Amsterdam UMC
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Amsterdam Neuroscience
Annual Report 2021

Colophon

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Amsterdam UMC
University Medical Centers

VU VRIJE UNIVERSITEIT AMSTERDAM

UNIVERSITY OF AMSTERDAM

Word from the directors

A remarkable ‘normal’ year

The year 2021 became the year of resilience. The COVID-19 pandemic continued and several ‘waves’ hit the Netherlands, our society, and our hospitals. As citizens, we showed our ability to be resilient in challenging times and changing situations. What’s more, this vein of resilience was also evident in our Amsterdam Neuroscience research institute, and our researchers and clinicians showed that it has many facets. Because what is resilience in terms of scientific definition? How does the human brain cope with different circumstances, what is the foundation of the brain’s resilience, is neuronal plasticity involved, and does it protect against stress and disease? And what about when it comes to dealing with the concept of resilience in terms of health care? Is it activated by social interaction, determined by our genetics, essential for understanding psychiatric disease? Are there biomarkers that are indicative of resilience, for instance, in brain imaging studies? It is a topic that we continued to discuss during our usual Annual Meeting in October 2021 and in the Amsterdam Neuroscience MAGAZINE. And it is also reflected in several of the studies that our colleagues published, and grants that were acquired.

It is the resilience of our investigators that made 2021 a remarkable ‘normal’ year. Because despite the pandemic and all the challenges it brought with it, the quantity and quality of research-funding, -appointments, and -output can only be described as (almost) business as usual. We published a few more publications than in previous years, and the acquired research funding was larger than expected. The appointments of new research staff may have been somewhat delayed until the start of 2022, but overall results were stable and solid for Amsterdam Neuroscience.

As a network organization we want to connect our researchers. For example, by expanding the reach of our investigators’ and teams’ stories. This year, we have chosen to use this Annual Report as another means and are highlighting a selection of the 90-plus news items and use-cases of 2021 that were previously published on our website (and via our newsletters). You may well have been one of the 23,000 unique visitors to the website last year and have already seen the pieces, but we are extremely proud of all the accomplishments and want to be sure that this overview gives everyone a taste of the incredible work performed in Amsterdam.

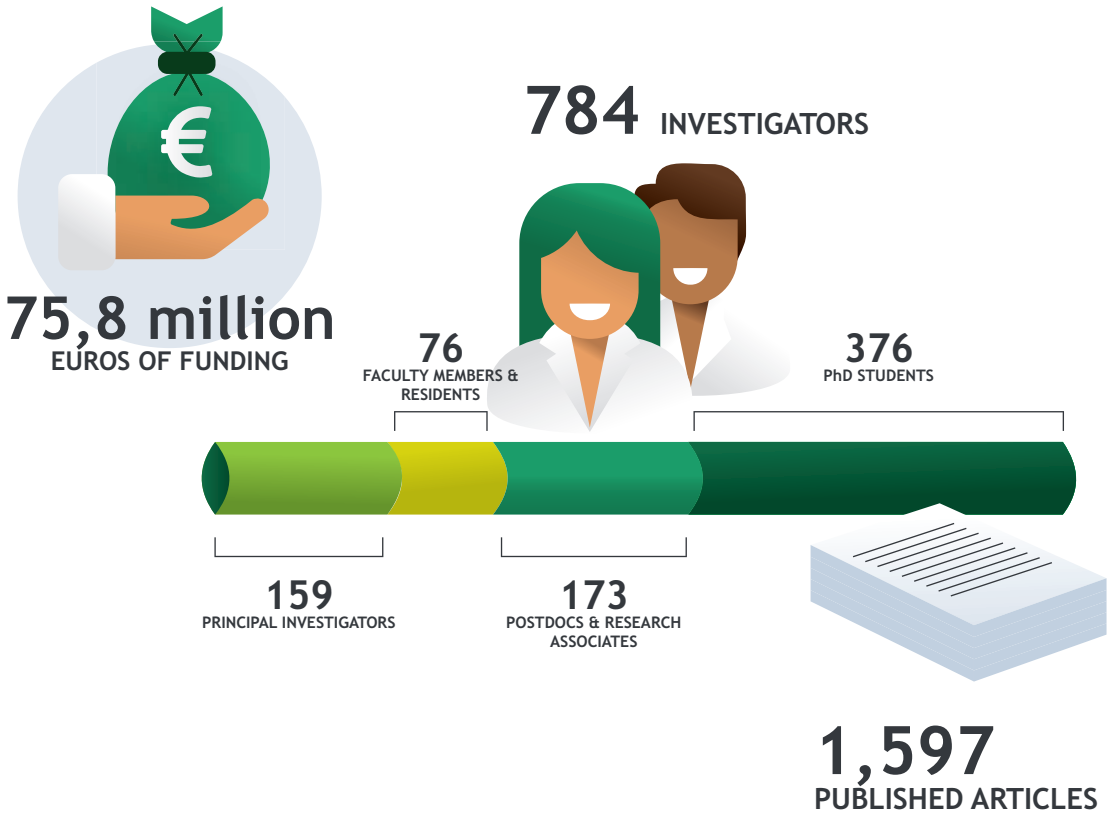
Hence it is with great pleasure we present our sixth Amsterdam Neuroscience Annual Report and we hope you enjoy reading the results.

Arjen Brussaard – director
Diederik van de Beek – co-director
Guus Smit – co-director

Contents

Executive summary

- The collective 'community' of the Amsterdam Neuroscience research institute is currently made up of 784 investigators. This includes 159 principal investigators, 76 faculty members & residents, 173 postdocs & research associates, and 376 PhD students.
- Over the course of 2021, Amsterdam Neuroscience investigators acquired a total of 75.8 million euros in conditional funding.
- This included one Veni, two Vidi, and one Vici grants, as well as major grants from other Dutch agencies, and funding from the European Commission (EC), amounting to a total of 32 million euros.
- This also included 29 million euros funding from non-profit (patient-oriented) organizations and around close to 14 million euros funding in contracted research from the biotechnology and pharmaceutical industries.
- In 2021, a total of 1,597 refereed articles were published, with 276 papers in the highest impact journals (impact factor > 10) and another 256 with a solid impact factor (> 5 < 10). Of these 1,597 unique papers, 150 had 'shared' co-authorship (i.e. 'bilocation' affiliations).
- Highlights throughout 2021 include a Veni grant for Philip Jansen; Vidi grants for Menno Schoonheim and Henne Holstege; a Vici grant for Erik Rietveld; breakthrough studies on blood-based biomarkers for Alzheimer's disease; the first publications from, and treatments by, the N=You Neurodevelopmental Precision Center; the acquisition of major grants for the iPS study titled 'Brain Model'; six TKI public-private partnerships grants equivalent to 2.8 million euros; the publication of several books; seed funding for both deep brain stimulation and TMS treatment for OCD and an award for ABOARD, a major public-private partnerships consortium led by Wiesje van der Flier.



About Amsterdam Neuroscience

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

To enable translational neuroscience research, we develop and translate neuroscience knowledge into applications for patients. Amsterdam Neuroscience focuses on scientific excellence, young talent, and innovation in four cross-disciplinary research programs. In addition, there are five clinical research programs that focus on both existing and new treatments for a number of brain and nervous system diseases, including neurological, neurovascular, and psychiatric disorders.

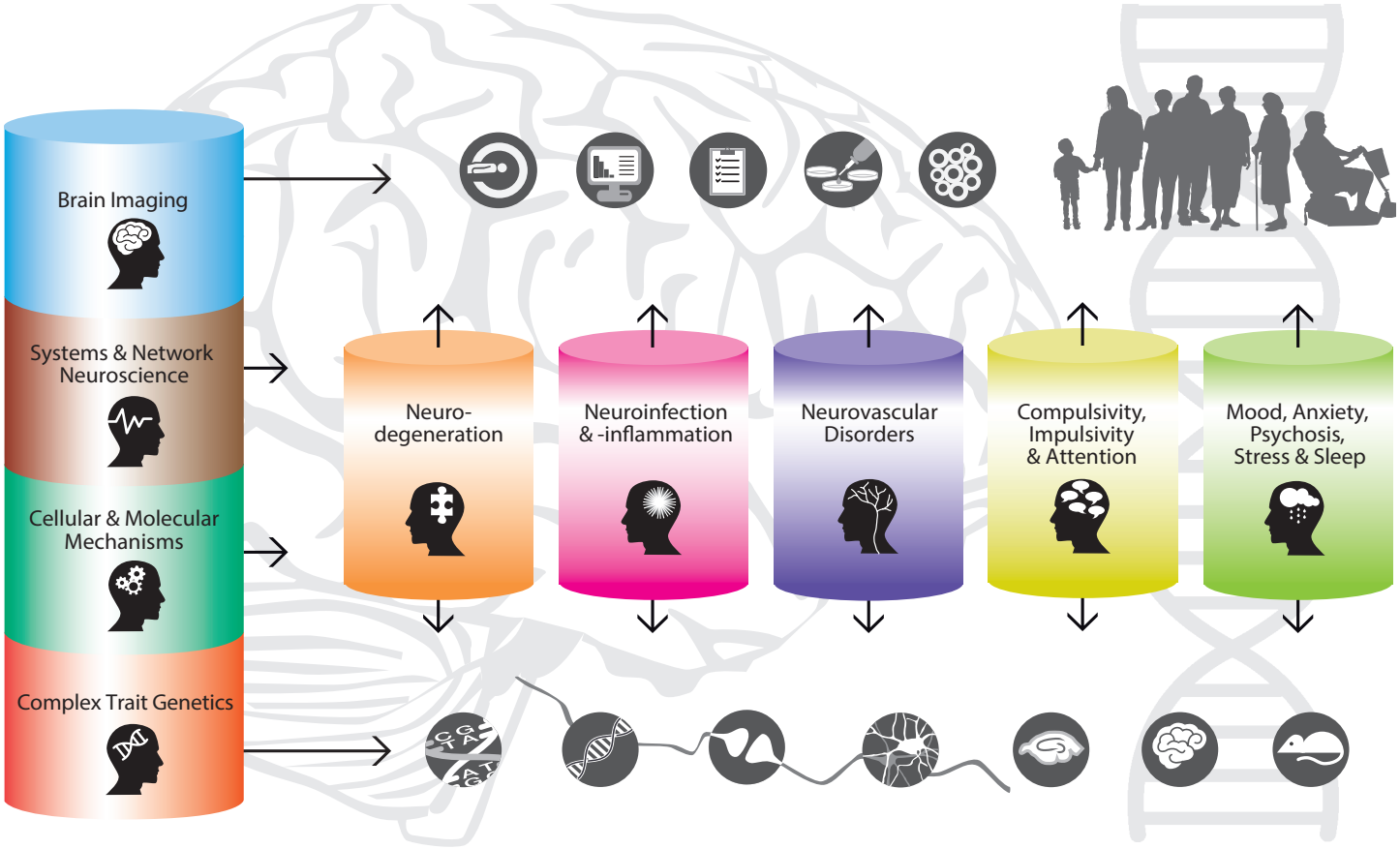
Amsterdam Neuroscience's overall mission is to broaden the fundamental knowledge of the human brain and nervous system, and to translate this into effective therapies and treatments for the individual patient.

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

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

Amsterdam Neuroscience

Research programs



Infographics of the research organization of Amsterdam Neuroscience in the period 2019-2021

Brain Imaging (bi)
Systems & Network Neuroscience (snn)
Cellular & Molecular Mechanisms (cmm)
Complex Trait Genetics (ctg)

Neurodegeneration (nd)
Neuroinfection & -inflammation (nii)
Neurovascular Disorders (ndis)
Compulsivity, Impulsivity & Attention (cia)
Mood, Anxiety, Psychosis, Stress & Sleep (mapss)

Governance

Management team

Arjen Brussaard (director)	Amsterdam UMC – location VUmc
Diederik van de Beek (co-director up to Oct. 2021)	Amsterdam UMC – location AMC
Guus Smit (co-director as of Nov. 2021)	Vrije Universiteit Amsterdam
Susanne la Fleur	Amsterdam UMC – location AMC
Paul Lucassen	University of Amsterdam
Brenda Penninx	Amsterdam UMC – location VUmc
Yolande Pijnenburg	Amsterdam UMC – location VUmc
Taco de Vries	Amsterdam UMC – location VUmc
Guido van Wingen	Amsterdam UMC – location AMC

Board of deans

Chris Polman	Dean Amsterdam UMC – location VUmc
Hans Romijn	Dean Amsterdam UMC – location AMC
Guus Schreiber	Dean Faculty of Science, Vrije Universiteit Amsterdam
Peter van Tienderen	Dean Faculty of Science, University of Amsterdam

Program leaders & taskforce members

Brain Imaging

Program leaders	
Dick Veltman	Amsterdam UMC – location VUmc
Liesbeth Reneman	Amsterdam UMC – location AMC
Taskforce members	
Fleur van Rootselaar	Amsterdam UMC – location AMC
Bart van Berckel	Amsterdam UMC – location VUmc

Systems & Network Neuroscience

Program leaders	
Huibert Mansvelder	Vrije Universiteit Amsterdam
Helmut Kessels	University of Amsterdam
Taskforce members	
Johannes de Boer	Vrije Universiteit Amsterdam
Rick Schuurman	Amsterdam UMC – location AMC

Cellular & Molecular Mechanisms

Program leaders	
Matthijs Verhage	Vrije Universiteit Amsterdam
Susanne la Fleur	Amsterdam UMC – location AMC
Taskforce members	
Marjo van der Knaap	Amsterdam UMC – location VUmc
Eric Reits	Amsterdam UMC – location AMC

Complex Trait Genetics

Program leaders	
Danielle Posthuma	Vrije Universiteit Amsterdam
Frank Jacobs	University of Amsterdam
Taskforce members	
Tinca Polderman	Vrije Universiteit Amsterdam
Karin Verweij	Amsterdam UMC – location AMC

Neurodegeneration

Program leaders

Wiesje van der Flier	Amsterdam UMC – location VUmc
Rob de Bie	Amsterdam UMC – location AMC

Taskforce members

Charlotte Teunissen	Amsterdam UMC – location VUmc
Lars van der Heide	University of Amsterdam
Wilma van de Berg	Amsterdam UMC – location VUm

Neuroinfection & -inflammation

Program leaders

Joep Killestein	Amsterdam UMC – location VUmc
Matthijs Brouwer	Amsterdam UMC – location AMC

Taskforce members

Elga de Vries	Amsterdam UMC – location VUmc
Filip Eftimov	Amsterdam UMC – location AMC

Neurovascular Disorders

Program leaders

Jonathan Coutinho	Amsterdam UMC – location AMC
Dagmar Verbaan	Amsterdam UMC – location AMC

Taskforce members

Gert Kwakkel	Amsterdam UMC – location VUmc
Charles Majoie	Amsterdam UMC – location AMC

Compulsivity, Impulsivity & Attention

Program leaders

Odile van den Heuvel	Amsterdam UMC – location VUmc
Dirk Jan Smit	Amsterdam UMC – location AMC

Taskforce members

Taco de Vries	Amsterdam UMC – location VUmc
Conrado Bosman	University of Amsterdam

Mood, Anxiety, Psychosis, Stress & Sleep

Program leaders

Sabine Spijker	Vrije Universiteit Amsterdam
Christiaan Vinkers	Amsterdam UMC – location VUmc

Taskforce members

Lieuwe de Haan	Amsterdam UMC – location AMC
Aniko Korosi	University of Amsterdam

Research staff

About the metrics

To be able to draft the metrics of our research institute we followed the Standard Evaluation Protocol (SEP) of the Association of Universities in the Netherlands (VSNU), the Dutch Research Council (NWO), and the Royal Netherlands Academy of Arts and Sciences (KNAW). As for funding categorization for the university medical centers we used the Netherlands Federation of University Medical Centres (NFU) criteria. In the ratio-conversion from personnel to the full-time-equivalent (fte) spend on research the default (HRM-SAP instructed) guidelines can be applied: full professor: 0.1-0.2 fte; strategic professor: 0.1 fte; associate professor: 0.4 fte; assistant professor: 0.4 fte; investigator: 0.8 fte; postdoc: 0.8 fte; PhD student: 0.75 fte.

Amsterdam Neuroscience – Research institute

The collective 'community' of the Amsterdam Neuroscience research institute is currently made up of 784 investigators. This includes 159 principal investigators, 76 faculty members & residents, 173 postdocs & research associates, and 376 PhD students.

Amsterdam Neuroscience – Research programs

Below are the affiliations categorized by research program of all personnel including PhD students as well as the metrics for PhD students only. Double affiliations were allowed.

All personnel **Persons**

	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Subtotal	95	61	216	78	150	106	71	102	88

PhD students only **Persons**

	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Subtotal	47	23	128	31	60	52	36	54	35

Funding

Amsterdam Neuroscience – Research funding

The table below shows the grand total, the subtotals per type of funding and the amounts per research program of newly acquired funding for the institute. The table quotes funding that is unique to each particular research program. Double affiliations are not shown.

	Grand total	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Total	€ 75,838,309	€ 3,168,770	€ 7,581,991	€ 11,789,080	€ 2,566,374	€ 22,442,323	€ 9,827,684	1,595,841	€ 13,127,942	€ 3,738,304

Conditional funding

	Subtotal	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
1e geldstroom	€ 415,921	€ -	€ -	€ 365,921	€ -	€ -	€ 25.000	€ -	€ -	€ 25,000
2e geldstroom	€ 32,088,842	€ 1,237,715	€ 855,000	€ 3,745,032	€ 1,939,192	€ 5,636,753	€ 5,964,102	€ 406,491	€ 8,676,153	€ 3,628,404
3e geldstroom	€ 29,435,643	€ 746,305	€ 6,691,397	€ 2,844,817	€ 528,072	€ 10,828,814	€ 3,087,634	€ 1,164,000	€ 3,530,704	€ 13,900
4e geldstroom	€ 13,897,903	€ 1,184,750	€ 35,594	€ 4,833,310	€ 99,110	€ 5,976,756	€ 750,948	€ 25,350	€ 921,085	€ 71,000

NFU definition

- "1e geldstroom": Only the internal so-called alliance funding (i.e. € 415,921) is shown here; the unconditional internal funding for tenured and other personnel is estimated to be >€ 50 M for 2021;
- "2e geldstroom": conditional funding by intermediary public bodies and agencies (ZonMw, NWO, KNAW, and the EU);
- "3e geldstroom": private funding by non-profit organizations;
- "4e geldstroom": private funding from commercial sources: contract research and clinical trial research funded by biotech and pharma industry and acquired by the Industry Alliance Office (IAO).

Research output & quality

Amsterdam Neuroscience – Research output

The table below shows the metrics for all types of publications. Double affiliations are not shown, i.e. each publication listed is only affiliated with one research program.

	Total	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Refereed article	1,597	187	41	203	105	258	229	176	132	266
Non-Refereed article (1)	74	7	2	11	9	15	13	7	6	4
Books	2	0	0	0	0	0	0	0	1	1
Book chapters	17	4	0	9	0	1	0	1	1	1
PhD theses	90	5	1	23	1	16	9	12	6	17
Conference papers	26	25	1	0	0	0	0	0	0	0
Professional publications (2)	40	0	0	3	1	5	3	2	10	16
Publications aimed at the general public (3)	3	0	1	0	0	0	0	1	0	1
Other research output (4)	48	9	11	3	3	2	8	3	3	6
Total publications	1,897	237	57	252	119	297	262	202	159	312
With impact > 10	Subtotal	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Refereed articles (selected output)	276	16	17	34	32	70	41	20	12	34
With impact > 5 < 10	Subtotal	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Refereed articles (selected output)	256	42	4	42	17	39	47	10	13	42

Notes on the distinct categories (according to the latest SEP protocol):

1. Articles in journals that are non-refereed, yet deemed important for the field;
2. Publications aimed at professionals in the public and private sectors (professional publications), including patents and annotations (e.g. law);
3. Also known as “populariserende artikelen”;
4. Other types of research output (if applicable), such as abstracts, patents, editorships, inaugural lectures, designs and prototypes (e.g. engineering), and media appearances.

High-impact publications

A total of 1,597 refereed papers were written in 2021 by Amsterdam Neuroscience researchers. Out of this, a total of 256 papers were published in international journals with an impact factor of between 5 - 10, and 276 papers were in journals with an impact factor of 10 or higher. Of the latter category, at least 52 papers were original research papers in the center of our core strategy and with the first and last authors coming from our organization. There were an additional 13 papers that were published as so-called perspectives and reviews in high-impact journals (i.e. > 10), with corresponding authors from our institute. What's more 81 publications appeared in international journals with an impact factor of between 10 and 20, and 160 publications in journals with impact factor between 10 and 20.

Bilocation authorships

In 2021, there were at least 150 'bilocation' papers (i.e. papers in which either VUmc and/or AMC shared co-authorship with university authors) written by Amsterdam Neuroscience researchers. VUmc had co-authors on all of these papers, while AMC participated in 80 bilocation papers. With regards to the universities' contribution to these bilocation papers, the VU Amsterdam contributed to 55 and the UvA contributed to 12.

Societal impact

The Amsterdam Neuroscience researchers promote high-class research output. But to understand the functioning of the human brain and nervous system, and the focus on the translation into effective therapies and treatments for the individual patients, Amsterdam Neuroscience also highly values societal impact. Our societal impact can be understood as stimulating valorization, boosting interdisciplinary collaborations, creating and maintaining societal awareness, and bridging the gap between fundamental and more clinical-oriented research results and their implementation. More information about the impact of our research is illustrated in the section of news items of 2021, listed in the second part of this Annual Report.

Hybrid Annual Meeting 2021

Recap of the Amsterdam Neuroscience Annual Meeting 2021

The sixth Annual Meeting of the Amsterdam Neuroscience research institute took place on September 30 and October 1, 2021. This time we organized a two-day hybrid event that started with the online poster market in Gather town on Thursday and continued with a plenary program on Friday with 200 attendees live at the Johan Cruijff ArenA and more than 300 participants that joined the Annual Meeting online.

Word of Welcome and Story Slam presentations

A familiar face on stage, our host Kim Coppes was back this year to guide us through the day and, together with Amsterdam Neuroscience's directors Arjen Brussaard and Diederik van de Beek, she opened this year's Annual Meeting. The trio highlighted the overarching theme of 2021 and launched the new online MAGAZINE 2021. Followed by three story slam presentations led by assistant professor Priyanka Rao-Ruiz of VU Amsterdam. Three PhD candidates took the stage: Aina Badia Soteras (Department of Cellular and Molecular Neurobiology, VU Amsterdam), Niek Brosens (Structural and Functional Plasticity of the Nervous System group, SILS, UvA), and Jeanet Karchoud (Department of Psychiatry, Amsterdam UMC).

Escaping cognitive decline: the science behind the story

Assistant professor and head of Genomics of Neurodegenerative Diseases and Aging at the Department of Human Genetics at Amsterdam UMC, Henne Holstege, entered the stage to explain her work for the 100-plus study at Alzheimer Center Amsterdam. Followed by an interview with one of the participants of the 100-plus study, Mr. Van Vollenhoven, who shed some light on his daily life and how to reach this age while maintaining his cognitive health. Mr. Van Vollenhoven ended the session with an amazing musical performance.

Network oscillations in Alzheimer's disease

The program continued with a fundamental science part including the research report by Ronald van Kesteren, team leader at the Center of Neurogenomics and Cognitive Research, on neuronal network alterations in early dementia. Followed by this year's keynote lecture by Li-Huei Tsai, director of the Picower Institute of Learning and Memory at the Massachusetts Institute of Technology. Li-Huei Tsai joined us via a live connection all the way from Cambridge Massachusetts, USA, and gave an exciting keynote lecture called 'Noninvasive sensory stimulation to induce gamma entrainment and neuroprotection' that showed that 40Hz light and sound stimuli show beneficial effects on many aspects of different disease models for Alzheimer's disease. Even more exciting: her preliminary work shows beneficial effects in human AD subjects as well. The public was engaged and she sparked an interest with her GENUS project.

Stress and resilience in psychiatry, from bed to bench side and back

A dialogue was held with Christiaan Vinkers, associate professor and psychiatrist at Amsterdam UMC and GGZ ingest, who was also recently appointed as faculty chair 'Stress and Resilience in Psychiatry'. Vinkers shed his light on the relationship between stress and resilience in psychiatry. For almost all psychiatric and neurological disorders, (traumatic) stress is a major risk factor. However, considerable interindividual differences exist in stress vulnerability and resilience. How can we shed more light on the fundamental (neuro)biological background of stress resilience, but also make sure that patients can eventually benefit? In other words, can an integrative and translational approach to resilience offer a way forward?

Recap of poster presentations & Award ceremony

The top four presenters of the online poster market presented their research on stage. Emma Coomans, Lynn van Olst, Aina Badia Soteras, and Ana Millan Vidal were in the running to win the title 'Best Poster Presentation 2021'. The audience of the Annual Meeting where the judges and they voted for Lynn van Olst as best presentation of 2021 with her poster entitled 'Aging blood factors promote CD8 T cell infiltration in the adult mouse brain'.

Selection of news items of 2021

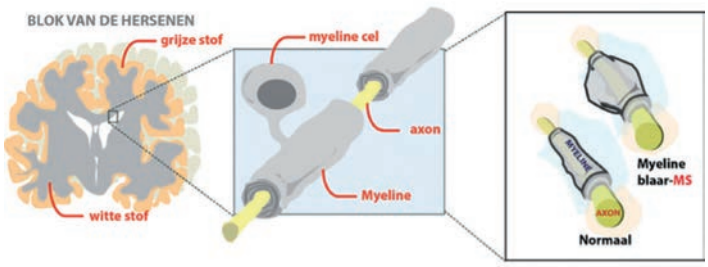
NWA-ORC grant for research on the circadian clock

Dutch researchers are joining forces to study the biological clock in our modern 24-hour society. Our 24-hour society disrupts the biological clock of many species, increasing the prevalence of mental and physical illness and threatening biodiversity on a global scale. Together with 58 partners, the research group of professor Andries Kalsbeek received 9.7 million euros from the National Science Agenda (NWA) for research into the biological clock in modern society.

As a contributor to this national consortium, Andries Kalsbeek, Dirk Jan Stenvers, and Joram Mul will investigate how physical activity influences the central clock in the brain in animal models. The researchers will develop strategies to restore and maintain clock function in society and healthcare, helping to ensure a sustainable future for our planet and its inhabitants. Additionally, they will study the right timing of physical activity and nutrition to reduce the adverse metabolic effects of working in shifts.

Axon-myelin unit disruption in Multiple Sclerose

Researchers from MS Center Amsterdam investigated the presence of axonal and myelinic morphological alterations which could implicate an imbalance of axon-myelin units as a primary event in Multiple Sclerosis (MS). Antonio Luchicchi, Bert 't Hart, Irene Frigerio, Anne-Marie van Dam, Laura Perna, Geert Schenk, Jeroen Geurts, and colleagues published their findings in the journal Annals of Neurology.



Demyelination is the main pathological hallmark of MS. There are different theories about the underlying mechanism of this demyelination in MS and it is poorly understood. The study by Antonio Luchicchi and colleagues shows new evidence for the inside-out theory that posits that MS autoimmunity occurs subsequently to primary CNS cytodegeneration. In the Annals of Neurology publication, the researchers describe several subtle changes to the myelin that could generate the harmful inflammatory responses, referred to as blister-like swellings formed by myelin detachment from axons. The impaired adhesion of myelin can induce defective expression of glutamate receptors and tethering/adhesion molecules and other morphological alterations which causes an inflammatory response. In the follow-up study, Luchicchi will investigate whether the blisters can indeed cause an inflammatory reaction.

No improvement for subarachnoid hemorrhage with ultra-early tranexamic acid

A study by Amsterdam UMC neurosurgeon René Post and his colleagues does not show any improvement of clinical outcome after subarachnoid hemorrhage, presumably caused by a ruptured aneurysm. The results of their study from 2013 to 2019, in which they enrolled 955 patients, are published in The Lancet.

Patients with subarachnoid hemorrhage can experience rebleeding from the ruptured aneurysm, which increases the risk of poor clinical outcome. Short-term antifibrinolytic therapy with tranexamic acid (TXA) has been shown to reduce the risk of rebleeding. The ULTRA investigators investigated whether ultra-early, short-term treatment with tranexamic acid improves clinical outcome at six months.

With the study of Post and his colleagues, that started in 2013, it can now be demonstrated that TXA does not improve the clinical outcome in these patients at six months' follow-up. The possible explanation of this is two-fold. Firstly, current guidelines advise treatment of the ruptured aneurysm as soon as feasible, preferably within 24-72 hours. However, treatment of patients with subarachnoid hemorrhage has changed over the years, resulting in increasingly shorter times for aneurysm treatment. This study showed that in half of the patients the aneurysm was secured within 14 hours. This early aneurysm treatment shortens the time-window in which TXA can be effective. Secondly, it is known that half of the rebleeding occur within three hours. Yet, despite the ultra-early initiation of TXA treatment, the reduction of rebleeding was not soon enough in this study to prevent a considerable amount of rebleeding.

EEG biomarker predict the effectiveness of antidepressants

The success rate of antidepressants in the treatment of depression can be greatly improved thanks to the use of a short brain examination (EEG) prior to treatment. A group of researchers including Martijn Arns of Amsterdam UMC examined, for the first time, the use of EEG as a biomarker in practice.

Until now, the choice for a specific antidepressant was mainly made based on experience and estimation of the prescribing physician. This trial-and-error approach can result in taking up

to three or four different courses of treatment before a patient responds adequately. The use of biomarkers, and therefore measurable predictability, greatly increases the effectiveness of treatment and can lead to a patient receiving the antidepressant that works for them sooner. This is a major step toward biomarker-based stratified psychiatry.

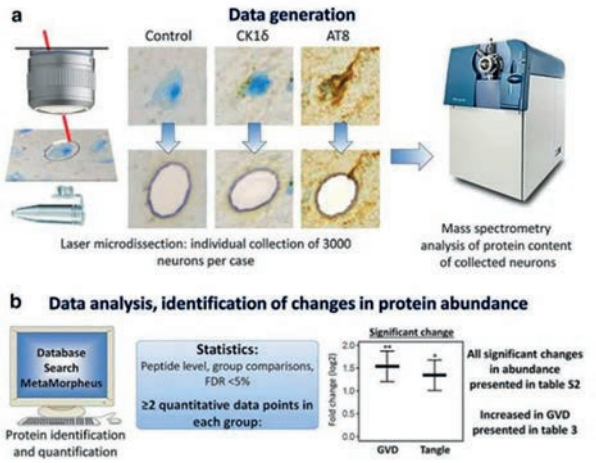

Martijn Arns

In an international collaboration with Amsterdam UMC, researchers have developed an algorithm that can accurately predict the effectiveness of the three most commonly prescribed antidepressants per individual. By applying this algorithm in practice, the researchers saw that the chance of full recovery almost doubled, compared to treatment as prescribed by the psychiatrist. This is the very first study worldwide to show that brain activity is a better predictor than the diagnosis of 'depression' per se as applied in practice.

Pre-stage of Alzheimer's disease neurons characterized

A new study by David Hondius, Frank Koopmans, and colleagues provide molecular evidence that so-called granulovacuolar cells are representing the pre-tangle neuronal stage in Alzheimer's disease. The study was published in Acta Neuropathologica.

Granulovacuolar degeneration (GVD) is a common feature in Alzheimer's disease (AD) which is closely related to that of neurofibrillary tangles (NFTs). The composition of GVD bodies, the mechanisms associated with GVD, and how GVD relates to NFTs is not well understood. By combining immunohistochemistry (IHC) and laser microdissection (LMD) the authors isolated 3000 neurons each with GVD or tangles separately from human post-mortem AD hippocampus.



The study identified many proteins that had not been associated previously with GVD or NFTs. The data show that GVD and neurofibrillary tangle bearing neurons are molecularly different but closely related. GVD bearing neurons have an increased presence of proteins associated with protein folding, endolysosomal function, and glycolysis, while there is a decrease of proteins involved in RNA processing and proteasome components. The data support the model that GVD is part of a pre-NFT stage representing a phase in which proteostasis and cellular homeostasis is disrupted.

State-of-the-art paper on anxiety disorders in The Lancet

Together with international colleagues, Professor Brenda Penninx from Amsterdam UMC and Vrije Universiteit wrote a seminar paper on anxiety disorders that was published in The Lancet. This article summarizes the scientific knowledge on the diagnosis, epidemiology, pathophysiology, and prevention with emphasis on evidence from the last five years.


Brenda Penninx

Anxiety disorders form the most common group of mental disorders and generally start before or in early adulthood. It involves dysfunction in brain circuits that respond to danger. The risk for anxiety disorders is influenced by genetic factors, environmental factors, and their epigenetic relations. Reducing the large burden of disease from anxiety disorders in individuals and worldwide can be best achieved by timely, accurate disease detection and adequate treatment administration, and scaling up of treatments when needed.

Evidence-based psychotherapy and psychoactive medications are both effective, facilitating patients' choices in therapeutic decisions. Although promising, no enduring preventive measures are available, and, along with frequent therapy resistance, clinical needs remain unaddressed. Ongoing research efforts tackle these problems, and future efforts should seek individualized, more effective approaches for treatment with precision medicine.

Progress in Alzheimer's disease over a five-year horizon

The Lancet published a seminar by Philip Scheltens and (inter) national fellow researchers about the main developments in the field of Alzheimer's disease over the past five years. This state-of-the-art overview highlights epidemiology, genetics, pathophysiology, biomarkers, and treatment options.

Five years ago, a similar seminar was published by Scheltens. Comparing the two papers illustrates the progress that has been made since then. Research on the underlying pathology, the recognition of multiple causative and protective genes, and the identification of new blood-based and imaging biomarkers have brought many new insights. And even the first cautious signals of positive effects of disease modifying treatments and lifestyle interventions are reported.
Alzheimer's disease is the leading cause of dementia and one of the most expensive, lethal, and burdening diseases of this century.

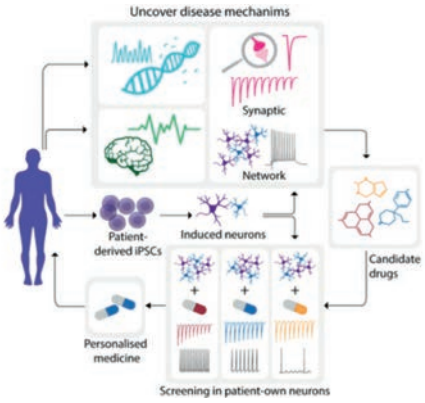
Alzheimercenter Amsterdam

Research over the past five years has contributed to a better understanding of the underlying pathology of the disease. Novel biomarkers include PET scans and plasma assays for amyloid β and phosphorylated tau, which shows great promise for clinical and research use. Furthermore, multidomain lifestyle-based prevention trials suggest cognitive benefits in participants with an increased risk of dementia.

First SNAREopathy treatment started in new N=You Center

A young patient who carries a SYT1 mutation is the first to receive a mechanism-based treatment with the prescription of bumetanide, aiming to reverse excitation/inhibition disturbance. The new N=You Center headed by Hilgo Bruining (Amsterdam UMC) and Matthijs Verhage (FGA, CNCR) uses new precision medicine approaches to treat children with neurodevelopmental disorders (NDDs).

Translational research at CNCR aims to elucidate disease mechanisms for a prominent class of monogenetic NDDs,



the SNAREopathies, and to establish in vitro models, based on the patient's own IPSC-derived neurons, to screen compounds, especially off-label drugs, and suggest the most suitable to N=You clinicians for treatment. CNCR scientists Maaike van Boven and Niels Cornelisse specialize in mutations in one SNAREopathy gene SYT1. In parallel to the treatment, Van Boven and Cornelisse are studying neurons from the first patient in vitro to better understand how the specific mutation in this individual leads to aberrant cellular functions.

Living with bipolar disorder

Annemiek Dols and Moniek van Dijk composed a photography book filled with personal stories of people with bipolar disorder, their loved ones, and healthcare professionals to show a realistic image of their lives. The book, published by Boom publishers, is called 'Tightrope Walkers' (Koorddansers in Dutch).

Annemiek Dols, psychiatrist and research associate at Amsterdam UMC, and Moniek van Dijk, nurse at GGZ inGeest, were driven by their passion to break the stigma of people with bipolar disorder. "There is a lot of misunderstanding and shame, among these patients themselves, their immediate environment, and within society as a whole." Says Dols: "Now it's time to break that stigma and illustrate the real lives of people with bipolar disorder and their loved ones." With this new book, Dols and Van Dijk want to open the doors to the lives of people with bipolar disorder and start a new era where psychological problems should not be kept a secret.

Bipolar disorder occurs in 2% of people in the Netherlands, just as often in men and women. In the Netherlands, many people with bipolar disorder have not yet been correctly diagnosed.

Among other reasons, people often do not seek help, because they are ashamed, or do not suffer from manic episodes themselves.

ABOARD: Stopping Alzheimer's before it starts

The Dutch project ABOARD (A personalized medicine approach for Alzheimer's disease), a collaboration of more than thirty partners, has been launched. ABOARD aims to prepare for a future in which Alzheimer's disease is stopped before dementia has started. ABOARD achieves this by improving diagnostic markers, developing personalized risk scores, and by focusing on prevention through increased awareness of dementia and brain health.

Wiesje van der Flier

Dementia is largely caused by Alzheimer's disease, for which there is no cure yet. To lower the number of individuals with dementia ABOARD focuses on the Alzheimer-stages before dementia onset. Researchers are going to develop tests that allow for an early and precise diagnosis of Alzheimer's disease. These tests must identify the first brain changes, and they need to recognize variability between patients. Based on these tests, we develop personalized risk profiles to predict individual disease trajectories.

Wiesje van der Flier, principal investigator of ABOARD and scientific director of the Alzheimer Center Amsterdam commented: "In addition, we want to increase the awareness of Alzheimer's among the general public and share knowledge about ways to boost your brain health. Supporting people with Alzheimer's is also a part of this project."

TETRO trial: Support for research into treatment-resistant OCD

With a grant of 2.8 million euros, several Dutch hospitals and mental health institutions are supported in their search into a new, promising treatment for treatment-resistant compulsive disorders. The research is led by professor of neuropsychiatry Odile van den Heuvel from Amsterdam UMC.

From a longer-term perspective, roughly 50% of the people with OCD can't be remedied with existing care (cognitive behavioral therapy and/or medication). Currently, there is no good alternative for them. The most far-reaching treatment (brain surgery or deep brain stimulation) is only an option for the most extreme cases.

Odile van den Heuvel

In the coming years, 250 patients will participate in the research study for a new, promising treatment for OCD. This promising treatment is repetitive transcranial magnetic stimulation (rTMS). An electric current in the brain is generated with the help of a magnetic field. This allows stimulating the brain circuit that is responsible for controlling emotions and behavior. This means the brain will be brought into an optimal condition to increase the effects of cognitive behavioral therapy.

When the results show that rTMS treatment is effective for the group of patients for whom nothing else currently helps, the treatment ends up in the basic insurance. Additionally, the grant also enables OCD specialists, to achieve national collaboration.

Seed grant for research into mechanisms of deep brain stimulation for OCD

The Foundation for OCD Research has awarded a Seed Grant to the research group of Ingo Willuhn. They will receive $800,000 over four years for exploring neural mechanisms of deep-brain stimulation in a mouse model for obsessive compulsive disorder (OCD).

Ingo Willuhn

Deep-brain stimulation (DBS) is an effective therapy for otherwise treatment-resistant OCD patients. However, optimizing DBS parameters requires months and its neural mechanism of action is largely unknown. With this grant, the research group of Ingo Willuhn wants to gain more knowledge on the neural mechanisms in an OCD mouse model. Willuhn explains: "To improve DBS therapy, we will use SAPAP3 mutant mice, a model system that captures key elements of OCD. We aim to characterize the effects of DBS on compulsive behavior and neural activity in OCD-relevant brain circuits in these mice."

Vici grant for Erik Rietveld

Erik Rietveld, Socrates Professor at Amsterdam UMC, received a Vici grant for his project 'Change-Ability for a World in Flux: The next step for an embodied cognitive science of brain-body-environment systems'.

Rietveld receives 1.5 million euros for his research project, which is targeted on collective behavioral change and artistic imagination.


Erik Rietveld

With this grant, he will develop the new Change-Ability Conceptual Framework (CAF). Together with his brother, Ronald Rietveld, and the team of RAAAF, Erik Rietveld spent the last 15 years becoming an expert on change-ability. Change-ability is defined as 'Skilled ways of coordinating with a rapidly changing world'. This project aims to open up a new perspective on change-ability, starting from the insight that what people do is both enabled and constrained by the action possibilities offered by their surroundings.

Claudia Persoon receives NWO Take-off grant for valorization

With the NWO take-off grant Claudia Persoon, postdoctoral researcher at the Center for Neurogenomics and Cognitive Research, will investigate the commercial potential of the human neuron cell models and imaging techniques developed at Amsterdam UMC and VU Amsterdam in search of new treatments for brain disorders.


Claudia Persoon

Neurological and psychiatric disorders present a staggering health care burden, costing around 800 billion euros per year in the EU and affecting almost 180 million people. Currently, the development of new therapies for these disorders is quite unsuccessful. Most therapy design relies on heterologous cellular models (mitotic cells). However, models that model the human brain (post-mitotic neurons) more closely are still scarce.

At the Functional Genomics lab, Claudia Persoon, Ruud Toonen, and Matthijs Verhage developed new preclinical screening assays for therapy design, based on functional, mature human neurons and CRISPR-Cas9 technology. Human neurons, derived from patient skin cells, mimic in a tissue culture setting the situation in the patients' brain ('patient-brain-in-a-dish'). High-end technology is established, such as live cell imaging and electrophysiology, to assess the efficacy of novel therapies. Together these assays will greatly enhance the identification of successful treatment strategies.

Claudia Persoon will reach out to and collaborate with the pharmaceutical industry through a spin-off company from the VU Amsterdam.

Babies face greater risk of problems after streptococcal infection

The largest study of its kind shows infected babies face a greater risk of neurodevelopmental impairments and underlines the need for follow-up care for survivors. This study was conducted through a partnership of the London School of Hygiene & Tropical Medicine, Aarhus University, Amsterdam UMC, and the Dutch National Institute for Public Health and the Environment.

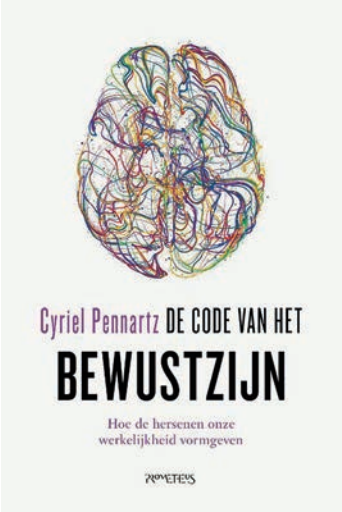
Invasive Group B Streptococcus (GBS) disease, notably meningitis, during the first days and months of a baby's life can have persistent effects on children and hence their families, according to new research. Published in The Lancet Child & Adolescent Health, the study is the first evidence of long-term effects including after GBS sepsis (infection in the bloodstream). This large study analyzed outcomes for nearly 25,000 children born in Denmark and The Netherlands, between 1997 and 2017. Results show that children who had invasive GBS infection are twice as likely to have neurodevelopmental impairments (NDI) and to require special educational support than children who did not have GBS disease.

Effects later in life are significant - about one in 20 survivors will experience some form of neurodevelopmental disability. The authors, including Merijn Bijlsma, Merel van Kassel, and Diederik van de Beek of Amsterdam UMC note that the majority of GBS infection survivors will not have long-term effects.

Book on the code of consciousness

Neuroscientist at the University of Amsterdam Cyriel Pennartz presents a new popular science book in Dutch: 'De code van het bewustzijn'. A book on how the brain shapes our reality.

"This is not a book for the faint of heart - it is for doubters, tinkerers, worriers, trackers, and other people curious about what's



going on up there in their head," thus Cyriel Pennartz on his new book. In the book, Pennartz takes the reader on an inspiring quest for one of the greatest scientific challenges of the twenty-first century: understanding the relationship between brain and mind.

Pennartz, a professor at the Swammerdam Institute for Life Sciences (SILS), has written this popular scientific work in Dutch. The issue of consciousness - and especially sensory consciousness - is central in it. How is the brain, this remarkable tissue where it literally crackles with electrical activity, able to let us experience the world with its wealth of qualities as if it's just regular matter? According to Pennartz, studying experience and consciousness is not an impassable road. In fact, over the past thirty years, studies of patients, computer simulations, and the electrical behavior of brain cells have paved the way for thorough research into brain mechanisms of consciousness.

Glucocorticoids alter the formation of memory engrams

A collaborative study reveals that elevated levels of the stress hormone corticosterone induce an increase in the size of a hippocampal fear engram and this change underlies generalized expression of fear in a neutral environment. Members of the Memory Circuit team of CNCR of VU Amsterdam worked together with the lab of Harm Krugers and Sylvie Lesuis of the University of Amsterdam. Their findings were published in Biological Psychiatry. Sylvie Lesuis and her colleagues demonstrate that mice that receive corticosterone treatment immediately after contextual fear conditioning show a fear response in a novel environment where the mice never had an aversive experience.

Although fear conditioning reduces the excitability of learning-activated hippocampal dentate gyrus neurons, corticosterone selectively increases the excitability of these cells. This is accompanied by a stable increase in the size of the engram cell population and these cells become reactivated when mice are exposed to a neutral context, suggesting that this drives the generalized fear response after elevated corticosterone levels. To confirm this, Michel van den Oever and colleagues used a viral-TRAP approach to express an inhibitory DREADD selectively in the corticosterone-enhanced engram cell population. Chemogenetic suppression of these specific neurons abolished the generalized fear response when mice were exposed to the novel environment.

Six TKI-PPP grants awarded to neuroscience researchers


Wilma van de Berg


Martijn Beudel


Henne Holstege


Laura Jonkman


Eric Reits


René van Rijn

Neuroscience researchers Wilma van de Berg, Martijn Beudel, Henne Holstege, Laura Jonkman, Eric Reits, and René van Rijn have been awarded a TKI-PPP grant varying from 339,000 to 640,000 euros for their research project in collaboration with an industrial partner. The funding is provided by the Dutch government (Ministry of Economic Affairs & Climate Policy) through the Top Sector Life Sciences & Health (Health-Holland). It is meant to support innovative research and development realized by public-private partnerships (PPP).

ADAPT-Parkinson's Disease
Wilma van de Berg has been awarded 420,150 euros to research dysfunctional adaptive immune responses that drive the disease progression of Parkinson's disease.

Adaptive I-Deep Brain Stimulation
Martijn Beudel has been awarded 520,320 euros for applying personalized neuromodulation using neural 'Fingerprints'.

Alzheimer's Disease-REPEAT
Henne Holstege has been awarded 640,000 euros for the comparison of genetic repeat expansions between Alzheimer's Disease patients and cognitively healthy centenarians.

PA-MRI in Alzheimer's Disease
Laura Jonkman has been awarded 642,031 euros for the research of pathological sensitivity of MRI biomarkers in Alzheimer's Disease.

Compound screening and validation to reduce mutant Huntington levels
Eric Reits has been awarded 440,481 euros for the compound screening and validation to reduce mutant Huntington levels.

AMESMC
René van Rijn has been awarded 339,000 euros for the automated Strabismus measurement.

Can I stop taking antidepressants?

Research in JAMA Psychiatry shows that brief psychological interventions such as Preventive Cognitive Therapy (PCT) and Mindfulness-Based Cognitive Therapy (MBCT) can be an alternative to long-term antidepressant use. This research was led by Claudi Bockting, professor of clinical psychology in psychiatry, and dr. Josefien Breedvelt, both from Amsterdam UMC, with the international consortium relapse prevention ITFRA. Most often, patients at high risk of relapse continue to take antidepressants long-term to prevent future relapse.

Claudi Bockting

This study, based on all individual participant data from RCTs on this comparison worldwide shows that psychological interventions can be an alternative to antidepressant continuation, even if a patient's risk of relapse is high. That is, they have residual symptoms of depression or a high number of prior episodes. These findings are of importance for (inter)national clinical guidelines and for clinical practice for patients who wish to taper or stop their antidepressants.

Parkinson's at the psychiatrist: a book with stories of love, grief, and resilience

Odile van den Heuvel and Sonja Rutten, both psychiatrists working at Amsterdam UMC, published a book where they write about the mental symptoms many patients with Parkinson's disease experience, such as anxiety, depression, and psychosis entitled 'Parkinson's at the psychiatrist' ('Parkinson bij de psychiater' in Dutch). They see the book as an ode to the resilience and creativity of people with Parkinson's disease (PD).

The book features twenty personal stories from people with PD, who opened up about their personal experiences in the hope that they can help other patients. For example, to recognize the psychiatric symptoms, being able to talk about difficult topics, seek help, and find a way to deal with the mental side of PD together with loved ones and therapists. As a reader, you get an insight into the perspective of the psychiatrist, and you are included in their observations and medical considerations. Van den Heuvel: "With this book, we show that we can treat many psychiatric symptoms. Sometimes, however, it is necessary to look for ways to cope well with persistent symptoms."

Elga de Vries receives funding for research on human cell model

The CONNECT project is awarded 1.3 million euros from NWO for the development of an innovative measurement method to better understand the brain. Elga de Vries, professor of molecular cell biology at Amsterdam UMC, and Elly Hol, professor of biology and brain diseases at UMC Utrecht, are working together on this research project which aims to develop a human cell model that is closer to the patient than current cell and animal models.

Elga de Vries

They do this by using the latest technology from human stem cells to develop blood-brain barrier cells and link them to mini-brains. Their research project, on innovative mini-brains, is one out of six that received NWO funding to work on better predictive health research and less dependency on animal experiments.

The focus of the funded public-private partnerships is the development of human measurement models for research into the treatment and/or prevention of diseases. It is expected that research models based on human material, such as cells and tissues, will better approximate the situation in humans than laboratory animal models.

Worldwide guidelines on the use of MRI in multiple sclerosis

Mike Wattjes, Frederik Barkhof, and Hugo Vrenken, from MS Center Amsterdam, together with international fellow radiologists and neurologists, have developed a new guideline for the use of MRI in people with multiple sclerosis (MS). It is a complete guideline that will be supported and used by radiologists worldwide. The guideline has been published in The Lancet Neurology.

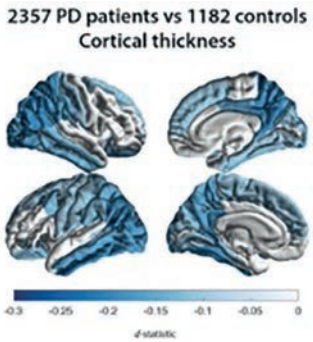
The 2021 revision of the previous guidelines on MRI use for patients with MS merges recommendations that translate research findings into clinical practice to improve the use of MRI

Frederik Barkhof

for diagnosis, prognosis, and monitoring of individuals with MS. These developments suggest a changing role of MRI for the management of patients with MS in the clinical setting. The new guidelines recommend changes in MRI acquisition protocols, such as emphasizing the value of three dimensional-fluid-attenuated inversion recovery as the core brain pulse sequence to improve diagnostic accuracy and ability to identify new lesions to monitor treatment effectiveness, and we provide recommendations for the judicious use of gadolinium-based contrast agents for specific clinical purposes. Additionally, the international consortium also extends the recommendations to the use of MRI in patients with MS in childhood, during pregnancy, and in the post-partum period.

Largest multicenter MRI study on Parkinson's disease reveals patterns of abnormal brain structure across its disease stages

In the largest collaborative MRI study on Parkinson's disease to date, coordinated by Prof. dr. Ysbrand van der Werf and PhD candidate Max Laansma of Amsterdam UMC, the anatomical scans and clinical data of 2357 persons with Parkinson's disease and 1182 healthy controls were investigated. Their findings offer new insights into patterns of abnormal brain structure in Parkinson's disease and how these relate to clinical staging. The study is published in the journal Movement Disorders.



The Parkinson's disease working group is part of the ENIGMA consortium, focused on elucidating imaging and genetic biomarkers of disease through worldwide collaboration. The publication presents the analysis of cortical and subcortical morphology in an unprecedented large sample. Laansma and colleagues demonstrated that, compared to healthy controls, the cortex of persons with Parkinson's disease was thinner in 38 of 68 regions. The bilateral putamen and left amygdala were smaller, while the thalamus was larger. Notably, the analyses on disease staging and cognitive performance revealed patterns of abnormal brain structure on a cortical and subcortical level that were strongly in line with an ongoing neurodegenerative process. These findings offer novel insights into the relationship between the clinical and biological staging of Parkinson's disease, highlighting the importance of adequately powered multicenter studies in the search for biomarkers.

UCB and CNCR join forces targeting genetic epilepsy syndromes

The global biopharmaceutical company UCB and the Functional Genomics lab of the Center for Neurogenomics and Cognitive Research (CNCR), led by Ruud Toonen, will invest 700,000 euros in joint research to develop new treatment strategies for genetic epilepsy syndromes. After previous collaborations between VU neuroscientists and UCB, both teams came to an agreement to develop treatment strategies for genetic epilepsy syndromes in the coming two years. On the Functional Genomics lab side Hanna Lammertse will manage the project.

Ruud Toonen

Epileptic seizures are important symptoms of several major brain disorders, including intellectual disability, learning disorders, autism spectrum disorder, and behavioral abnormalities. Synaptic dysfunction is a central aspect of these diseases leading to disturbed brain activity (excitation/inhibition balance) and dysfunction of neuronal networks. Current treatments are limited to symptomatic medications that provide limited relief and cause unpredictable and adverse side effects.

Menno Schoonheim and Henne Holstege awarded with Vidi grant

Neuroscientists Menno Schoonheim and Henne Holstege have been awarded a Vidi grant by the Dutch Research Council NWO. The grant enables them to develop their own innovative line of research and set up their research group in the coming five years.

Menno Schoonheim

Henne Holstege

The collapsing brain in MS: Using networks to predict clinical progression
Multiple sclerosis (MS) is a complex neurological disease, where most patients become impaired in motor and cognitive function. In this project, Menno Schoonheim is to understand and predict progression in MS by studying how damage spreads throughout the brain network. I will also implement these latest insights in daily clinical care.

Spotlight on the neglected genome to escape dementia
Repetitions in the DNA-code influence the chance of Alzheimer's Disease. Henne Hostege: "To increase our understanding of the heritability of Alzheimer's Disease, we will compare repetitive sequences in Alzheimer's patients and healthy centenarians. This allows us to use individual genomes to predict who should be treated to prevent AD-associated brain damage, and how."

Global genetics consortium uncovers COVID-19 risk factors

An international collaboration, including researchers from Amsterdam UMC, has identified several host-specific genetic factors associated with SARS-CoV-2 infection and COVID-19 severity. This global genome-wide analysis of 50,000 COVID-19 patients and 2 million controls was published in Nature and indicates 13 locations in the human genome associated with SARS-CoV-2 infection or severe manifestations of COVID-19.

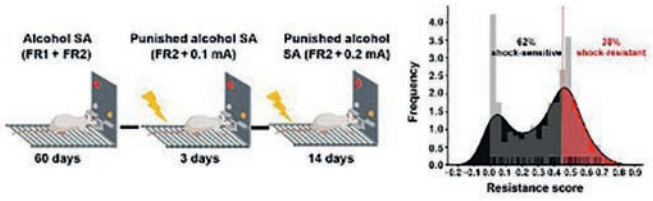

Matthijs Brouwer

Since March 2020, this global effort, called the COVID-19 Host Genetics Initiative, was founded by bringing together the human genetics community to generate, share, and analyze data on COVID-19 susceptibility, severity, and outcomes. With data from nearly 50,000 COVID-19 patients from 46 studies across 19 countries, more than 3,300 authors contributed to this large-scale study, which makes it one of the most extensive collaborations in human genetics. The COVID-19 Biobank of Amsterdam UMC contributed to this study and consortium by providing DNA and data from COVID-19 patients. Additionally, other Dutch knowledge institutes participated, e.g. Erasmus MC and Leiden University Medical Center.

"This project is team science on a world level," Matthijs Brouwer from the Amsterdam UMC COVID-19 biobank says. "In addition to this landmark publication, this project has generated many sub-studies that will further help our understanding of COVID-19. New results are continuously shared online through the project's website and provide a basis for a multitude of follow-up studies. We are happy to be able to contribute to such an important project with the COVID-19 biobank."

Identification of neurons that promote compulsive alcohol use

Michel van den Oever and Esther Visser of the Center for Neurogenomics and Cognitive Research at VU Amsterdam were involved in a study on compulsive alcohol use led by Markus Heilig and Esi Domi at the Linköping University in Sweden. Using the viral-TRAP technique developed by the Memory Circuits team, they identified a small population of PKC-delta-expressing neurons in the central amygdala that drives footshock-punished alcohol intake. Their findings are published in Science Advances.



Compulsive alcohol use can be modeled in rats by pairing operant alcohol self-administration with adverse footshocks. Domi and colleagues found that similar to humans, a small fraction of rats is resistant to this negative consequence and will continue to self-administer alcohol. In this resistant subpopulation, they discovered that PKC-delta-expressing neurons in the central amygdala are activated during punished-alcohol self-administration. Selective suppression of these activated neurons in the central amygdala (using viral-TRAP) or local knock-down of PKCdelta expression reduced alcohol consumption. Together, this study reveals a novel neuronal substrate that controls compulsive alcohol use.

Patients with carotid web have a high risk of recurrent stroke

A study, coordinated by neurologist at Amsterdam UMC Jonathan Coutinho, investigated the risk of recurrent stroke in patients with symptomatic carotid web. Their findings suggest that medical management alone may not provide sufficient protection for recurrent stroke. This study was published in the journal JAMA Neurology.

A carotid web (CW) is a shelf-like lesion along the wall of the internal carotid artery after the bulb. It is an under recognized cause of stroke in the young. The CWs bulge into the lumen of the carotid artery causing flow disruption and blood stasis. This again results in thrombus formation and ischemic stroke. High-

Jonathan Coutinho

quality data on the risk of recurrent stroke was lacking. Therefore, Valeria Guglielmi and colleagues investigated the risk of recurrent stroke in patients with symptomatic CW. The researchers conducted a comparative cohort study using data from both a randomized clinical trial conducted at sixteen centers in the Netherlands (MR CLEAN trial) as well as data from a nationwide observational cohort study (MR CLEAN registry). They obtained two-year follow-up data for 30 patients with ipsilateral CW with a comparator cohort of 168 patients.

The results showed that during a two-year follow-up, 5 of the 30 patients (17%) with CW had a recurrent stroke compared with 5 out of 168 (3%) patients without CW. Moreover, for the patients with CW, the recurrent ischemic strokes were in the same area as the CW. The patients with ipsilateral CW all received medical management after the index stroke, mostly with antiplatelets. These data suggest that standard medical management alone may not provide sufficient protection for the high recurrent stroke risk observed in these patients.

Combining strengths to spur innovations in oncology and neurology

The mission of Amsterdam Oncology and Neuroscience Research (ADORE) is to propel research into the development and application of next generation therapeutics. The initiative combines the strengths of different disciplines – oncology and neuroscience - to investigate disease mechanisms and new treatment options using different perspectives and methods. ADORE is a joint initiative from Amsterdam UMC and the VU Amsterdam, under the direction of Cancer Center Amsterdam and Amsterdam Neuroscience.

Innovation Center ADORE will also connect science and business by offering companies access to unique scientific and clinical expertise, as well as research facilities via the Industry Alliance Office (IAO) and Innovation Exchange Amsterdam (IXA). The collaboration with industry partners aims to accelerate innovation in the development and application of cell and gene therapy in the fight against cancer and neurological diseases. To achieve this goal, new facilities will be set up, including a good manufacturing practice (GMP)-grade facility for the development of new cell therapies, and a highly sensitive whole-body PET-CT imager for radiolabeling and tracking studies involving patients.

A dedicated team of business developers is working as knowledge providers and ambassadors, side by side with scientists, to market scientific and clinical expertise and access to the state-of-the-art facilities within ADORE Innovation Center. The team is led by Marianka van der Tol (IXA-Cancer Center Amsterdam) and Sasja Heetveld (IAO-Amsterdam Neuroscience). Timo Smets and Mark Mizee have joined the team to help bridge academic and industry needs. Please reach out to us to get acquainted and discuss how you can accelerate your research through industry partnerships.

Novel genetic risk factors detected for Alzheimer's disease

Douglas Wightman, PhD student at the Complex Trait Genetics group of the CNCR published his results in Nature Genetics. The large-scale genetic study resulted in the discovery of novel genes and biological mechanisms that contribute to the pathogenesis of Alzheimer's disease.

Douglas Wightman

Genetics might help to understand the underlying biological mechanisms that are involved in the initiation of pathological processes leading to clinical Alzheimer's disease (AD). The current research includes over a million individuals and is the largest genetic study for AD so far. The results pointed towards the involvement of genes specifically expressed in microglia, indicating that these types of cells, which are known to be involved in the immune

system, are important in the pathogenesis of AD. Further results highlighted a role for biological pathways concerning amyloid protein, neurofibrillary tangles, immune cells, and glial cells in AD. “As a whole, the results highlighting amyloid protein, a biomarker for AD aggregation in the brain, and microglia, the constituent immune cell within the brain, support the current hypothesis that AD pathogenesis is caused in part by protein aggregation and dysregulation of the immune response within the brain,” says professor Danielle Posthuma.
The study identified 7 regions of the genome not previously associated with AD and implicated 9 specific genes across 38 regions. However, AD is a complex disease with many environmental and genetic contributors, with many associated regions of the genome yet to be discovered. The current results explain a moderate amount of the genetic risk for AD and highlight interesting new genomic regions but there is further work to be done.

Neurofilament light chain and glial fibrillary acidic protein levels hold promise as biomarkers for Metachromatic Leukodystrophy

A retrospective study, coordinated by Professor Charlotte Teunissen and neurologist Nicole Wolf of Amsterdam UMC, compared neurofilament light chain and glial fibrillary acidic protein levels in the CSF and blood of patients with metachromatic leukodystrophy. Their study indicates that both the proteins may be considered a non-invasive biomarker for clinical phenotype and that neurofilament light chain might enable neurologists to make a better-informed treatment decision. This study was published in the journal Brain.


Nicole Wolf

The study compared CSF and blood samples of 40 metachromatic leukodystrophy (MLD) patients between the ages of 0 and 42 with 38 healthy children and 38 healthy adults. The blood neurofilament light (NfL) levels at diagnoses were significantly increased in both pre-symptomatic and symptomatic patients. The glial fibrillary acidic protein (GFAP) levels were only increased in symptomatic patients. Next to this, higher blood NfL and GFAP levels at diagnoses were associated with rapid disease progression in late-infantile and early juvenile patients. This study showed that both proteins hold promise as biomarkers for MLD disease stages in both clinical and research settings.

New Amsterdam Neuroscience MAGAZINE – The 2021 edition

The third edition of the Amsterdam Neuroscience MAGAZINE covers the overarching theme: resilience. This magazine dives into the understanding of the brain, via resilience, prognosis, and prevention. You will find a series of interviews with a selection of neuroscientists from our Amsterdam Neuroscience research institute. Each of them is studying resilience in some way — be it directly or indirectly — and they discuss the above-mentioned aspects in more detail.

Study on tailor-made treatment for MS drug ocrelizumab

For the drug natalizumab, it is already possible to create a treatment regimen tailored to the individual. Because of the custom-dosed treatment, patients visit the hospital less often for an infusion and are less likely to experience serious side effects. In addition, medical costs are also lower. Whether this also applies to the MS drug ocrelizumab is being investigated in a new national study set up by MS Center Amsterdam. Neurologists Joep Killestein and Zoé van Kempen have been awarded 1.3 million euros for this study, by ZonMw and the Treatmeds Foundation.


Joep Killestein


Zoé van Kempen

The study compares two groups of 150 people with MS. One group will receive the standard treatment with ocrelizumab and the other group will receive personalized treatment. These groups will be compared on: MS attacks, MRI characteristics, blood values, side effects, complications, quality of life, treatment burden, and costs. Zoé van Kempen: "A survey among people who use ocrelizumab showed that they have a need for this study into a personal treatment regimen. Also, during these times of COVID-19, a treatment that does not impact the immune system more than necessary is highly relevant."

Not only do patients find this new MS study important. Many hospitals and MS centers in the Netherlands that heard of the study have joined Killestein and Van Kempen. The research is made possible by a subsidy from ZonMw in the Good Medicine Use program and is financially supported by the Treatmeds Foundation, an initiative of Dutch health insurers. This enthusiastic involvement of the health insurers is an important step in transferring future results to regular care.

Brainmodel: precision medicine for brain disorders

The new BRAINMODEL consortium consisting of researchers from six Dutch knowledge institutions, coordinated by the Center for Neurogenomics and Cognitive Research of VU Amsterdam and Radboud UMC, has been awarded a grant of 4 million euros from ZonMw, to develop new research methods to improve treatment for neurodevelopmental disorders.

For many brain disorders, it is becoming increasingly clear which DNA variation contributes to the disease. However, an effective systematic approach for linking this knowledge and the underlying biological mechanisms to treatment options is mostly lacking. BRAINMODEL's new approach is based on patient-derived cells where networks of living nerve cells are produced in a culture dish, known as 'pluripotent stem cell technology (iPSC)'. These closely resemble the neural networks in our brains and offer new opportunities in terms of understanding human diseases and finding personalized treatments.
The BRAINMODEL consortium aims to integrate these methods with diagnostic techniques and relate them to other technologies such as EEG to find the best possible treatment for individual patients. The researchers will subsequently test whether abnormal cellular properties, which cause an imbalance between the positive and negative signals that nerve cells send to one another, can be remedied with existing medication in the iPSC-based analyses.

Reviewing the Alzheimer's drug development landscape

Pieter van Bokhoven, the new Chief Scientific Officer of the Industry Alliance Office (IAO) of Amsterdam Neuroscience, wrote with his colleagues a review on the landscape of Alzheimer's disease (AD) drug development over the last 15 years. This review gives insight into the status of AD drug development by comparing drugs in preclinical development to drugs currently tested in clinical trials and is published in the journal BioMed.

Pieter van Bokhoven

The research field investigating neurodegenerative diseases, such as AD has made significant progress over the last 15 years. Diagnoses have altered from a syndrome diagnosis towards a biomarker construct. However, drug development for AD has been proven to be difficult, and despite failures, the field has not lost confidence in drug development for AD.
In the review, Van Bokhoven found a higher proportion of preclinical interventions targeting molecular pathways associated with sporadic AD genetic risk variants, compared to clinical stage interventions. These include apolipoprotein E (ApoE) and lipids, lysosomal/endosomal targets, and proteostasis.
He also witnessed a trend suggesting that more traditional therapeutic modalities are developed for novel targets, such as apolipoprotein E and lipids, lysosomal /endosomal targets, and proteostatis. More novel treatment modalities such as gene therapies and enzyme treatments on the other hand are in development for more traditional targets such as amyloid B and tau. Interestingly, the percentage of amyloid β targeting therapies in preclinical development is even higher than the percentage in clinical development indicating that diversification away from interventions targeting amyloid-beta has not materialized. Inflammation is the second most popular target class in both preclinical and clinical development.
These observations show that the AD drug development pipeline is diversifying in terms of targets and treatment modalities, while amyloid-targeting therapies remain a prominent avenue of development as well.

Incorporation of functional brain measures in autism spectrum disorder treatment

A study, under the supervision of researchers Klaus Linkenkaer-Hansen and Hilgo Bruining of VU Amsterdam and Amsterdam UMC, investigated the neurophysiological effects of bumetanide and its relation to clinical outcome variability in autism spectrum disorders. They showed that bumetanide has neurophysiological effects in children with autism spectrum disorder and can improve stimulus processing. Next to this they also looked at the potential for machine-learning-based predictions of meaningful clinical improvement.

Autism spectrum disorder is a heterogeneous group of neurodevelopmental disorders. Some forms require medicine to cope with severe social, sensory, and affective symptoms. However, a drug intervention is often accompanied by extensive variability in treatment responses. The incorporation of functional brain measures related to the mechanistic effects might help successful application. In the study of Linkerkauer-Hansen, Bruining, and colleagues, several EEG measures before and after 91-days bumetanide treatment in this autism medication study were taken. Based on the observed EEG effects of this study, bumetanide might enter the brain sufficiently to alter both power and network-level E/I ratio of neuronal oscillations after 1,5 months of treatment. Changes in brain activity after bumetanide were related to improvement in repetitive behavior in more responsive subsets, in whom prediction of improvement were feasible by implementing pre-treatment EEG and clinical severity in machine-learning analysis.

Blood-based biomarkers for Alzheimer's disease

Charlotte Teunissen, professor in neurochemistry at Amsterdam UMC, and colleagues review the highly dynamic and accelerating field of blood-based biomarkers for Alzheimer's disease. In their review in the Lancet Neurology, they provide insight into the current state of the blood test and discuss which steps must be taken to be able to implement this in practice.

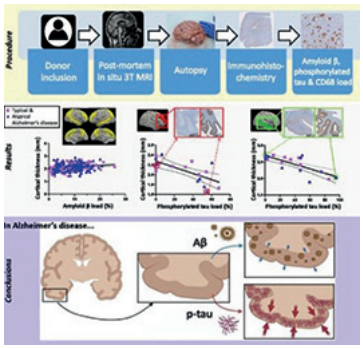
Charlotte Teunissen

Classic pathophysiological hallmarks of Alzheimer's disease (AD), think of amyloid-beta, tau, and neurodegeneration, can be detected using cerebral spinal fluid (CSF) or imaging techniques such as PET scans. However, these methods are invasive or expensive. There is a need to identify cost-effective biomarkers that can easily be obtained in a less invasive manner. Blood-based biomarkers seem to be the best option in this scenario. Recent results have shown that these blood-based biomarkers for Alzheimer's disease are becoming more and more reality.
Due to the availability of ultrasensitive detection methods the use of blood-based biomarkers for diagnosing AD is close to clinical use. Blood levels of the proteins amyloid and tau correlate strongly with levels of these proteins in CSF, and with evidence for the presence of AD on PET scans. These blood measurements provide information about the disease progression and can potentially monitor the effects of the treatment.

Distinct pathological markers correlated differently with cortical atrophy in Alzheimer's disease

A study by the research group with Laura Jonkman, Wilma van de Berg, Baayla Boon, and Irene Frigerio from Amsterdam UMC aimed to identify the histopathological correlates of MRI cortical atrophy in Alzheimer's disease. Until now, the relative contribution of pathological hallmarks to cortical atrophy was unknown. Their research indicates that distinct histopathological markers correlate differently with cortical atrophy. The results are published in Brain Communications.

Previous studies, using MRI and PET imaging, showed that tau tracers on PET images correlate with cortical atrophic patterns on MRI, while amyloid-beta deposition does not. However, PET imaging has limited resolutions, therefore this study investigated the association between post-mortem in-situ MRI



cortical thickness and histopathological hallmarks in pathologically-confirmed AD subjects. In the study, 19 Alzheimer's disease (AD) and 10 non-neurological control brain donors underwent post-mortem MRI scans. Upon subsequent autopsy, regions were immunostained for amyloid-beta, p-tau, and reactive microglia. Next to this, post-mortem MRI was also compared to antemortem MRI of the same AD donors. Their findings showed that in AD, amyloid-beta load correlates with a slightly increased cortical thickness relative to the atrophic AD cortex. P-tau is the strongest contributor to regional cortical atrophy in formal and temporal regions. Finally, reactive microglia load is the strongest correlate of cortical atrophy in the parietal regions. Distinct histopathological markers correlate thus differently with cortical atrophy.
Next to this, they also explored the AD phenotypes, and showed that reactive microglia load is increased in atypical AD, but not in typical even though no differences were found in MRI-pathology associations. Moreover, the study also showed that post-mortem in situ MRI can be used as a proxy for ante-mortem in-vivo MRI.

Research criteria for behavioral variant of Alzheimer's disease

A review and meta-analysis, conducted by Rik Ossenkoppele, Ellen Singleton, and Yolande Pijnenburg of the Alzheimer Center Amsterdam, looked into the research criteria for the behavioral variant of Alzheimer's disease (AD). The data indicated that the behavioral variant of Alzheimer's is most similar to the behavioral variant of frontotemporal dementia, while it shares most pathophysiological features with typical AD. This study was published in JAMA Neurology.


Rik Ossenkoppele

Alzheimer's disease (AD) is a heterogeneous disease, with the behavioral variant being rare. This behavioral variant of Alzheimer's disease (bvAD) is characterized by early and predominant behavioral deficits and personality changes caused by AD pathology. The challenge of clinical diagnosis lies in the fact that the bvAD clinical syndrome overlaps substantially with that of the behavioral variant of frontotemporal dementia (bvFTD). Therefore, to better understand the bvAD phenotype, researchers performed a systematic review and meta-analysis of the clinical neuroimaging, and neuropathology bvAD literature and applied the outcomes to develop research criteria for bvAD.
The review showed that, at the time of diagnosis, bvAD showed more severe neuropsychiatric symptoms and other behavioral deficits compared to typical AD. The neuroimaging literature revealed two bvAD phenotypes: one with an AD-like pattern and one with a relatively more bvFTD-like pattern. The AD-like patterns however are more prevalent. Overall, this analysis showed that bvAD is clinically most like bvFTD, while sharing more pathophysiological features with typical AD.

Veni grant for Philip Jansen

Philip Jansen, resident of clinical genetics at Amsterdam UMC, has been awarded the Veni grant by the Dutch Research Council NWO. NWO has awarded 89 highly promising young scientists from the ENW and ZonMw domain a Veni grant worth up to 280,000 euros. The grant provides the laureates with the opportunity to further elaborate their own ideas during a period of three years.

Identifying targetable mechanisms of insomnia in brain aging and dementia


Philip Jansen

Insomnia (sleep problems) is associated with aging of the brain and dementia. Whether insomnia is a cause or consequence of normal and accelerated brain aging, and through which mechanisms, is currently unexplored. Philip Jansen will use large-scale brain imaging and genetic data to elucidate causal pathways between insomnia, brain aging, and dementia.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