Amsterdam Neuroscience MAGAZINE

We care about the brain

Cover:
Mrs Bastiaanse de Boer (1914; left) is a participant of geneticist Dr Henne Holstege's 100-plus Study. With the help of some very special centenarians, Dr Holstege (right) is working hard to uncover the genetics of healthy ageing.

Word from the directors

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

We believe that Amsterdam Neuroscience provides common ground for clinicians and basic scientists in the neuroscience field in the Amsterdam area. The institute helps to showcase and support excellent and outstanding neuroscience research resulting in great papers and important societal impact. In the first three years, researchers of the Amsterdam Neuroscience community of investigators have published more than 3,600 peer-reviewed papers and have acquired more than €120 million in research funding. This has led to ground-breaking clinical trials, translation and major innovation within our nine research programmes that are, at times, world-leading. We have also provided an excellent graduate training environment for the 500-plus PhD students currently embedded in Amsterdam Neuroscience. This Amsterdam Neuroscience MAGAZINE is to celebrate the achievements and hard work of our investigators and colleagues. In the first edition you will find eight in-depth interviews and eight short profiles of prominent senior and junior investigators, interviewed by science journalist Marieke Buijs, and portraited by photographer Bas Uterwijk, in a way that illustrates the exciting neuroscience research community in Amsterdam.

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

Diederik van de Beek & Arjen Brussaard

As co-directors of Amsterdam Neuroscience they open up the doors for unique research collaborations by bringing together many talented neuroscientists from different research angles.

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Yolande Pijnenburg & Annemiek Dols

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Frank Jacobs

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“Imagine that someone with a favourable genetic make-up for happiness or well-being reports symptoms of depression – we could think about interventions from the field of positive psychology as an addition to the commonly used interventions.”

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Huibert Mansvelder

“Obtaining human brain tissue was a big step. A huge step, in fact, because my group was one of only a handful of labs worldwide that had access to living human brain tissue.”

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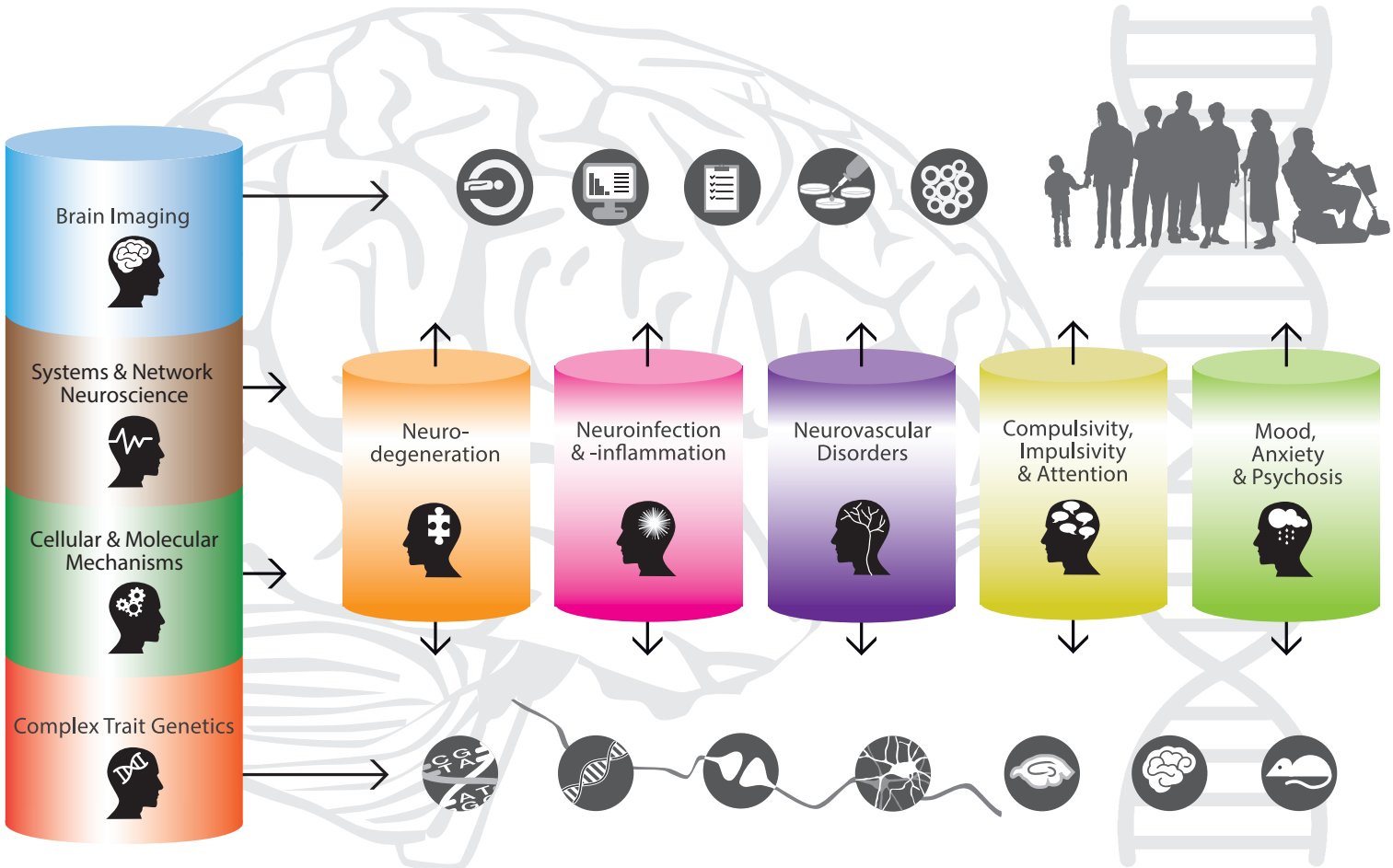


Amsterdam Neuroscience

Amsterdam Neuroscience
A high-profile research organisation

Amsterdam Neuroscience aims to contribute to the understanding of the functioning of the human brain, the peripheral nervous system and their disorders. We perform integrated basic, translational and clinical research in order to improve our understanding of the human brain and nervous system in health and disease. Understanding healthy brain function aids the development of a wide variety of innovations needed to eventually apply these to study neurological, neuroimmunological and neuropsychiatric disorders. This allows early diagnosis and prevention of such disorders, and gives guidance to clinical trials and related research programmes.

To reach these objectives Amsterdam's two academic medical centres and both universities joined forces in 2016 to study the brain and nervous system function and disease mechanisms through an integrated approach. The four organisations have a long tradition in basic and translational neurosciences. In recent years the scientific excellence of neuroscience in the Amsterdam region has developed to an extent that is unique in the Netherlands. All research activities are essentially interdisciplinary and include the newest theoretical, methodological and application paradigms currently available.

Amsterdam Neuroscience aims to strengthen collaborations between investigators by focusing its research strategy on nine research programmes, as illustrated here. Five research programmes that focus on specific brain and nervous system disease mechanisms are complemented by four programmes that focus on innovation, which provide proof-of-concept insights into the causal relationships in brain and nervous system function mechanisms. At Amsterdam Neuroscience, innovation takes place at all levels of study – from molecular to cellular, to circuitry and intact brain and behaviour, both at individual as well as population level.

The nine research programmes outlined on the facing page act as steering committees, each with more than fifteen scientists and Principal Investigators (PIs). Shared infrastructure and translational efforts will be realised, and graduate trainees and residents are being guided with integrative feedback within each of the research programmes.

A Good Match

As co-directors of Amsterdam Neuroscience, Diederik van de Beek and Arjen Brussaard open up the doors for unique research collaborations by bringing together many talented neuroscientists from different research angles.

There are some things that Diederik van de Beek and Arjen Brussaard cannot pinpoint or explain. For example, they cannot exactly recall the first time they met as co-directors-to-be. Even though it was not that long ago, five years perhaps. "We simply started to walk alongside each other like on a mountain hike," Brussaard explains, using a metaphor that exemplifies his 'imaginative' use of language as Van de Beek teasingly refers to it. "And then we just continued walking together." Something else they cannot explain outright is the trust they describe as the core value in their collaboration. They look at each other, questioningly. "It just came naturally," Van de Beek attempts. "And it has never been violated."

They think that the fact that so much of their connection is implicit and self-evident, difficult to describe in words, is a sign that they are just a good match. Which is just as well, because as co-directors of Amsterdam Neuroscience they represent and bring together over 1,000 neuroscientists, neurologists, psychiatrists, neuropsychologists and many others that care about the brain. One – Van de Beek – the clinician, ERC- and VICI-laureate, and leader of his own research group – or, as Brussaard puts it, a 'general carrying the scent of gunpowder'. The other – Brussaard – more the managing director and diligent organiser with a strong track record in fundamental neuroscience research. As such, they sit down together every week to discuss and take actions needed to facilitate the course of the neuroscience institute.

Explaining the organisation they created and their own role in guiding it, they show impressive infographics in the vibrant colours of Amsterdam Neuroscience ("our club colours"). "In order to make research collaboration sustainable, you need to create an organisational matrix. And decisions often need to be made at these intersections," Brussaard says, and points out the four programmes on the left-hand side of the matrix where innovation and fundamental research takes place, oriented towards and enabling the five more disease-oriented research programmes aimed at translational interventions for brain disorders such as Alzheimer's and Parkinson's disease. For those who are less specialised in business models, they offer an easier description of their role. They see themselves as matchmakers, cupids of neuroscience. Together with the programme leaders and taskforce members, they try to connect people "from both sides of the Amstel" – clinicians as well as basic scientists – to carry out research, translating findings from a petri dish in the lab to a treatment in the hospital. Meanwhile, this connection also translates the unmet needs of patients seen by their doctors in the examination room back to the lab, where they generate novel questions to be answered by means of fundamental research.

Brussaard first felt that there was a need for this role while working as a postdoctoral fellow in the US. "I got to watch and learn at the best labs in the world, with professors that ended up winning a Nobel Prize later on." While there, he noticed that

CV Arjen Brussaard

2017 - present	Full professor in Translational Medicine in the field of Neurology and Psychiatry, Amsterdam UMC – location VUmc
2013 - present	Chief Scientific Officer of the Industry Alliance Office, Amsterdam UMC
2016 - present	Director of Amsterdam Neuroscience, Amsterdam UMC
2008 - 2015	Director of Neuroscience Campus Amsterdam, VUmc
1999 - 2016	Full professor in Experimental Neuroscience, Vrije Universiteit Amsterdam

CV Diederik van de Beek

2016 - present	Co-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

success came about when talented scientists from different research angles came together around specific themes such as memory and learning. He believed that would also be the best way forward for brain research back in Amsterdam, and he has been building towards that for the past 25 years: lobbying, taking MBA-like courses to learn how to guide an organisation in transition, and most significantly, eventually resigning as head of a research group to free up the time and energy needed to make this collaboration a success. In 2016 he was formally joined by Van de Beek, and the community that had already formed at the Vrije Universiteit Amsterdam (VU) was enriched by its University of Amsterdam (UvA) and Academic Medical Center (AMC) counterparts.

Van de Beek and Brussaard take turns answering questions and listen intently when the other talks. They share a thorough commitment to the institute, and they sense they are not the only ones. "Moments where we all feel the momentum and energy are the Amsterdam Neuroscience annual meetings where 650+ colleagues come together, such as those in 2017 and 2018 in the Johan Cruijff Arena," Brussaard recalls. "Yes! People are always enthusiastic to be there," Van de Beek agrees. "Scientists fly halfway across the world to visit conferences where they can meet inspiring people to collaborate with, and at our gatherings they realise they can also find that inspiration and collaboration right here in Amsterdam. They only need to cross the Amstel."

Can you give an example of meaningful new collaborations?

Simultaneously: "Many!"

Van de Beek: "For example, there is a research group at VUmc [Vrije Universiteit Medical Center Amsterdam] that studies the blood-brain barrier and a group at AMC focusing on stroke. After a stroke, the blood-brain barrier is affected due to inflammation, which could cause harm to the patient. Now these two research groups have joined forces to study the effect of stroke on the blood-brain barrier in an animal model. These projects are so obviously valuable that it's hard to understand why they did not materialise before. But I guess people are absorbed in their daily work and if that work goes well, there is no incentive to change."

Brussaard: "And of course there are scientists who did look for collaborations before. The most dedicated ones always made it across to find counterparts on the other sides, but we want everyone to benefit from these possibilities."

> “We are all-inclusive by nature; everyone is welcome to join our institute.”

What is needed to achieve that?
Van de Beek: “It actually does not require much. Mostly it’s about creating opportunities to meet each other, so things like gatherings, presentations, meetings and drinks. And also, a bit of money. Funding for proposals for joint research.”
Brussaard: “And sometimes it also takes persuasion to get people to quit their unfounded hobby projects – individual research projects that do not really fall into any of our programmes.”
Van de Beek: “We are all-inclusive by nature; everyone is welcome to join our institute. But we do make choices, focus our research, prioritise and join forces on specific topics.”
Brussaard: “So the organisation also depends on team players. We need people to see the value in our programme and to have the drive to contribute. People who can set aside their pride and understand that sometimes there are solid arguments for focusing our means on a specific project at that moment – even if it is not theirs. People who want each other to succeed and support each other in doing so.”

While discussing their work, they realise they both have approximately three jobs, which they try to squeeze into one week. Besides leading Amsterdam Neuroscience, Van de Beek works as a neurologist and as a professor leading a research group. “I could not really tell you how much time I spend on work, to be honest. It just never ceases.” He does not unplug, discussing the research of PhD students during evening phone calls while also being on-call for the hospital. “But I thoroughly enjoy my work, so I don’t see any reason to do it differently.”

Beside his two days a week for Amsterdam Neuroscience, Brussaard is also Chief Scientific Officer of the Industry Alliance Office. “And you always get lured into these committees, organising things for the hospital for example,” Van de Beek adds, looking at Brussaard. “It’s true! They always manage to find him. And I understand why. He is a really good organiser and leader.” Through the years Brussaard has become more conscious of his work-life balance. “Professionally, I have become more of a marathon runner. I work steadily from eight till six each and every day, and then the other part of my life starts. I need time to recharge.” He sings in a close harmony choir, rides his racing bike and has a holiday cottage in Overijssel. “There, away from the city, I touch base with the countryside and spend time with friends and family every now and then.”

Man on a Mission

Philip Scheltens has made it his life's work to raise Alzheimer's research to a higher level. And as director of the Alzheimer Center, he's in a prime position to do so.

Philip Scheltens
Director of the Alzheimer Center, Professor in Cognitive Neurology and former member of the Management Team of Amsterdam Neuroscience

"Two years before I finished my neurology training in 1991, I got a lucky break. A colleague of mine went on sabbatical for a year and asked me to take over for him as a doctor for dementia patients. I instantly felt captivated by these patients and the tragedy they went through, losing their memory, speech and control over their lives. Sometimes this happens at a very early age, around 50, where people not only forget where they left their reading glasses but also lose their ability to function at work or within their family. Life and identity are shaped by memory, and I knew I wanted to focus on this group of patients that had lost theirs. Not only in my work as a clinician, but also as a scientist. People looked at me with great scepticism at the time. Here I was, a junior staff member pleading with the hospital to get them to focus on this illness. Many colleagues did not even consider Alzheimer's an illness; they thought it was an inevitable part of old age. That sentiment has changed greatly over the last two decades, and now we really have the wind under our wings.

I think Amsterdam Neuroscience is unique in bringing together experts who used to be in some sort of competition with each other, working for four different institutes. Collaborating brings research to a higher level and is an important factor in the momentum for Alzheimer's research in Amsterdam. The connection between fundamental and clinical research brings about promising new ideas. We are considering, for example, if there are ways of using cells of patients who carry the heritable form of Alzheimer's disease and turning them into neurons to study in the lab. Another promising path that came about within these collaborations is exploring the role of cholesterol in the brain in causing Alzheimer's disease.

I still see patients every Wednesday and as a former member of the Amsterdam Neuroscience management team, I try to incorporate the perspective of these patients into our research endeavours. Unfortunately, I cannot offer my patients a cure yet, and so despite my care their disease will progress. That is sad, but it does not bring me despair. It motivates me to keep trying my best for the ongoing research."

Double Up

By combining their strengths and expertise, and holding consultations with patients together as one, neurologist Yolande Pijnenburg and psychiatrist Annemiek Dols are able to provide a more efficient level of help. This joining of forces seems such a simple concept, yet it is strangely still a rarity in the Netherlands.

Yolande Pijnenburg (left) and Annemiek Dols (right)

The sense of wonder is almost tangible in the examination room of neurologist Yolande Pijnenburg as resident geriatrician Katja Kaland describes the remarkable story of the incoming patient. A fifty-something man, let's call him Paul, is being sent in after having received a letter of dismissal from his employer. They have built a case against him, describing how he took sick leave for several months, claiming to have broken his ankle while there were no indications of that happening. When asked about the employer's letter of dismissal by his wife, Paul stresses he has no idea what his employer is talking about and claims to have never taken the sick leave, despite the existence of documents he signed while visiting the company doctor. During his alleged sick leave, he always left home as if he was going to work, so his wife never noticed something was off.

What is going on here? Is this a malevolent employer trying to get rid of an ageing employee? Or are these signs of a developing psychiatric or neurologic disorder? Pijnenburg and psychiatrist Annemiek Dols listen to Kaland as if they are detectives looking for crucial clues. They ask about Paul's psychiatric history (none), education, job

CV Yolande Pijnenburg

2002 – present	Neurologist, Amsterdam UMC – location VUmc
2010	Received a personal fellowship from de Hersenstichting to start Late Onset Frontal Lobe study
2007	PhD: Frontotemporal dementia; towards an early diagnosis
2016	Initiation of Neuropsychiatric International Consortium on Frontotemporal Dementia with Dols

CV Annemiek Dols

2009 – present	Psychiatrist, Amsterdam UMC – location VUmc, and GGZ inGeest with focus on mood disorders complicated by somatic or cognitive symptoms and neuropsychiatry
2009 – present	Consultant for the Alzheimer Center, Amsterdam UMC – location VUmc
2016	Start of the Social Brain Project with Pijnenburg
1999 – 2002	PhD in Portland, USA: Immunotherapy strategies in breast cancer and melanoma

and neuropsychological test results. They also look at his brain scan (no abnormalities) and other lab results. The two doctors seem puzzled. "This is very atypical for frontotemporal dementia [FTD]," Pijnenburg says, "because we don't see any abnormalities on the brain scan, but also because he managed to have his leave of absence go unnoticed by his wife. Could it be dissociation?" She looks over at Dols sitting next to her. "I doubt it, because he has no psychiatric history," Dols responds and then turns to three doctors-in-training sitting in on the session. "Dissociations usually occur in people who have experienced severe trauma in their youth, like sexual abuse. They manage to endure the situation by tuning out from reality, and sometimes this happens again when facing stressful situations in later life." Could it be a factitious disorder, they wonder? "But why?" asks Dols. "Because he does not like his job? Or his wife? Or his life?" The doctors decide they want to provoke him to get a better sense of what's going on. And they want to see him without his wife.

"Together we can really oversee all aspects of a person's mental and behavioural problems, so we can come to a deliberate conclusion"

The briefing takes place at the start of a unique consultation hour, where a neurologist and a psychiatrist combine forces to see patients together. The two professions were once harmonised in the role of the neurologist but grew apart in the ever-more specialising field of medicine. For Pijnenburg and Dols, however, it is very clear that their patients have a lot to gain by reuniting this expertise in the examination room.

Initially the combined session was set up because Pijnenburg was looking for ways to recognise FTD at an earlier stage. "Some patients are treated for depression for quite some time, not making any progress, before we realise something different is at play and are able to diagnose a neurodegenerative disorder, such as a form of dementia," she explains. "And we see the opposite as well," adds Dols. "Patients with a potentially treatable condition such as depression risk missing out on treatment when a misdiagnosis of FTD is made." But the joint consultation has proved to be useful for other patients too, to distinguish between forms of dementia and primary psychiatric disorders, and now Pijnenburg and Dols see about 20 percent of the patients that come to the Alzheimer Center for screening.

Kaland brings in Paul, who is dressed in a blue sweater, jeans and trainers. Pijnenburg explains they do not understand what is going on in his life and are hoping he could help them figure it out. Paul glances up from the table. "It's a long story," he warns them. His subsequent story, however, is not long at all. "I am just forgetful. And they found out at work." While Dols invites him to be more specific, Pijnenburg leans forward, carefully observing the patient at their table. Paul's narrative does not satisfy Dols: he does not offer any explanation for the discrepancy between his experience of going about his usual work at a utility company and the month-long leave of absence his employer accuses him of. Dols bluntly points out the discrepancy, suggesting that either he is wrong, or his employer is setting

him up. “I just don’t remember,” Paul repeats again and again. Pijnenburg tries another approach and interrupts with a question about a recent news event. Paul answers hesitantly, but correctly, which gives an indication of functioning memory.

Many patients see both a neurologist and a psychiatrist, but it is this rare opportunity to see them both at the same time that is most valuable. “Obviously we could call each other and discuss a patient we have both seen,” Dols explains. “But then we never know whether different impressions of the patient are due to differences in his or her behaviour during the consultation or to how we interpret the behaviour. Here we witness the same behaviour and we can discuss the interpretation. That makes our communication and decision-making much more effective.” Pijnenburg continues, “And together we can really oversee all aspects of a person’s mental and behavioural problems, so we can come to a deliberate conclusion – even in cases when we do not find any well-defined disorder. Today we told a patient that, after two years of searching for a diagnosis, we can responsibly conclude that at the moment he does not have any disorder. We are able to close a case, while many patients get sent back and forth endlessly between psychiatrists and neurologists.”

Despite the expanse of Pijnenburg’s and Dols’ combined knowledge, Paul proves a difficult case to unravel. “I feel stuck,” Pijnenburg says, frustrated, when the team gathers in an unoccupied examination room for a quick consultation. They ponder the possibilities. “I don’t get a sense that it’s factitious,” Dols says. “Those patients generally present themselves as hyper-demented.” The doctors consider how to progress, and contemplate a more extensive neurological diagnostic course, where they screen for rare types of epilepsy and look into potential hereditary forms of dementia. “But I think we should also explore the psychiatric track,” Pijnenburg suggests. “So we have a complete picture.”

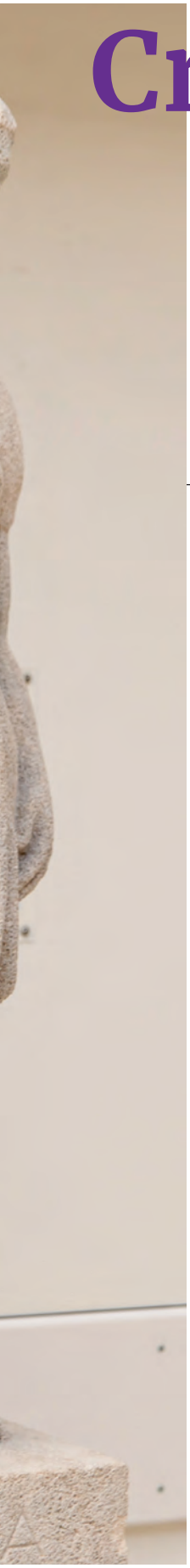
“This is perhaps disappointing for you to hear, but we do not yet know what is going on,” Pijnenburg tells Paul and his wife, who has now joined him, as the doctors return to the room. “We can think of three scenarios, and all three of them are unlikely. However, we do think that something is wrong, so we want to explore these unlikely scenarios.”

Many patients see both a neurologist and a psychiatrist, but it is this rare opportunity to see them both at the same time that is most valuable.

Pijnenburg’s and Dols’ collaboration not only benefits patients; the doctors themselves have also learned from it. The neurologist explains that she has gained a better understanding of how vulnerable psychiatric patients can be. “Traditionally as neurologists, we tend to downplay the severity of mental problems that don’t have a clear biological underpinning. Now I am more aware of the way people can suffer from psychiatric disorders. How hard or even impossible it can be for them to lead the life that I tend to think people should be able to live; one where they work and are self-sufficient. I realise more and more that, as a society, we cannot expect that much from them, however sad that realisation is.” Psychiatrist Dols, on the other hand, has learned to pay more attention to underlying pathology when interacting with her other patients, who are often elderly with bipolar disorder. “Considering them from a more neurological perspective, I started wondering how a depressed mood might go alongside problems with planning and organising, and how their social life suffers from those impairments. And indeed, I noticed that if we take those things off their hands and organise social events for them, their social lives improve and alongside that, I notice their mood lifts. It’s remarkable to witness those changes.”

In order to respect the privacy of the patient, his name and recognisable characteristics have been altered.

"As a scientist who aims to solve the problems patients face, I need to see patients regularly and get a sense of what they struggle with."



Cracking the Challenges of Clinical Trials

Professor Rob de Bie has a skill that is highly respected in the field of medical science: he knows how to set up and carry out clinical trials – something that appeals to his analytical as well as practical expertise.

In Professor Rob de Bie's office at the Academic Medical Center (AMC) in Amsterdam, there's an unassuming plastic bag, sitting on the floor underneath a framed picture of his two kids and a bookshelf upon which a human skull has been casually placed. The bag contains an important potion: a bottle of champagne. Today calls for a celebration, because today sees a study that sprung from De Bie's imagination seven years ago finally make its way into the world. De Bie and his colleagues have shown that starting Parkinson's medication at an early stage of the disease is better than the conservative approach medical doctors generally take. The group managed to publish the findings in the prestigious *New England Journal of Medicine.* But what is most significant to De Bie is that he can now tell his patients with certainty that they do not have to fear repercussions from starting medication early, which would relieve them of some of the life-altering symptoms of their disease. "To be able to provide answers to questions that are important to my and other patients, to offer them guidance in their difficult situation, is what I aspire to do as a scientist," De Bie says. Hence the champagne.

De Bie was trained at AMC, then left the Netherlands for a fellowship in Canada and eventually came back to his alma mater. He was offered a full professorship in 2017 to study neurological movement disorders. Much like any professor in a hospital, he has a busy schedule: supervising PhD students and resident doctors, and seeing patients, both complicated cases that are sent to him for a second opinion as well as regular neurology patients, also over weekend shifts. "I want to continue my clinical work because as a scientist who aims to solve the problems patients face, I need to see patients regularly and get a sense of what they struggle with. If I would only do research, I would eventually lose this inspiration and motivation." Surprisingly, his hectic schedule is in no way apparent in his demeanour. He speaks slowly and deliberately, with a hint of irony in his voice.

When asked about his favourite moment in the week, De Bie does not need a lot of time to reflect. "Friday afternoons, where we discuss a new, potentially protocol-altering publication with the staff and doctors-in-training. Together we try to determine whether the study at hand indeed calls for an alteration of our practice. Are the methods thorough? Do the results justify the conclusions? These are my favourite moments because they are most challenging intellectually." He fetches the article that will be discussed at the upcoming meeting. It's about a new tool for the diagnosis of Creutzfeldt-Jakob disease. De Bie scans the front

CV Rob de Bie

Active in Amsterdam Neuroscience as programme leader

2017 - present	Full professor of neurological movement disorders, Amsterdam UMC – location AMC
2011 - present	Group leader Movement Disorders, Amsterdam UMC – location AMC
2006 - present	Neurologist, Amsterdam UMC – location AMC
2005 - 2006	Clinical Fellowship, Toronto Western Hospital, Canada

page. "The new method is a hundred percent reliable," he notes, sceptically. "Well, then you already know you need to be very, very wary in judging the study. Nothing is a hundred percent correct."

The intellectual rigour needed for judging the publications is exactly what De Bie also enjoys about his own scientific work. He mentions a scenario in which, based on theory, some doctors target nucleus A for Deep Brain Stimulation in patients with Parkinson's disease, whereas other neurologists target nucleus B. How do we establish which practice is best? "Which outcome variables do we measure? Stiffness? Or tremor? Or both? How do we measure them? How many patients should we include to be able to measure the minimal meaningful difference? Setting up a trial and getting patients to participate is an enormous amount of work, so I need to make sure I'm very careful in determining these parameters. The goal is to be able to tell patients which regions they should opt for, in which nucleus they should get a device implanted, so we need to make sure we get it right."

"You can imagine that, for neurologists, it is not easy to bring up our study right after sharing news that completely upsets the life of the patient sitting opposite to them."

But intellectual thoroughness is not sufficient for running a clinical trial. When De Bie explains how he manages to administer these trials, with budgets that are 30 to 40 times smaller than those the pharmaceutical companies have for similar research, creativity and people skills stand out. For the newly published study about early initiation of medication in Parkinson's, De Bie needed to include almost 450 patients. "And not just any patients; we needed to invite them right after they received their diagnosis. You can imagine that, for neurologists, it is not easy to bring up our study right after sharing news that completely upsets the life of the patient sitting opposite to them." In order to find out how to get doctors on board, De Bie made some calls to pharmaceutical companies. Although pharmaceutical companies can pay doctors for the time invested in a study, whereas De Bie does not have any money to offer, he got useful advice: doctors need to be reminded of the study as much as possible. "And so we sent cakes, decorated with the logo of our study. This spurred the inclusion of patients temporarily but did not prove sustainable. We realised we needed something doctors cannot eat. We printed mugs and pens, sent out newsletters. I tried to talk to all neurologists individually. We organised drinks at conferences. We were very commercial about it, but I did not mind, because I believe in the value of the study and was willing to try anything that would help make it a success." Most importantly, De Bie tried to make it as easy as possible for doctors to raise the issue with their patients by teaching them how to bring up the topic. De Bie straightens his back and recites the three sentences he asked doctors to use with their patients who had just been diagnosed. "'We do not know whether it is wise to start levodopa treatment at an early or at a later stage of the disease. A current study is addressing this question...'" and then, finishing off with an encouraging swing of his arm, "'Would it be ok if one of the scientists contacts you to explain more about this research?'" Who could object?

Explaining the subtle craft that goes into running a clinical trial, De Bie sounds weary. "When thinking about all the work it entails, I do feel overwhelmed at the prospect of starting anew," he sighs. "Do you know how hard it is to just get a neurologist on the phone? They are constantly seeing patients and their secretaries try to keep distractions at bay." Luckily, by now De Bie knows how to fight the

> “If I answer a few more of these big questions for patients, I can retire and be content.”

feeling of being overwhelmed. “I have learned to break the large study up into tiny, manageable steps and to not think about the big picture too much.”

What also helps him persevere is the fact that De Bie loves his job. “Even if I won the lottery, I would continue doing my work.” And, then after a second: “Well, perhaps I would spend more time with my sons. But apart from that, this is what suits me best. This is where I can make a difference. If I answer a few more of these big questions for patients, I can retire and be content. My name and these impact scores will be forgotten in no time, but if I have meant something to the lives of the millions of people suffering from Parkinson’s disease worldwide, I feel very proud.”

Building Bridges

As a psychiatrist and a researcher, Odile van den Heuvel is able to combine her clinical work with her research to help build the bridge between the neuroscience campus and a patient's experiences.

"I'm both motivated and inspired by my interactions with patients. I mostly see people who suffer from a combination of neurological and psychiatric problems. Knowledge about the disease mechanisms helps us understand what patients experience, and also helps us improve our practice by developing new treatment targets. We continuously interact with patients, when brainstorming about such treatment innovations, and they also act as patient researchers in our studies.

For patients with Parkinson's disease, for example, one major inconvenience is the wearing-off phenomenon, when the symptoms of the disease get worse right before the next dosage of medication is due. These symptoms often consist of both motor problems, like rigidity, and non-motor symptoms, like anxiety or a bad mood. Generally, people are referred to either a physiotherapist for the physical symptoms or to a psychologist for the mental symptoms. Interacting with patients and my knowledge about the brain network function helped me realise that this approach falls short. Fear prevents people from doing the exercises that might help them physically, while the physical symptoms hamper effectiveness of exposure therapy against the fear. Therefore, I got together with a group of patients, their partners, psychologists and physiotherapists to come up with a more integrated approach, and we initiated a programme for combined therapy with a psychologist and physiotherapist to help patients deal with both aspects of wearing-off simultaneously. What strikes me is that this new therapeutic approach makes complete sense if you take the structural and functional mechanisms of the brain into account. The emotional and motoric brain systems are intertwined, and both are affected in Parkinson's disease. A same cross-talk between neuroscience and clinical practice exists in my work for Obsessive-Compulsive Disorder (OCD). Knowledge about the altered network function in OCD patients stimulates me to think about therapeutic strategies to modulate these networks, by using transcranial magnetic stimulation for example.

As a psychiatrist, I try to have a positive influence in the lives of my patients. The satisfaction is not strictly connected to the optimal outcome of treatment – a cure – since it is often not possible to take the disease away. That is why I also feel fulfilled if I can help a Parkinson's patient towards a peaceful end. As a scientist, my main drive is to guide young researchers. I want to share my enthusiasm for science and help our undergraduate PhD students and postdocs become independent, critical scientists who will work with integrity and social engagement."

Odile van den Heuvel
Psychiatrist and professor of Neuropsychiatry at Amsterdam UMC – location VUmc

Into the Deep

Together with a team of scientists and mental-health professionals, professor Damiaan Denys is exploring the unknown waters of Deep Brain Stimulation and the effects it has on processes of the mind, such as fear, compulsion and confidence.

CV Damiaan Denys

2016 – present	President Dutch Psychiatric Association
2013 and 2016	Production and performance of an 'anxiety monologue' in theatres
2007 – present	Professor of psychiatry Amsterdam UMC – location AMC
2000 – 2004	PhD in psychiatry Utrecht University

"We're in a tricky situation with the electrodes that can both measure and influence neural activity," says professor Damiaan Denys at the lunchtime meeting of his Deep Brain Stimulation (DBS) research group. Ten scientists and mental-health professionals gathered around the table listen attentively as he lays out an odd problem. The stock of the electrode they use in one of their research lines has run out. Completely. A hundred electrodes were produced worldwide and now research groups from different corners of the world are bickering about who gets to use the last five available. "I've managed to convince the supplier to give us at least one more, but whether we get another one is still up in the air," Denys tells his team.

It is one of the more mundane – but no less important – issues encountered by people who do research on the outmost boundaries of human understanding. Of course, scientific research is all about exploring things we do not have a full understanding of. But sometimes this exploration takes place in tranquil little pools, surrounded by safe shores of knowledge. Denys and his team, on the other hand, are waist-deep in unchartered, open waters, trying to claim islands of knowledge from the deep unknown. To make matters not only more urgent, but also more fragile, this unknown is the human mind and brain and the connections between the two. What happens to processes of the mind, like fear, compulsion or confidence, when you tinker with the electro-chemical signalling in the brain?

Embarking on such an exploration is difficult and that is the reason that once every two weeks, on Thursday afternoons, the scientists cram together in a small meeting room to discuss, over lunch, the issues they face. Issues like the dwindling supply of crucial hardware. But also the question of whether they should accept the application for DBS made by a young adult in a forensic institution. The team cannot elaborate on the case due to privacy concerns. "But accepting him, placing electrodes in his brain, will have pro-

found consequences for him and his loved ones and it has societal and legal implications," Denys explains. These things have not been done before, there is no protocol to follow. "And so we need to combine the knowledge of people from different fields to make wiser decisions. We need clinical expertise of the symptoms patients suffer from, insights in associated brain circuitries, the neurosurgical possibility of treatment, ethical expertise regarding acceptance of invasive brain treatment and psychotherapeutic expertise for additional treatment."

What happens to processes of the mind when you tinker with the electro-chemical signalling in the brain?

Diving into these unchartered territories results in new insights that go beyond the theoretical frameworks available. Psychiatrist Nienke Vulink, head of the department of anxiety disorders, describes a patient who had religious compulsions, spending the better part of her day in prayer, out of fear of not being pious enough. This ritual got in the way of other activities such as work and investing in social connections. Neither cognitive behavioural therapy, nor pharmacotherapy offered any relief and so the patient was referred for DBS. An electrode was placed in the internal capsule, the region connecting the striatum, involved in emotions like fear, with the frontal cortex which is crucial for planning and inhibition. This proved effective. With stimulation, the woman spent less time in prayer, freeing up time and energy for other things. And she remained religious, to the relief of her family. "Ironically, they perceived the transition as a miracle from God," says Vulink.

What struck Vulink in her patient was that, with the decrease in compulsive prayer came a rise in confidence. And that boost in self-confidence was noticeable in many patients, the team realised during previous lunch discussions. Now the mechanism behind the confidence boost is a topic of discussion. Vulink theorises that a debilitating psychiatric illness such as severe Obsessive-Compulsive Disorder (OCD) or anxiety impedes the opportunities for self-development, and alleviating this obstruction results in a rise in self-confidence. Denys argues, on the other hand, that the confidence boost is almost immediate after the stimulation starts and is not necessarily associated with a simultaneous decline in compulsive symptoms, so he suspects it to be a separate dimension in the healing process. "For me this is part of the beauty of Deep Brain Stimulation," Denys says. "It teaches us about mental disorders irrespective of frameworks. None of the diagnostic handbooks mention self-confidence as something to consider when establishing OCD and yet we realise it might play a role in the original pathophysiology and also in how people suffer from their illness." This belief led the team to take up a new research project, trying to unravel the neural correlates of self-confidence and tracking whether effective DBS triggers changes in these correlates.

The fact that DBS brings about new observations about the mechanisms involved in OCD illustrates how ground-breaking the technique is. The team has carried out approximately 80 surgeries on patients with OCD, and psychiatrist Marloes Oudijn now also assesses whether the technique might be of help for people with severe, treatment-resistant anorexia nervosa. Four patients have been operated on and although they show signs of improvement, three of them have also been in troublesome situations after surgery. The diminution of eating disorder symptoms like binge eating and purging reveals – sometimes severe – underlying emotion regulation problems that need treatment as well. The team is aware of the precariousness of interfering with the signalling of a patient's brain. "It is an invasive procedure and it can feel quite daunting

at times," Oudijn explains, "especially in people with anorexia, some of whom only weigh 30 to 35 kilos and are susceptible to somatic deterioration due to being severely underweight. But we keep a close eye on them, and we can always decide to seize stimulation or even remove the electrodes if things go wrong." Vulink adds forcefully: "Of course it is invasive to interfere in people's brains, but I see it as a precious opportunity to help severely ill patients. They have tried every single form of therapy and nothing works. I had a patient who has had both cancer and compulsions and she told me that she would rather have the cancer return than the OCD, which she experienced as more life-shattering. Seventy-five percent of patients with severe OCD indicate they do not want to continue living. So yes, it's scary. But the status quo is even more frightening."

If the research group can get their hands on more of the rare electrodes Denys is after, they might embark on a new route for treatment, where the stimulators not only change neural activity, but measure it simultaneously. It is the first step towards therapy where the electrodes will learn to recognise specific patterns of neural activity related to – for example – compulsions, and subsequently interfere with that activity. "Ultimately this would mean that the electrode provides tailor-made interference so that the patient wearing it will never even have to experience the fear," says Denys. "This project may help unravel the complex neurobiology of compulsive behaviours and offer a tailor-made, more effective treatment approach."

> "For me, this is part of the beauty of Deep Brain Stimulation, it teaches us about mental disorders irrespective of frameworks."

Healthy Hundreds

With the help of some very special centenarians, geneticist Henne Holstege is working hard to uncover the genetic secrets of ageing without cognitive decline.

CV Henne Holstege

2014 - present	Assistant Professor and team leader of the 100-plus Study, Amsterdam UMC – location VUmc
2013 - 2014	Postdoc Alzheimer Genetics, Amsterdam UMC – location VUmc
2013	Start of the 100-plus Study
2010	Postdoc at department of Clinical Genetics, Amsterdam UMC – location VUmc

"It was not an easy decision, you know." The demeanour of Mrs Bastiaanse (104 years old) suddenly changes. She's been cheerful all afternoon, but now she sounds fragile. "I did wonder what God would..." Her voice breaks. "...Would think about me donating my brain to science. But I realised, even if it would help just one person, God would approve." She bows her head and looks over her glasses at geneticist Henne Holstege sitting beside her. "We are very grateful for your decision," Holstege replies. "And I am sure it will be of help. Not just for one person, but for many, many people." Holstege, Mrs Bastiaanse, her daughter Thecla, and research assistant Debbie Horsten are having vegetable soup with meatballs at Mrs Bastiaanse's apartment in a retirement home overlooking Vlissingen. The wind roars around the building, but inside it is nice and comfortable – the thermostat shows a subtropical 24°C.

"Being as old as Mrs Bastiaanse and still having such a clear mind is a statistical anomaly."

Mrs Bastiaanse has just finished a set of tests to assess her mental capabilities and defied all odds by scoring 30 out of 30 in the Mini-Mental State Examination. She is one of the 359 centenarians who are part of Holstege's 100-plus Study research project. Not many people live to see the age of 100 – in the Netherlands there are currently around 2,500. And even fewer people turn 100 without symptoms of cognitive decline. Holstege has made it her goal to unravel what it is that protects people like Mrs Bastiaanse from the cognitive decline most people at that age endure. "Our body gathers all kinds of wear and tear over the course of decades. Being as old as Mrs Bastiaanse and still having such a clear mind is a statistical anomaly. But Mrs Bastiaanse exists, which suggests there might be something in her genes or lifestyle that makes her resilient against the wear and tear that most others from her generation succumbed to a lot earlier. Therefore, I am convinced that Mrs Bastiaanse and other centenarians like her can provide a wealth of information about how to prevent developing symptoms of dementia."

Holstege's interest for this elderly population was sparked through her father, Gert Holstege. In 2003, when he was a professor of neuroanatomy at the University of Groningen, he received an intriguing phone call. Mrs Van Andel-Schipper, born in 1890, had asked the director of the residential care home

in which she lived to call the hospital in Groningen. When she was 82, she had agreed to donate her body to science but was unsure whether it would still be useful for the university since she was now 112. "My father was fascinated by the fact that the eldest person alive in the Netherlands had taken the initiative for such a phone call and so he decided to pay her a visit."

Around the time Gert visited Mrs van Andel-Schipper, Henne went over to her parents' place for dinner. "And so, I got to see my father after his meeting with Mrs van Andel-Schipper. She had made a big impression on him with her sense of humour and the fact that she was really up to date on politics and the football results. She was fully in control of her life. He told me that after leaving her apartment, he had sat down on a bench outside her care home and let the experience sink in. And his enthusiasm was contagious, perhaps that is genetics at play between my father and me too. A seed of interest was planted then and there."

Three years after the encounter, Mrs van Andel-Schipper passed away. Gert studied her brain and observed that the damage usually present in the brain of elderly people was almost completely absent. Henne subsequently studied Mrs van Andel-Schipper's genome in an attempt to unravel which genes were at the cause of this extraordinary feat. In retrospect, that marked the start of her 100-plus Study.

Mrs Bastiaanse is not as old as Mrs van Andel-Schipper – yet. But she is old enough to casually mention her parents' grocery store getting broken into by people suffering from starvation during World War I, or fleeing her house during World War II, or her mother-in-law getting trapped during the flood of 1953. But also, less-dramatic historical happenings such as the introduction of jeans. "I could not stand them!" she cries out in horror. "I was a seamstress and made the most beautiful clothing, but my very own daughters wanted to wear jeans!" Thecla laughs. "Yes, the jeans! How you resented them," she remembers. "Oh mum, people who meet you now think you are so gentle and friendly, but you used to be quite fierce." "It's true," Mrs Bastiaanse says. "But we learn during our lives and

> "We can see that genetically, our participants have a well-adjusted immune system that protects them from the wear and tear of life."

I have learned that I do not always need to be so strict." And as an afterthought, she adds: "What also helps is that I do not have to raise any of you anymore, you are all grown up."

Research assistant Debbie Horsten has visited Mrs Bastiaanse once a year for the past four years. She assesses her general cognition, asks about changes in health and lifestyle over the past year (such as the pneumonia that hit Mrs Bastiaanse last summer) and collects blood samples. Now she pulls a kind of handlebar from her backpack that serves as a tool to measure strength. The centenarian is aware of her audience and puts on a little performance. She closes her eyes, leans forward and gives a loud groan while she squeezes, a playful smile visible on her face. The collection of all this data over the past few years proves to be useful. "We have the first results," says Holstege, "and we can see that genetically, our participants have a well-adjusted immune system that protects them from the wear and tear of life."

Butter and sugar

Nowadays, Holstege does not visit her elderly subjects that often. "I spend most of my time applying for grants and filling out the forms required to do this type of research on human subjects," she explains. "Society is completely obsessed with eliminating all risk and it can be frustratingly time-consuming to accommodate for that." She was blissfully unaware of these practical challenges when she first conceived the project. Holstege announced her interest in healthy ageing on national radio and asked centenarians to get in touch with her. Seven people did and she jumped into her car to visit them. "I do really miss those visits; they are inspiring. I visited someone who had fallen and acquired a big wound on her leg. But, only weeks later, she had a beautiful white scar. That made me wonder if our centenarians might have good wound-healing properties. Would that be something that reduces the risk for all kinds of infections?"

But even without that type of inspiration, research ideas flow freely in Holstege's mind. At the moment she is captivated by

the possibilities offered by a technique called long-read sequencing, which helps unravel differences in the 98 percent of DNA that does not code for any proteins, the so-called 'dark DNA'. "We know dementia is 60 to 80 percent heritable, but we can only explain a fraction of that percentage by the genes we have currently uncovered. So, there must be something in this dark DNA and I am convinced we should fully embrace this new technique." And again, she just pursues her convictions, unafraid to try an unconventional approach. "I'm exploring the options for setting up this research, looking for sponsorships or into the possibilities for outsourcing the experiments."

While Holstege tries to unravel the secrets of the healthy brain, Mrs Bastiaanse offers some of her own explanations for her exceptional state. "Well I have never been poor or hungry. That helps. But apart from that, I don't know. I just eat whatever is on offer, use proper dairy butter and stir a spoonful of sugar into my tea. Nothing special."

When saying goodbye, Mrs Bastiaanse shows some of what Holstege recognises in many of her participants: a deeply rooted appreciation for the positive things in life. "It was so nice of you to come! I hope to see you next year!" Mrs Bastiaanse tells her visitors. "We hope so too, you are not done here yet it seems," replies Holstege. "Not at all! I enjoy life," says Mrs Bastiaanse. "People complain that there's nothing on TV, but I like what they show: *Antiques Roadshow*, the news or politics. And in a few weeks, when the weather gets better, I will take my mobility scooter and drive to the boulevard. I love sitting there and watching the ships."

It's moments like these that illustrate why Holstege is happy with the course she took. "Dementia is a devastating disease. People lose themselves while their body just continues to live. I feel useful contributing to solving that overwhelming problem. And I am grateful that I chose to learn from the lucky few that manage to evade the odds. We work in close interaction with the centenarians, it is a true collaboration in our mutual quest to rid dementia. I am really proud of that!"

From Apes to

After the exciting discovery of a human-specific gene in our brains, evolutionary neuroscientist Frank Jacobs is now engaged in a rapidly developing study involving the cerebral differences – and similarities – between humans and primates.

Humans

The newest member of Artis' western lowland gorilla group sits on its mother's back. When mum sits still, the baby – three months old and about the size of a chihuahua – seizes the opportunity to crawl around her broad back; when mum starts moving, the baby grabs her hair and holds on tight. Evolutionary neuroscientist Frank Jacobs observes mother and child attentively. "Look how able this baby gorilla is in comparison to a newborn human," he says. "All we humans are able to do when we are three months old is lie about. On the other hand, we can afford to give birth to such reliant creatures because we manage to create a safe environment for them, thanks for example to the social structures we built." Our societies, houses and ergonomically designed prams provide a safe space for our highly dependent babies.

Jacobs studies the differences between humans and other primates. Since about six million years ago, when humans and chimpanzees diverged from their last communal ancestor, the brain of the branch leading to Homo sapiens tripled in size. By comparing the genetic make-up of humans with that of other primates, he tries to unravel the genetic differences underlying this cortical expansion. What happened in our recent evolutionary history that makes us so different from our nearest relatives in the animal kingdom?

> "Many of the attributes that we consider crucially human are actually also present in other animals."

Jacobs carries out his studies in the lab. He keeps stem cells of the animals in a fluid containing the growth factors that trigger them to develop into brain-like clusters of cells, called organoids. So, observing apes in real life, albeit within the confinement of a zoo, is not his daily habit. He came to Artis despite the fact that he doesn't favour the concept of a zoo. "I think a zoo shows visitors the wrong image of wild animals. We can get very close to these animals because they are confined. It does not teach us much about how the animals live their normal lives in the wild." Nevertheless, he does feel excited when he sees the apes he spends so much time thinking about, and takes pictures of the gorilla mother and child on his smartphone.

Complexity

After the relatively helpless start of life, humans do catch up. The adult brain contains, on average, 86 billion neurons, each fine-tuning thousands of connections with other neurons. In comparison, gorillas have about 33 billion neurons and chimpanzees roughly 28 billion. Given the striking genetic similarities between

CV Frank Jacobs

2018 – present	Associate professor, University of Amsterdam
2014 – 2018	Assistant professor, University of Amsterdam
2009 – 2014	Postdoc at University of California, Santa Cruz
2004 – 2009	PhD in Molecular Brain Development, Utrecht University

humans and chimpanzees – the human DNA differs by just three to four percent from the DNA of chimpanzees and the genes are generally highly conserved – this discrepancy is remarkable. In an attempt to shed more light on the issue, Jacobs dove into a part of the human DNA that proved to be difficult to read. What was going on there? He identified a new gene expressed in the brain which was absent in monkeys, present in a single non-functional form in chimps and present as four functional copies in the human genome: NOTCH2NL.

The significance of this double duplication for the human brain started to dawn on him about seven years ago, while he was staring into a microscope. "We had introduced this new gene in mice embryos. Looking at slices of their brains, I felt a rush of excitement. I was intrigued to see large, tumour-like cell clusters. I knew that meant something was up. And to be honest, all the work of the recent years sprang from that moment." Jacobs was initially working by himself on this project, but he soon got to form his own research group, getting young scientists to help him explain his observations. Continuing the study in brain organoids from different primates, they discovered that NOTCH2NL is responsible for slowing down the differentiation of stem cells into neurons, which allows for the production of more neurons over the course of embryonic development. And when it comes to neurons, quantity is important. "For complex behaviour like forming the social structures we live in, or reflecting on our past and future, we need complex brain processing. And the number of neurons is one of the factors that determines our capacity for complexity." But before rushing to conclusions about how NOTCH2NL is what makes us human, Jacobs stresses that he expects the expansion of our brain to depend on many more genetic factors than just this one gene. "A handful have been discovered so far, with NOTCH2NL being one of them."

Pressure

Not only does Jacobs downplay the significance of NOTCH2NL for the humanness of the human brain, he also warns against overestimating the differences in abilities between humans and the great apes. During his visit to Artis, he watches the chimpanzees, forced by cold and snow to hang around in their small indoor confinement. Every now and then they will get in each other's way and start to scream and puff themselves up, seeming quite aggressive to the observing humans. At one point a smaller chimp picks up a wooden duster – which apparently serves as a toy – and lifts it above his head, threatening to hit a larger chimp. But eventually he decides against it and flings the duster in another direction. "Many of the attributes that we consider crucially human are actually also present in other animals," Jacobs notes. "Think about communication, forms of learning, applied intelligence. And the inhibition of our emotional impulses is not uniquely human either, as we were just able to observe."

> "What I hope to get across to the PhD students I supervise is that they should follow their passion."

The fact that Jacobs has been able to build his own research group has thoroughly changed what his work entails. "I am not doing experiments myself anymore. Instead, I have become more of a manager of a group of young scientists and I spend a lot of time thinking about where our research is taking us in the future." Being a leader proves to be mainly enjoyable. "Having more people on board allows me to pursue a much broader approach in studying the

functional implications of genetic changes in our recent evolution. And besides, I really enjoy discussing the research with the group and hearing someone propose a hypothesis or theory that I could have proposed myself. It brings me joy to notice the group is coming together." At the same time Jacobs has had to adjust to being put in a leadership role. "I can come across quite firm and I had to learn what effect my statements can have on junior scientists. When I say: 'We need to make sure this gets done', I do not mean to say it needs to be done by tomorrow or next week, just that this is an important next step to take. But I found out that some people did interpret me that way. So, I've learned to explain my intentions and take some of the pressure off of the people I work with."

At the same time Jacobs is perfectly honest about the pressure he puts on himself, although he would not consider it as such. "What I hope to get across to the PhD students I supervise is that they should follow their passion." From the moment he was able to determine his own course in research, he decided to dive into the topic of human brain evolution. "A lot of neuroscience research happens in mice; I also studied mice. But I think for some human evolution-related questions, it is more informative to focus on our closer primate relatives, because of the closer genetic relationship between us and them. Being able to follow my passion has meant that I am still intrigued by the puzzles I am solving. And that is absolutely necessary. As a scientist I spend so much of my time and energy on my research, there is just no other way. I always enjoy taking time to think about any of the mysteries we are trying to solve in our research, so for me there is no such thing as overtime. That can be a pitfall sometimes, but for me it is the only way to progress as a scientist."

Keeping it Personal

When it comes to helping her patients, Zoé van Kempen places great emphasis on establishing a strong connection and making sure her patients feel heard.

Zoé van Kempen
Neurologist-in-training, currently in her sixth year, and doing a PhD on personalised medicine in Multiple Sclerosis

"When I started the neurology internship during my medical studies, my housemates complained because I wasn't socialising as much as I used to. They were right. I felt the urge to know everything about the cases I encountered during my shifts in the hospital, so at night I dove into the precise workings of the nervous system. In that sense, not much has changed. Working partly in an academic hospital, I encounter many rare cases, so I still often spend my free time researching what the diagnosis might be, always trying to deepen my understanding.

I chose to specialise in Multiple Sclerosis [MS] because it's a very dynamic field. I'm not simply learning tricks that I will be executing for the next 30 years; I need to keep track of the research and adjust my practice constantly. Doing a PhD helps me in that regard. It challenges me to stay up to date on the science and helps me develop my own vision on the studies I come across, judging which ones are most reliable. I often hear myself tell patients: 'Recent studies show that...'

In my own research, I try to establish whether the standard four-weekly intravenous administration of natalizumab, an effective drug used for MS, is the most efficient approach. We have shown that the large majority of patients needs a less-frequent natalizumab infusion without experiencing a decrease of efficacy. My research is very practical; I often hear from patients that it means a lot in their daily lives and for their well-being if they can scale their hospital visits from once every four to once every six weeks.

My sister told me once that in looking for a career, one should aspire to experience, what she calls, a 'yes!' moment at least three times a week. I have managed to achieve that. I feel it when I succeed in establishing a difficult diagnosis. Or when I submit a paper I'm proud of. But also when a patient tells me they appreciated a consultation. The dialogue with patients means a lot to me. Especially in MS, where patients are often young and very involved. They know a lot about their disease, and I want to listen to them and determine the course of treatment together."

Puzzling Out DNA

Fascinated by research, Philip Kremer takes great pleasure in studying how biology and evolution work, and the role that plays in meningitis.

"My research invites me to reflect on the fundamental mechanisms of evolution and that is something I thoroughly enjoy. How does genetic variation lead to certain beneficiary characteristics? I am amazed by DNA. These four simple atomic structures can somehow code for all substance that makes up an organism and determine complex outcomes, such as the colour of the eyes or the risk of falling ill.

Most people carry potentially dangerous bacteria in their mouth or pharynx without experiencing any problems. But in some people these bacteria cause serious harm, specifically meningitis. I try to understand why and how this happens. What is it in the genetic make-up of those people that causes them to become infected? And how do genetic factors in specific bacteria contribute to either the effective mode of infection or the severity of the disease? I do research without any presumptions, testing large data sets to gain new insights about the infection mechanisms and the interactions between bacteria and host.

Philip Kremer
Neurologist-in-training, currently in his fifth year at Amsterdam UMC – location AMC, and doing a PhD on the genetics of meningitis

The great thing about studying bacteria is that I get to observe the direct relationship between certain DNA sequences and the characteristics that emerge from them. For example, how changes in DNA can result in resistance for antibiotics.

My research plays out on such a fundamental level that it does not directly affect my practice as a doctor, but I do enjoy the complementary rhythm the two parts of my job provide. Whereas for my research I submerge myself in a specific part of the study for months or even years, the work with patients is more immediate.

As a clinician I am most energised when tackling the rarest cases. Working in an academic hospital, I am regularly confronted with disorders I have never seen before and I love the challenge of trying to understand what is wrong, registering subtle clues that might be informative. Being part of a team that works together to solve such puzzles, even in very rare and challenging cases, is a true inspiration for me."

A Matter of Confidence

Just how much does confidence play a role in compulsive behaviour? Senior postdoc Judy Luigjes is finding out.

"Compulsive behaviour fascinates me. The fact that people feel the urge to do certain things, like clean their counter, while simultaneously dreading that very same action: this internal struggle can create tremendous suffering. Beside getting in the way of work or family time, the behaviour itself torments people and inhibits their sense of freedom.

There are many initiatives for research collaborations, and it can feel forced at times. But after attending a few meetings of the Compulsivity, Impulsivity and Attention programme, I was convinced of its value for research into a complex concept like compulsion. The programme offers opportunities for a layered research approach, combining expertise from scientists studying animal models of compulsive behaviour, to psychologists studying human subjects, to psychiatrists treating people who suffer from Obsessive-Compulsive Disorder (OCD). One precondition for people to actually reach out for this type of collaboration is that they know each other on a personal level. As programme leader, I want to help foster these connections by meeting up in both formal contexts and informal, social settings.

In my own research I focus on the role confidence plays in compulsive behaviour. People make decisions all the time: Will I get across the street before that car gets here? Can I ask for a promotion? Usually our sense of confidence reflects the amount of evidence that backs up a decision. Which is useful: we will be more careful in crossing a street when we are not sure it is safe to do so, or more forceful asking for the promotion if we feel entitled to it. Yet, we theorise that if people consistently have mismatches between the amount of evidence available and their confidence it can contribute to compulsive behaviour. When we are less confident than the evidence merits, always second-guessing ourselves, we can develop OCD compulsions, like constantly washing our hands for example. On the other hand, when we tend to be unjustifiably confident about our decisions, this might result in another form of compulsion or involuntary behaviour, such as gambling addiction. Indeed, our preliminary results seem to fall in line with this theory. Which is exciting. If the findings prove to be robust, we could start looking at ways of training realistic judgement confidence as a way to alleviate suffering brought about by compulsive behaviour."

Judy Luigjes
Senior postdoc studying compulsive behaviour in psychiatry, and Amsterdam Neuroscience programme leader for Compulsivity, Impulsivity and Attention


DO
WHAT
MAKES
YOU
HAPPY
BEHAVIORAL GENETICS

The Image of Happiness

Professor Meike Bartels opted to take a very different path in her choice of research: happiness instead of illness or depression. This topic fits perfectly with her own optimism and the paradigm shift has made her rather successful.

"I want people to want to be here and work on fascinating research questions, rather than feel pressured to work."

One of the things that brings Professor Meike Bartels joy is people-watching. One example is observing family dynamics at departures and arrivals in Schiphol Airport. "How do they act? Who stands in the back and who pushes themselves all the way to the front? Who is related? And in which way? It strikes me how a son can have the physical features of his mother and combines those with the introversion of his father, or so it becomes apparent when I see him welcoming an arriving family member." It's a good way of passing time, especially when you take the study as seriously as Bartels does. "Look, for example, at the similarities in how people walk. Their posture, how big their steps are. Children do not get taught how far exactly they should kick their foot forward before placing it on the ground. So, when father and daughter have the exact-same gait, that is genetics at play."

The way genes and environment shape people fascinates Bartels. Over the course of her career she decided to focus that fascination specifically on the way these factors influence happiness and well-being. That represents quite a shift in paradigm because most of the research is focused on nature and nurture in negative traits, like how they contribute to developing depression or other mental illnesses. When observing Bartels, her decision to zoom in on those who feel well seems almost too obvious. First of all, the walls in her university office are covered with cheerful photographs and one-liners like 'Smile, happy looks good on you'. Moreover, she displays a sincere positivism and attention to well-being. As the leader of a research team – which works together with neuroscientists, philosophers, statistical geneticists, biological psychologists and developmental psychologists – she will often check in with her PhD students. "I ask them how they are doing and why they are here. If they answer, 'because I need to finish this', or 'because I need to get the results before the competition does', I'll probably send them home to get some rest or do something else. I believe that passion is what drives people and I really want to foster that passion in my research group. So, I want people to want to be here and work on fascinating research questions, rather than feel pressured to work. Pressure and stress are not conducive to passion."

By choosing well-being as her topic, Bartels dove into a scientific niche. Despite the prominent place it fulfils in our daily experience, little is known about which factors are most important in bringing it about or specifically explain differences between people. "The field is very sensitive to over-interpretation," Bartels mentions. "We know, for example, that there is a positive correlation between exercising and well-being. Often this is presented as 'exercising makes you happy' or 'people who exercise are happier', but none of these claims are backed up by research. There is some evidence for protective effects of depressive symptoms, but that it not the same as 'it makes everybody happier'! I want to contribute to real insight on the topic."

CV Meike Bartels

2014 - present	Professor in Genetics and Wellbeing, Vrije Universiteit Amsterdam
2017	Consolidator Grant from the European Research Council
2006	NWO open competition grant
2004	Veni grant from NWO
2003	PhD: Behaviour problems, cognition and hormones. A longitudinal-genetic study in childhood

So far Bartels and her colleagues have identified over 300 genetic variants for well-being. Additionally, they identified three variants related to a meaningful life. "For me, this is a proof of concept. The findings show that we can observe differences on a genetic level that are associated with differences in well-being." Bartels emphasises that the fact she found this association does not mean that it is predetermined whether someone ends up happy or unhappy in life. "It means that genetic differences make some people more sensitive to experiencing higher levels of well-being than others. But the end product is a complex interplay of genetic predisposition and environmental exposure."

So far Bartels and her colleagues have identified over 300 genetic variants for well-being.

From the identification of these genetic variants, many new questions arise. Where in the body are these genetic variants expressed? Can we uncover biological mechanisms? How can we help people who are less prone to being happy? The fact that answering each of these questions requires daunting amounts of research does not deter Bartels. Writing research proposals is one of the things she likes most in her job. "Most scientists dread this part because, while writing, they worry the proposal will get rejected. But I love thinking about interesting new research we could do. I only see the possibilities, I don't pay attention to potential difficulties until I am actually confronted with them. Of course, it is problematic if I do not get funding; doing research is costly, but I will deal with that when it happens. I consider myself to be a bit of a naïve optimist, but that makes life a lot easier with respect to grant writing."

One of the things Bartels is currently working on is assessing the environmental factors that might contribute to differences in happiness. She is planning on doing so with the same scrutiny she brought to the genetic side of research. "Rather than just picking one environmental factor for happiness – let's say a green environment or weather conditions – and assessing its influence, I want to look at all possible environmental factors and try to untangle how they interrelate." Bartels is currently in the phase of preregistering the study. "We want to be transparent about the data we will be using and the way we will be analysing it."

The big goal Bartels has in mind for the future is determining who is at risk of unhappiness and which intervention is most promising based on the individual's genetic profile. "There is a long way to go to use this in a reliable way," she warns. "But imagine that someone with a favourable genetic make-up for happiness or well-being reports symptoms of depression – we could think about interventions from the field of positive psychology as an addition to the commonly used interventions, because positive psychology is aimed at feeding the available talent for happiness, focusing on possibilities."

Genetic research has made Bartels more aware of the profound differences between people, in all aspects of life, such as intelligence, musicality, motivation or sensitivity to stress. That awareness has made her more tolerant. "I realise now that someone else's experience can differ from mine and this makes me less likely to want to 'normalise' their choices or behaviour. It's easy to be judgmental about a passive lifestyle or smoking, for example. But understanding genetic differences made me more aware of the fact that different people have different needs, ambitions and qualities. I hope that broadening our knowledge of genetics will contribute to more tolerance in society at large, where we will accept others as they are. With their talents and their weaknesses alike."

Big Thinker

Guus Smit believes that studying the brain is of the utmost importance. Because everything we do in our existence on this planet stems from that one wonderful organ.

Guus Smit
Director of the Center for Neurogenomics and Cognitive Research and part of the Management Team of Amsterdam Neuroscience

"I was still a kid when I decided that I wanted to spend my life discovering things. But what exactly? I was interested in astronomy and physics, but at some point realised that this organ inside our skull contains great potential for discovery. Understanding how the brain functions became my ambition, because everything we do on this planet is governed by the activity of that one organ. Both on a micro-scale, like when we forget our bike keys at the grocery store, and on a very large scale, like collectively tackling climate change.

Climate change is the biggest challenge we are facing at the moment. People gather data about melting ice sheets, process that data, build models. But we also communicate about it, trying to convince others that this problem is real and urgent. And everything that happens in the debate about climate change happens through our brains. Understanding the brain means understanding people, understanding cultural differences and opinions, and improving interaction on things that really matter.

The complexity of our brain brings us curiosity, makes us aware and enables us to remember. We treat these capabilities as part of our normal lives. However, for many, their lives may be disrupted by some kind of malfunction. In the Netherlands alone, hundreds of thousands of people suffer from one brain disorder or another. We need to understand the complex working mechanisms of the brain to repair what might have gone wrong. Only collaborative research activities can bring about those insights.

Fortunately, in Amsterdam there are thousands of scientists studying the brain. At molecular and cellular level, like me. But also, on the level of circuitry or systems, in computer models, on a behavioural level or through brain imaging. As one of the leaders of Amsterdam Neuroscience, I see it as my mission to work towards integrating these levels of analysis. This is not easy; it is almost as if people with diverse research backgrounds speak different languages. But we need to work on it; it is of the utmost importance if we truly want to understand the brain and ourselves and be able to direct our future."

Sleep Therapy

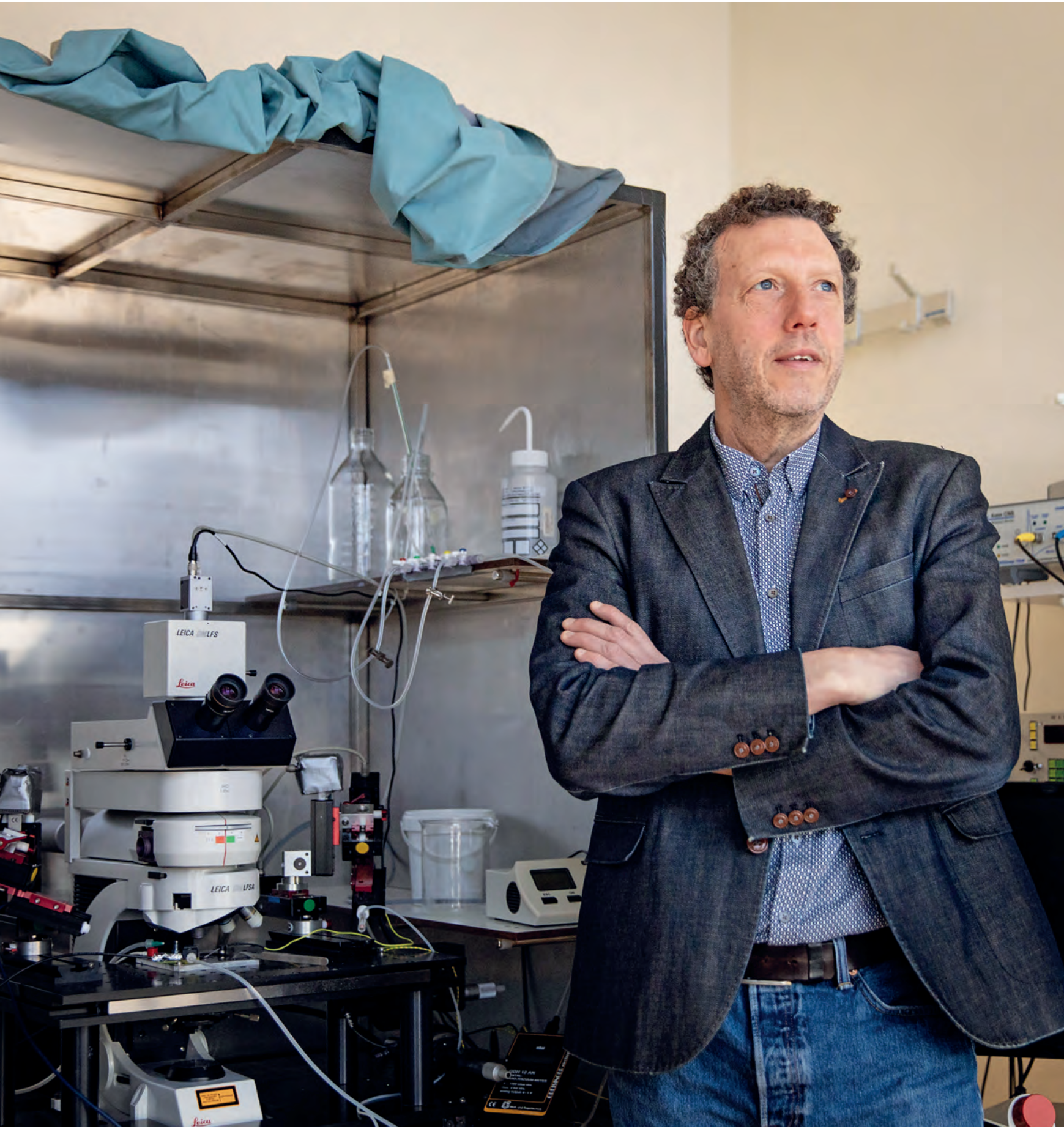
Hein van Marle strongly believes in using our understanding of the brain when exploring new treatments in psychiatry. He's currently looking at the therapeutic benefits of sleep.

"For as long as I can remember, I have been intrigued by human nature and what goes awry in mental disorders. What is it that makes a patient with a borderline personality disorder feel intense emotional pain one instant and nothing at all the next? That is why I wanted to become not only a psychiatrist, but also a neuroscientist. I think that if we as psychiatrists gain a better understanding of the brain, we can significantly improve our practice. Think about EMDR, for example. We all use it in our treatment, and we see that it works, that symptoms of Post-Traumatic Stress Disorder (PTSD) become less pervasive. But many psychiatrists have no idea how it works. Neuroscience tells us that every thought or feeling or action has a substrate in neural activity that arises from electrochemical signalling in our neurons. I want to build from these certainties of neuroscience to understand the volatility of people with psychiatric problems.

Thousands of scientists worldwide study brain function, like memory, in animals or in healthy subjects. Many of these studies identify the important role of sleep in memory consolidation, along with ways to optimise this function of sleep. And inevitably they mention in the discussion section of their publications how valuable these insights might be in helping people who suffer from psychiatric illnesses, like PTSD. But as far as I know, not many groups are trying to translate these new insights to a clinical population.

In our study we try to enhance the positive effects of exposure-based therapy by using the memory-boosting potential of sleep. We treat people with PTSD with a regular, daytime EMDR session. In EMDR we activate the traumatic memory by asking patients to picture a scene that is key in their trauma. Meanwhile we ask the patient to pay attention to a specific sound pattern, overloading their working memory. This results in re-encoding of the memory with less negative valence and less arousal. After a successful EMDR session we invite the patient for the second, nightly, part of the therapy. They sleep in our laboratory and when they reach a specific phase of deep sleep, we repeat the sound pattern, triggering the brain to prioritise the sleep-dependent memory consolidation of the newly updated, less negative memory in an attempt to increase therapeutic effectiveness. We are the first to test this new technique, referred to as Targeted Memory Reactivation (TMR), in a clinical population. It will take some time before we get our results, but if our intervention indeed enhances the effects of EMDR, we will have opened up sleep as a new therapeutic window in the treatment of traumatic memories. In addition, sleep interventions could help patients with all types of problems related to maladaptive memories, like specific phobias, but also addiction, where positive associations with the substance are at the root of the problem. It is a challenging project, both conceptually and methodologically, but I want to pursue it because I believe that patients have a lot to gain by this type of neuroscientific research in psychiatric disorders."

Hein van Marle
Psychiatrist and senior researcher at Amsterdam UMC – location VUmc, and GGZ inGeest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Master of Revolution

Huibert Mansvelder refuses to follow the trodden path, preferring to follow his own course, no matter how unusual it may be. It's no wonder then that, with this willingness to think outside the box and embrace innovative ideas, he is the author of numerous top publications.

A little over a decade ago, Huibert Mansvelder had an encounter that would radically change his work. He was introduced to Hans Baaijen, an inspiring neurosurgeon at VUmc (Vrije Universiteit Medical Center Amsterdam), who treats people suffering from epilepsy or brain tumours by removing tissue from their brains. Part of that tissue would be studied by a pathologist, and the rest would largely be discarded. For Mansvelder, it was clear that this discarded tissue contained a wealth of valuable knowledge about the workings of the human brain. "In neuroscience, we tend to use mice as a model for research," he says. Then laughs. "You could even say that we are really good at curing mice from the diseases we inflict on them in the first place." Realising some of this human tissue would just perish without ever being studied, he decided to try and save it for the sake of science and Baaijen happily cooperated.

Pursuing an unusual opportunity like this is typical for Mansvelder's career, where he tends to disregard the paths that are smoothly laid out for him and somehow creates his own route instead. He plays the cello and studied Sound Engineering at the Royal Conservatory in The Hague, followed by biology and philosophy. After working as a postdoc in the US, he came back to the Vrije Universiteit Amsterdam where, for the past ten years, he has been head of the Integrative Neurophysiology department. In that position he also keeps things unpredictable, bringing together physicists, psychologists and everything in between to try and understand the influence that processes at a cellular level have on human behaviour and cognition.

In fulfilling this aspiration to tie cellular processes to behaviour, obtaining human tissue was a big step. A huge step, in fact, since his group was one of only a handful of labs worldwide that had access to living human brain tissue. "That put us in the luxury position where we were able to do unique research and ask questions no one had asked before." But that does not mean that Mansvelder tried to exploit this advantage over other research groups. Quite the opposite. "As attractive as our unique position might sound, it is also very boring to be one of the few scientists that follow a particular approach. So, we actually try to cultivate a group of peers, teaching others on how to go about setting up a supply chain for human tissue." They have been successful. Research groups that make use of their approach are at, for instance, University of Southampton in the UK, Hebrew University of Jerusalem, University of Cape Town in South Africa, and the Allen Institute for Brain Science in Seattle, US. "Of course, this also entails the risk that someone will come up with a particular finding we were also pursuing, but the dynamic is much more interesting. We are inspired by observing the research of others and by discussing our research with a wider group of interested peers."

CV Huibert Mansvelder

2012 – present Director of Master of Neurosciences Education programme, Vrije Universiteit Amsterdam
2008 – present Full professor of Neurophysiology, Vrije Universiteit Amsterdam
2006 – 2011 Member of the Young Academy of the KNAW
2001 – 2002 Postdoctoral Researcher at Columbia University

This high-risk, high-reward approach to work is also visible in the way Mansvelder set up his lab. "During my postdoctoral research in the US, I was drilled with the dogma that, in order to be successful as a scientist, you need to focus. You need to be the world-specialist on a certain topic and the only way to achieve that is by picking a really narrow topic." But this approach does not work for Mansvelder. "I cannot focus on one protein for the rest of my life; I want to know what this protein does in the cell, what that means for the network of cells and how that influences the functioning of the brain and subsequently the behaviour or cognition of the person. That is always the goal. The same way I am not specifically interested in the inner life of mice, I am also not necessarily concerned with the working of a cell per se; I always want to know how it relates to the human being."

"We are inspired by observing the research of others and by discussing our research with a wider group of interested peers."

Recently Mansvelder's team managed to unravel the entire trajectory from cell to cognition by studying the tissue from 46 of Baaijen's epilepsy and cancer patients. Mansvelder and his colleagues discovered that the brains of people with a higher IQ have neurons with larger dendrites, which are able to generate action potentials at a higher pace, especially during bursts of intense activity in that neuron. The study is the first to relate properties at the level of a single neuron to a complex higher order property like intelligence. When asked what it means to make such a discovery, Mansvelder seems uncomfortable. He glances sideways and taps his fingers at the surface of his desk. When he answers, his tone stays unassuming, but his words are not. "Progressing our communal understanding of ourselves and our brains, by this small step that no one had taken before, feels very satisfying of course. This is a dream come true. Even better, because during my academic training I never dreamed that we would be able to do this, that technological progress would make these kinds of discoveries possible."

Doing research on living human neurons is not an easy feat, however. The human brain tissue is viable for about 30 hours, so after it arrives in the lab from the hospital, PhD students and postdocs work through the night to get the most out it. "We do not force anyone to work those hours, but the chance to work with live human brain tissue is motivation enough for people to join," says Mansvelder. "And students report that it is actually a lot of fun to work with a group on this exciting material at odd hours."

Mansvelder attributes his scientific success to the diversity of scientific disciplines within his team. "It is such a joy to discuss our research together and to hear someone propose an explanation or theory that I could not have come up with myself." The computer model they made to predict the effect of larger dendrites on the level of a neural network, for example, was proposed by a PhD student with a background in physics.

The fact that Mansvelder is convinced of the value of this diversity in his research group does not mean he finds it easy to lead such a team. "The diversity means that PhD students sometimes propose an approach that I have less faith in, and which seems inefficient to me. I can have a hard time fostering the patience to go along with that." When asked why he does not tell his students to take a different approach, he seems surprised at the suggestion. "That is not an option when working with smart people. Leading smart people means you have to allow them to do what they believe in. Otherwise they will continue their own approach and keep you at bay, or even worse, they lose their motivation. And in the end, it is these leaps of faith that sometimes result in the most valuable insights."

Governance

Management Team

Arjen Brussaard (director)	Amsterdam UMC – location VUmc
Diederik van de Beek (co-director)	Amsterdam UMC – location AMC
Damiaan Denys	Amsterdam UMC – location AMC
Susanne la Fleur (as of 2019)	Amsterdam UMC – location AMC
Jeroen Geurts (2016-2018)	Amsterdam UMC – location VUmc
Paul Lucassen	University of Amsterdam
Brenda Penninx (as of 2019)	Amsterdam UMC – location VUmc
Yolande Pijnenburg (as of 2019)	Amsterdam UMC – location VUmc
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Guus Smit	Vrije Universiteit Amsterdam
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Peter Beek	Dean Faculty of Behaviour and Movement Sciences, Vrije Universiteit Amsterdam

Programme Leaders

Dick Veltman	Amsterdam UMC – location VUmc
Liesbeth Reneman	Amsterdam UMC – location AMC
Huibert Mansvelder	Vrije Universiteit Amsterdam
Helmut Kessels	University of Amsterdam
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Jonathan Coutinho	Amsterdam UMC – location AMC
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Judy Luigjes	Amsterdam UMC – location AMC
Christiaan Vinkers	Amsterdam UMC – location VUmc
Sabine Spijker	Vrije Universiteit Amsterdam

Forging Meaningful Collaborations

Pieter van Bokhoven is a man driven by curiosity and a desire to further the progress of science. He uses these motivations to the full when mediating between different research parties.

"For as long as I can remember, I have asked lots of questions. To my parents and my teachers in school, for example. I wanted to know why the world is as it is. And luckily, in this job, I am continually learning new things: about the brain, scientific progress and how drug development companies operate.

For many neurological diseases like Alzheimer's disease, treatment is unfortunately very limited at the moment, and neurologists can only hope for innovations to eventually make a difference in the lives of their patients. At universities we carry out fundamental research to unravel disease mechanisms, but for the development of novel treatments we rely on biotech and pharmaceutical companies. So, in order for us to help realise new treatments for brain diseases, I try to forge meaningful collaborations between drug-development companies and Amsterdam Neuroscience. We have a lot to offer these companies because, within the institute, we cover all steps in the drug-development pipeline; from testing compounds in cell cultures, all the way to clinical trials under the supervision of our neurologists.

I really enjoy navigating this process. It might seem like corporate and academic interests do not always align, because companies want to protect their intellectual property while for scientists it is important to publish research in scientific papers. But actually, there is always a way to harmonise interests, since in the end both parties have a lot to gain. In these collaborations, we as academic hospitals can learn a lot from biotech companies about new, cutting-edge interventions, like CRISPR or antisense oligonucleotides. Likewise, companies can learn a lot about patients and their diseases. What is relevant for the patient? Which biomarkers can we use to establish whether an intervention is promising for further development? I very much enjoy working in this environment, utilising academic expertise and knowledge alongside the dynamics from industry.

By definition these projects are large and complex, with respect to both science and interests at stake. This can make timelines long and it's sometimes difficult not to get impatient. But I have learned that all things take their time. When I'm struggling with a complex situation or a difficult choice, I always ask myself: Why do I do this job? And when I realise I do it to help science progress, it becomes clear which path to take. I think the scientific approach is a way of thinking and living that is the most rational and most valuable for society. I want to make my contribution to this progress and development. Being aware of that drive always helps me go forward."

Pieter van Bokhoven
Senior Business Developer at the Industry Alliance Office of Amsterdam Neuroscience

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Amsterdam UMC
University Medical Centers