl in 2019 for their work. "Patients were already willing to take part when the project was still on the drawing board. They wanted to help us develop something they find really useful," says Van Maurik. "Working closely together with the patients feels natural to us." "And it is necessary," adds Van der Flier. "AD is such a large healthcare problem in our society, and we cannot get to the bottom of it alone. No one single discipline, department, university, company or research group will solve it. We all need each other."

Gaining new knowledge and sharing best practices does not stop at the boundaries of disease indications such as AD. Each week, Van Maurik shares her insights with colleagues in the decision modelling center at Amsterdam UMC's Department of Epidemiology and Data Science. With a combined position at both departments (i.e. Neurology, and Epidemiology and Data Science), she knows how team science can promote cross-fertilisation. "The ABIDE research method is now adopted, and being applied in, other disease fields." Van der Flier underlines the positive aspects of Van Maurik's combined position: "Flexible working, literally working at multiple desks, is the only way to bridge the gap between departments," she says.

Working in teams feels natural in research, and is part of their culture for Van Maurik and Van der Flier. It has also acted as a catalyst for new research. "During my PhD, Wiesje opened doors for me and created multiple opportunities, which helped me to obtain two new grants for the future, one of which is for our current ADDITION project," says Van Maurik. "In this European project, we aim to further develop and validate the individualised risk-prediction modelling. We want to improve prognoses by developing individualised predictions of outcomes that matter to patients, such as quality of life, institutionalisation or remaining independent. With the results, we hope to provide clinicians with tools to better answer the question all patients ask: 'Doctor, what can I expect?'."

"The aim of all our projects is a future where clinical intervention in patients really works for the individual patient;

Ingrid van Maurik

- Postdoctoral Researcher at the Alzheimer Center Amsterdam
- Postdoctoral Researcher at the Department of Neurology and Department of Epidemiology and Data Science, Amsterdam UMC – location VUmc

Wiesje van der Flier

- Head of Clinical Research at Alzheimer Center Amsterdam
- Professor at the Department of Neurology and Department of Epidemiology and Data Science, Amsterdam UMC – location VUmc
- Research program leader of Neurodegeneration, Amsterdam Neuroscience

a treatment that is tailor-made," says Van der Flier. "This is a fantastic time to work in AD research, particularly in a wonderful team like ours, and with international collaboration. It is our joint responsibility to explore the brain on the individual level, with the ultimate aim to translate this into personalised prevention."

POLAR Project

Not only does COVID-19 pose us with a huge healthcare problem, it also confronts us with large societal challenges. People with cognitive decline and dementia are hit twice as hard. Firstly, as a vulnerable population, they are at increased risk of getting severely ill from the disease. Secondly, they are hit hard by the COVID-19-related rules and regulations. There is a great deal of coverage in the news regarding nursing homes and their inhabitants, yet the majority of people with cognitive impairment and dementia live in their own homes.

Our new POLAR project aims to boost resilience in people with Alzheimer's disease and other types of dementia against the consequences of COVID-19 regulations. Specific objectives are (i) to map out the effects on behavior and mood, daily functioning, the burdens on relatives/caregivers and utilization of care, thereby identifying the most vulnerable subgroups, and (ii) to develop applicable information products about (dealing with the consequences of) COVID-19 regulations, with the goal of contributing to a resilient and dementia-friendly society, both during and after COVID-19.

POLAR is a joint initiative of Alzheimer Nederland, Pharos and Alzheimer Center Amsterdam.

An Entrepreneurial Pair

In 2017, Dr. Lars van der Heide and professor dr. Marten Smidt decided to challenge themselves further by entering the world of business when they started up their own company in a bid to secure funding for future research and get their scientific knowledge out into the market.

Lars van der Heide and Marten Smidt seem to embody the knowledge triangle. Both are active in the field of education, research and innovation. During their collaboration, which started around 2002, Van der Heide and Smidt have learnt a lot about research, funding and entrepreneurship.

"I already knew Lars from his PhD time at UMC Utrecht when he was working on insulin signalling in the central nervous system and its regulation of forkhead box transcription factors," says Smidt when he starts talking about their collaboration, to which Van der Heide adds: "I had a particular interest in signal transduction, so after my PhD I switched to cancer research to gain more knowledge about signalling in tumour cells. For several years I focused on the pathways that control cell death and survival."

"During that time, we kept in touch every now and then," says Smidt. "I had just started at the University of Amsterdam (UvA) as head of the Department of

Lars van der Heide
- Assistant Professor, University of Amsterdam
- Program Director of the Biomedical Sciences: Neurobiology Master's Program, University of Amsterdam
- Founder and CEO, Macrobian Biotech

Marten Smidt
- Professor Molecular Neurosciences, University of Amsterdam
- Director of Swammerdam Institute for Life Sciences
- Founder and CEO, Macrobian Biotech

Molecular Neuroscience and wanted to work out the dopamine system. Lars was a signalling expert and I thought that it would be of great relevance to study that in the dopamine system, particularly in relation to Parkinson's disease (PD). So, I asked him to join our team as a signal transduction expert. Which seemed to be a complementary fit."

"Since PD patients progressively lose dopamine neurons, we initially focused on the mechanisms that keep these neurons alive. Complementary to this we also identified a mechanism that enables these neurons to produce more dopamine," Van der Heide explains. "As the latter mechanism seemed more suitable for a possible future clinical approach but funding via the established agencies seemed improbable, we decided to start our own spin-off company. We attended an entrepreneurship bootcamp organized by the Amsterdam Center for Entrepreneurship (ACE) Incubator. At first, Marten and I repeatedly questioned ourselves and what we were doing. After all, we were researchers who were entering a new world of science and business; it was a whole different ball game. But by the end we saw the opportunities of combining excellent science with the world of business. With the support of UvA's Faculty of Science, UvA Ventures Holding B.V., and Innovation Exchange Amsterdam, we founded our company Macrobian Biotech in 2017."

"The essential part in our business development was that we did the bootcamp together, as a team," Smidt explains. "In the beginning, colleagues were skeptical of us starting this company, but we were determined to continue our journey and secure more funding for our research projects. At the start we received some proof-of-concept funding and a valorisation fund from our faculty." "That helped us to hire some residents. And with support from the Dorpmans-Wigmans foundation we were able to purchase some lab equipment," says Van der Heide. "And since we are located at Amsterdam Science Park, our equipment is available to others as well," adds Smidt.

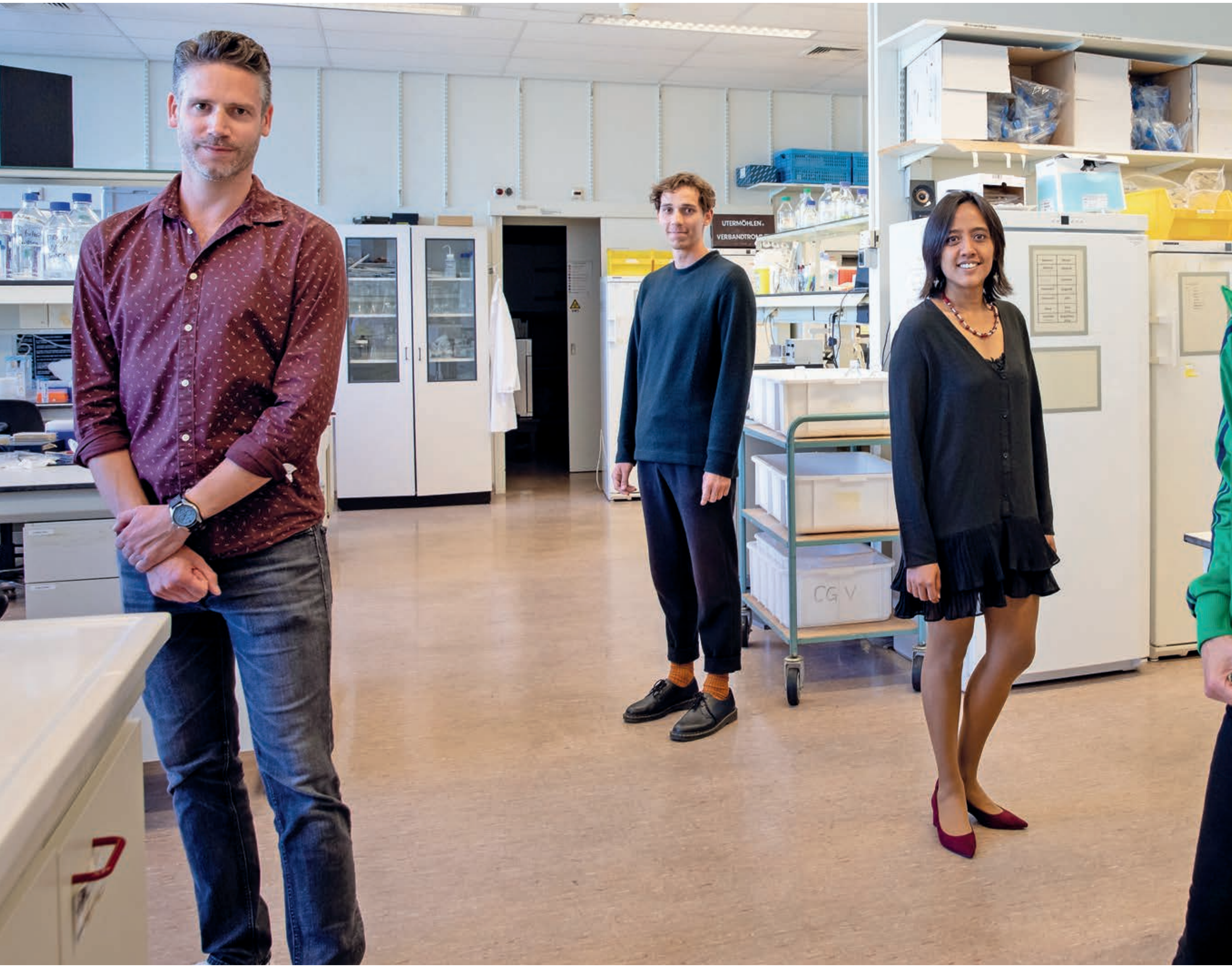
Van der Heide proudly elaborates on their work and the mechanism that may allow dopamine neurons to produce more dopamine. "First we characterized the molecular components in dopamine cells and identified novel compounds that are able to modulate this dopamine production mechanism specifically in mice midbrain dopamine neurons and other ex vivo models. The next step is to investigate the efficacy of these novel compounds in a PD mouse model." Smidt adds: "We hope to get solid proof-of-concept in an animal model within two years." Both men emphasize the potential of their inventions for PD patients. "It would be incredible to boost the quality of life of patients suffering from PD," Van der Heide says.

Via the Amsterdam Neuroscience network, Van der Heide and Smidt maintain contact with the clinicians of Amsterdam UMC. "It is good to focus on the clinical and human aspect, since we work on the rather fundamental part of a potential therapy," Smidt says. "Eventually we want to translate it from the animal model to humans. The more we know about the cellular and molecular components, the better we can understand the disease. During our search we also found interesting, unexpected differences between mouse and human tissue. Translation, especially in neuroscience, is not easy. Sometimes you just need to figure out things that are not that impactful in science and will not be of interest for high-impact journals. That causes issues when it comes to getting funding for your research, even in the Netherlands. But we hope that, with Macrobian Biotech, we will get that support from investors in the long run.

"After three years it is still an amazing learning experience. Working together with a partner like Lars is definitely of extra value. Close collaboration like this prevents you from having complete tunnel vision in your work and keeps you alert," Smidt continues. "Since we are both the founders and CEOs of Macrobian Biotech, we always enter a business meeting with two pairs of eyes and consequently we take every important decision together, as a team. Starting up our company has been an extraordinary experience and something we both value and explicitly take with us in our educational activities and implicitly in our academic research within the Swammerdam Institute for Life Sciences."

A Gift of a Job

For Danielle Posthuma, team science is not merely a buzz concept, but an approach demanded by the complexity of life in all its variations. A Gravitation grant from the Ministry of Education, Culture and Science allows her to use that insight to guide a diverse group of scientists through a 10-year-long research project.



CV Danielle Posthuma

2016 – present	Full Professor, University Research Chair, Amsterdam UMC – location VUmc
2011 – present	Full Professor, Vrije Universiteit Amsterdam
2011 – 2014	Visiting Associate Professor Erasmus University Rotterdam
2010 – 2015	Associate Professor, Amsterdam UMC – location VUmc
2006 – 2010	Associate Professor, Vrije Universiteit Amsterdam
2003 – 2006	Assistant Professor, Vrije Universiteit Amsterdam
1996 – 2003	PhD and Postdoc, Vrije Universiteit Amsterdam

Thinking back to one of the most exciting moments in her scientific career, Danielle Posthuma remembers how it felt like Christmas Eve. It was about 13 years ago; research with twins had shown that the risk of depression is largely hereditary, and the department where trained psychologist Posthuma worked had gone through the immense task of overseeing a study of 6,000 people with a promising new genetic approach. They tested thousands of locations in the genetic code for associations with the disorder. Posthuma was part of the team who got to analyze the data and would have the first insight into the genes responsible for the disorder that troubles so many people worldwide. Or at least, that's what they thought.

"It took some time to process the data so it could be properly analyzed," Posthuma recalls. "I felt so excited, so optimistic." But once she had the results, the excitement evaporated. "We found no significant associations, it was so disappointing." Perhaps they had made a mistake somewhere along the way, Posthuma and her colleagues thought. But soon after, several similar studies into other mental disorders were published, which also did not identify specific genes at play.

Luckily, the scientific field proved resilient and researchers began working together to rise to the challenge of understanding the complexity of genetic processes involved in psychological vulnerability. Now a professor in Complex Trait Genetics at the Vrije Universiteit Amsterdam, Posthuma is the leading researcher of the BRAINSCAPES consortium, a 10-year project where 21 scientists from different backgrounds combine their expertise. "Suffering from depression, an eating disorder or schizophrenia is so disruptive, it overshadows everything in a person's life," says Posthuma. "As scientists we can contribute to understanding what is happening in the brain, and I hope that by doing so we can help alleviate the suffering."

After the lack of anticipated breakthroughs in the first wave of genome-wide association studies for mental suffering, it did not take long for geneticists to realize what the issue was. Rather than one or a few aberrant genes causing mental disorders, it turns out that thousands of genes are at play in psychological vulnerability. In order to identify them, the research needs to take place on an entirely different scale. Rather than comparing 3,000 patients with 3,000 control subjects, as in Posthuma's first attempt, geneticists are working together across continents to ramp up the volume to an astounding one million patients and a similar number of controls.

"I still wake up in awe of the speed at which this progress in the genetic field is taking place. From determining the relative contribution of genes and environment to specific traits, to studying the effects of a specific gene on the organism, to the sheer scale of the current projects." These collaborations have resulted in the identification of thousands of genes implicated in the risk for various mental disorders.

BRAINSCAPES brings about a familiar sense of anticipation for Posthuma about discoveries to be made in the next step: identifying what these genes do in the body to contribute to the development of psychological suffering. For this, she got together with other geneticists, as well as bioinformaticists and neurobiologists, to come up with an intricate blueprint for BRAINSCAPES.

> "I still wake up in awe of the speed at which this progress in the genetic field is taking place."

First, Posthuma and her colleagues will compare the relative importance of the thousands of genes associated with a risk for brain disorders to gene expression patterns across different cell types. If a particularly influential set of genes is specifically expressed in a certain type of neuron or glial cell, that cell might be implicated in the disorder. The team will validate these leads by checking post-mortem brain tissue of patients and controls for abnormalities in the identified cell type. If validated, they will try to unravel the function of these cell types and their circuitries by selectively disrupting them in 'healthy' animals, as well as in animal models for addiction and mood- or eating disorders, in order to study the behavioral and neurological consequences.

At the end of this project, they plan to translate their findings to research in collaboration with the pharmaceutical industry. As Posthuma explains: "It would be a shame if our findings do not result in something that is useful for patients."

Posthuma says that the nature of teamwork has changed quite a lot since the time that she started working in academia. "As geneticists, we were confronted with the fact that we could not gain the understanding we desired if we did not work together and share our data," she explains. "Some scientists who had invested a lot of time in gathering data from their patients may have been reluctant to share these precious datasets at first, but they soon realized that only if we collaborate and share can we gain insight into the genetic causes of brain disorders. For the new generation of geneticists, team science, open science and data sharing is the norm; that is very promising for the future."

With so many scientists from different fields collaborating together at BRAINSCAPES, Posthuma explains the importance of team science and how one of her main tasks is to make sure they do not work as a collection of separate islands concerned with their individual projects. "I already addressed this when selecting collaborators on the Gravitation grant," she says. "Three core scientific fields are involved and we specifically want to work with people who are open to looking beyond the boundaries of their own knowledge. This collaboration requires a lot of effort, especially in the start-up phase, where we are educating and critically listening to each other."

It's important that the group feels like a team with a common goal says Posthuma when talking about the kind of group dynamcs she wishes to foster in these collaborations. "We want to bring about a paradigm shift in our fields and can only do this together. We look for researchers with an intrinsic motivation to understand the world around them, rather than being motivated simply by their own career.

“For the new generation of geneticists,team science, open science and data sharing is the norm; that is very promising for the future.”

Scientists who also want the best for the people around them, especially the new generation. You can see this by looking at someone’s resume: Does this principal investigator also provide a platform for junior scientists or does he or she always claim the prestigious authorship on a paper? We invest heavily in the younger generation, so they can take over once they feel ready.”

Furthermore, Posthuma wants people to feel at ease in the group, and therefore she discourages internal competition as it creates a “toxic and unsafe environment in which researchers don’t feel comfortable discussing their projects or struggles, which in turn impedes progress,” she says. Instead, when there is a situation where two researchers come up with a similar plan, she encourages them to work on it together.

This desire for a healthy atmosphere is also evident when it comes to Posthuma’s own lab. “I love my job. I would do this kind of research regardless of my position and whether I would get paid for it,” she says. “I want the same experience for the researchers in my group. This means I try to keep a close eye on them. If they seem frustrated, I’ll chat with them to see what they’re up to and if I can help out, or whether they need to reduce the load they’re carrying.”

Posthuma’s aspiration to have her employees be as happy at their job as she is herself means she allows for a lot of flexibility. “They are all superstars, but in their own way. Some researchers enjoy the full trajectory, from coming up with a research plan to data collection, processing, analysis and writing academic papers. Others love part of the process and dread other aspects. I want my junior scientists to feel safe to tell me if that is the case. I’m happy to try and come up with solutions, finding people who enjoy complementing aspects of science and getting them to collaborate. I love the enthusiasm those adjustments can bring about.”

Sadly, the current COVID-19 situation has affected group processes quite significantly. “We were only able to physically get together once with the BRAINSCAPES consortium before the pandemic hit,” Posthuma says,“which is unfortunate because now is the time we need to invest in personal connections and for those to arise you need to bring people into the same room. As far as my own group is concerned, I miss the casual check-ins. It is much more difficult to get a sense of how they are doing at the moment. I look forward to the time when we can physically get together again, and I can hear the laughter and animated discussions in our office kitchen.”

Emil Uffelmann

University Research Fellow, Complex Trait Genetics

"After some twists and turns in my studies, I found myself in Compex Trait Genetics and it suits me well. I love the fundamental question: How do these four simple nucleotides of our DNA create such complexity and diversity in life around us? And I like coding, solving puzzles to gain insight out of a seemingly inscrutable dataset.

"When it comes to research, teamwork is indispensable. The questions we try to answer are so complex, one cannot solve them alone. Working with Danielle, I have the impression that it is easy to set up collaborations, but maybe that is just because she has a great overview of the field, picks her collaborators with care, has an impressive track record and is pleasant to work with as she really cares for the people in her lab.

"As a first step into team science I started a journal club. I think we should pay more attention to the methodological issues around reproducibility. This is something we can learn from my old field, psychology, where there is great awareness of this problem. In neuroscience we have the same issue but we lack the awareness. For the journal club gatherings, we read a meta-science article and discuss its implications, for example about the ethics and logistics of sharing data and analysis scripts. In some fields this is the standard now, as I think it should be. It means the results of a study can be scrutinized, but it is also a matter of efficiency. The cost of gathering data is very high and once you have performed your analysis you might never use it again, while it might be a valuable source for others. Especially for junior researchers who do not have the grant money to gather their own. This is something I hope the journal club can contribute to."

Priyanka Rao

Research Associate, Molecular and Cellular Neurobiology

"I joined BRAINSCAPES because the consortium offers a fantastic opportunity to tackle research questions across multiple levels of analysis, from bio-molecules all the way up to circuits and behavior. Memory is the phenomenon I'm most intrigued with. It is fundamental in our daily lives and plays a role in many neuropsychiatric disorders such as addiction, trauma and, of course, Alzheimer's. Despite its relevance, however, we have a limited understanding of memory. I study the bio-molecular architecture of memory storage, and at BRAINSCAPES, I will apply this experience to unravel the molecular framework that supports the neuronal circuitry identified for addiction, depression and other disorders.

"Meanwhile, I am also in the process of forming my own research group. In doing so I pay special attention to communication. How are people doing? Are they happy with the way they are being supervised? I think science works best if we utilize different ideas floating around. So I plan regular one-on-one meetings with my students, where I allow them the time to form and express their own ideas. I also watch my language; I don't want to use the words 'right' and 'wrong', 'mine' and 'yours'. We are in this together. I make sure to mention my students during presentations to let them know I appreciate their work and to give them a platform to further their careers. I learned this from my own mentors, but also from courses and social media, especially Twitter. The latter enables open communication about science and provides a valuable stage for both young and experienced PIs to share insights on scientific leadership

Michel van den Oever

Assistant Professor, Molecular and Cellular Neurobiology

"As a neuroscientist, working together with geneticists at BRAINSCAPES provides me with a new angle to study the brain. I try to understand which neuronal networks are implicated in memory storage and retrieval and whether we can alter those networks to prevent people with addiction problems from relapsing. People with an alcohol problem, for example, can quit drinking for months or even years, but then relapse all of a sudden. Often, this is caused by exposure to a cue associated with the rewarding effect of alcohol: seeing people in a bar or passing the local liquor store. We try to understand the memory processes at play here in order to prevent these cues from triggering a relapse.

"The idea of using the results from genome-wide association studies as guidance in the search for the neuronal networks involved in addiction and other brain disorders is promising. This type of truly innovative research can only come about thanks to the combination of expertise of scientists from different backgrounds. Consider, for example, optogenetics. This technique, in which laser light runs through an optical fiber to alter the activity of specific modified neurons, is the result of a collaboration between physicists and biologists and is now a precious part of the standard research arsenal for neuroscientists.

"One of my tasks within BRAINSCAPES is to determine whether identified neuronal subtypes are indeed causally implicated in addiction. After the geneticists and bioinformaticists compare the genome-wide association study data to expression patterns of different cell types, I zoom in on those networks. Are these neurons indeed active during a memory task in mice? And what happens if I alter the activity of that specific network? Do the mice lose the ability to store or retrieve certain memories? Insight into these causal relations could really advance the search for treatment options for addiction."

Food for Thought

An impromptu meeting at a dinner party more than 15 years ago has led to a close collaboration – and friendship – between Susanne la Fleur and Mireille Serlie. Today, the two professors and their team focus on trying to understand the contribution specific brain areas have on obesity in humans.

Mireille Serlie
- Professor of Medicine, Nutrition and Energy Metabolism, University of Amsterdam
- Endocrinologist, Amsterdam UMC – location AMC

Susanne la Fleur
- Professor Neurobiology of Energy Metabolism, University of Amsterdam and Amsterdam UMC – location AMC

The collaboration between Susanne la Fleur and Mireille Serlie goes back more than 15 years when, at a dinner party, Serlie's mentor Hans Sauerwein urged them to take a seat next to each other, with a clear message: "Start collaborating!" Now, in 2020, the two professors have seized this plea and translated it into creating a breeding ground for new translational research in the field of obesity and energy metabolism.

In 2008, La Fleur started at location AMC as a principal investigator in neuroendocrinology. She wanted to unravel the mechanistic link between diet composition and the development of obesity and diabetes, focusing on the role of the brain. "I had already had some good discussions with Mireille on how to study glucose metabolism in animal models," says La Fleur, "so I was really excited to be able to work with her at location AMC." Serlie, who was already working as an internist and endocrinologist at that time, adds, "During my PhD I became interested in studying metabolic fluxes in relation to obesity and insulin resistance in humans. This interest later expanded into the more neurobiological aspects on the topic." La Fleur and Serlie's common interest resulted in a translational team, in which research questions are studied in both animal models of obesity and human experimental studies.

A highlight during their collaboration was their work on the role of striatal dopamine in systemic glucose regulation. "The striatum was well known for its role in motivated behaviour and we, and others, found functional striatal changes in humans with obesity," says Serlie. "Since obese humans are often characterized by insulin resistance, a pre-diabetic condition, we next studied whether the striatal dopamine system was involved in glucose metabolism. We showed that increasing striatal dopamine through deep brain stimulation in non-diabetic patients with an obsessive-compulsive disorder increased insulin sensitivity. In a subsequent study we found that lowering dopamine showed the opposite effect, a decrease in insulin sensitivity. Finally, studies in mice, in collaboration with the DiLeone lab at Yale University, showed that one of the dopamine receptor subtypes in the nucleus accumbens might mediate the observed effects."

"We wondered which brain circuits are involved in the central control of glucose," continues La Fleur. "For example, how does the striatum communicate with the hypothalamus to control glucose metabolism? Using modern techniques, we were able to study these questions in more detail in rodents." "This is a great example of translational science," says Serlie to complement La Fleur. "We found an association between striatal dopamine and glucose in human studies and studied the underlying mechanisms in animal models. We were the first to identify this brain dopamine-nucleus accumbens-peripheral glucose connection and were very excited about the potential implications of that."

"Trying to understand the contribution of specific brain areas to obesity in humans is really important," Serlie explains. "Not only from a scientific perspective and how to possibly intervene, but also in my role as a doctor. Knowing that there are differences in brain areas related to the regulation of food intake in humans with obesity makes it easier to understand how difficult it is to lose weight and, more importantly, how to maintain a lower body weight."

Grasping clinical information and the fundamental scientific knowledge is something that Serlie and La Fleur capture in their weekly Monday meetings. The size of these meetings varies from a small group of Master's students, PhD students or postdocs, up to a meeting of around 20 people. "We think it is important to discuss the potential clinical implications and relevance of our data and at the same time we really want to stimulate cross-fertilization. It is also a good moment to discuss new projects with the whole team and keep an eye on the pertinence for the patients," says La Fleur, while Serlie adds: "It is a moment where they can challenge each other. We expect everyone to go in-depth with each other's studies, which is sometimes difficult, but it helps them broaden their education."

Serlie and La Fleur experience a very positive open and collaborative culture at location AMC. "This seems facilitated by the fact that we work in close proximity on the same floor," Serlie emphasizes. "It would be nice if the topic of translational research became a fundamental component of the curriculum, so students can learn to speak each other's language, especially within neurosciences," La Fleur adds. "We will continue our partnership in research, as well as our friendship, and will always look after each other, especially in times of stress, deadlines and disappointments." To which Serlie says with delight: "In such situations it is so nice to work alongside a colleague that I also consider a friend."

A Vision for the Future

Professor Pieter Roelfsema and postdoc researcher Xing Chen are working together on a visual cortex implant that will hopefully help restore vision in blind people. Thanks to a generous grant and numerous collaborations, they are well on their way to reaching their goal.

Xing Chen
- Postdoctoral Researcher at the Netherlands Institute for Neuroscience

Pieter Roelfsema
- Director of the Netherlands Institute for Neuroscience
- Professor Cognitive Neuroscience of Brain Stimulation, Department of Psychiatry, Amsterdam UMC – location AMC
- Professor of Neurobiology of Cognition and Behaviour, Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam

For several years Pieter Roelfsema and his colleagues collected information on understanding cortical mechanisms of visual perception, memory and plasticity. Six years ago, Xing Chen joined Roelfsema and his team as a postdoc researcher. It was then that they started a close collaboration and took important steps towards the goal of Roelfsema's Vision & Cognition research group: to create a visual cortical prosthesis that would restore a rudimentary form of vision in blind people.

"It would be nice to create an interface that restores vision in blind people," Roelfsema says. "In 2014, we felt like we had collected enough knowledge on the visual cortex and perception to be able to take the next step. Instead of implanting the usual two hundred electrodes in the visual cortex area, we wanted to take it up a notch to a thousand electrodes, with the aim of stimulating patterns on the cortex." Chen had years of experience with the visual system in non-human primates and already knew Roelfsema from her time as a PhD student. "As soon as I saw the position in the Vision & Cognition lab, I knew that I wanted to work on this project with Pieter," she says.

"It took us several years to carry out the development of the electrodes and customised implants, as well as develop surgical insertion techniques and create the entire neuronal recording and stimulation system in the lab," continues Chen. "In collaboration with Blackrock Microsystems, we developed a prosthesis for chronic recording and electrical stimulation of primate visual cortex. I spent a lot of time training my monkeys and developing the neuroprosthesis system. Now Pieter and I are working with a global network of partners, building consortia and securing funding."

"We are working closely together with six European institutes and organizations on a new project, called NeuraViPeR, which is supported by the European Union with funding of four million euros," adds Roelfsema. "Furthermore, we have joined forces with other universities and industry partners via the NeuroTech-NL consortium on neurotechnology. Our goal is to restore lost function using brain implants in people who are blind, deaf, paralyzed or who have epilepsy. The Dutch Research Council (NWO) awarded our INTENSE project as part of the NeuroTech-NL consortium with a budget of fifteen million euros."

Roelfsema and Chen enthusiastically explain the general concept of their prosthesis consisting of over a thousand electrodes. "When the visual cortex is electrically stimulated through a single electrode, the user perceives a small dot of light. With a thousand electrodes, we can project several symbols, shapes, numbers or characters – similar to a matrix board on the highway," Roelfsema illustrates. Chen adds to his explanation: "The monkeys were initially trained to report the location or shape of a visually presented stimulus, such as a dot or a letter, on a computer screen. After the surgical implantation of our visual prosthesis, instead of showing a real stimulus on the computer screen, we electrically stimulated the visual cortex, generating artificial images. Our results provided proof-of-concept, showing that the monkeys were capable of recognising artificially induced shapes and percepts."

"The electrodes that we currently use last approximately one year," Roelfsema continues. "The next step is to make the implant durable for a longer time period and to work on its safety. To continue the development towards restoring vision in blind people, we consult with a team of experts and collaborators, including neurosurgeons at Amsterdam UMC (location AMC), researchers at Maastricht University, and researchers at Spain's Miguel Hernández University of Elche, who are carrying out a clinical research study in which blind human subjects are implanted with one hundred electrodes. In 2019, we started the spin-off company Phosphoenix to help attract investors for this next step. Our ambition is to develop a device for implantation and use it for the first time in blind people in 2023."

"As a young scientist it is great to work closely together with an experienced researcher such as Pieter," says Chen. "I've learnt how to write project proposals good enough to win grant funding, and have collaborated closely with neurotechnology companies to develop the device." And Roelfsema's viewpoint on their teamwork? "It is a perfect exchange," he emphasizes, "since I get to work with someone with a lot of energy and ideas."

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