Amsterdam UMC
University Medical Centers

Amsterdam Neuroscience

Annual Report 2019

Colophon

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Word from the directors

The overall mission of Amsterdam Neuroscience is to broaden the fundamental knowledge of the human brain and nervous system, and to translate this knowledge into effective therapies and treatments for patients. The year 2019 turned out be an excellent year for our institute. We are proud to present great metrics in this report. The research highlights are just a selection of Amsterdam Neuroscience news items of 2019, but they echo the importance of 'team science' within our institute. The impact of team science was reflected in numerous collaborative high-impact publications. Furthermore, some major consortium grants, including a Gravitation grant, were awarded to a number of Amsterdam Neuroscience teams around key opinion leaders. We will continue to foster our team science projects.

As a research organization we have arranged our research in a focused manner along the nine translational research programs, each around specific brain and nervous system diseases, disease mechanisms, or technology innovations. We will continue to maintain this focus. What's more, we want to stimulate young and promising researchers to be part of these research programs. With this purpose, over the past four years (2016-2019), 84 outstanding proof of concept - and collaborative projects were funded, to a total of 9.2 million euros. We believe that this program-oriented strategy has been a meaningful and effective one, and our institute's metrics and highlights for 2019 support this view. It is with great pleasure that we present this fourth Annual Report.

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

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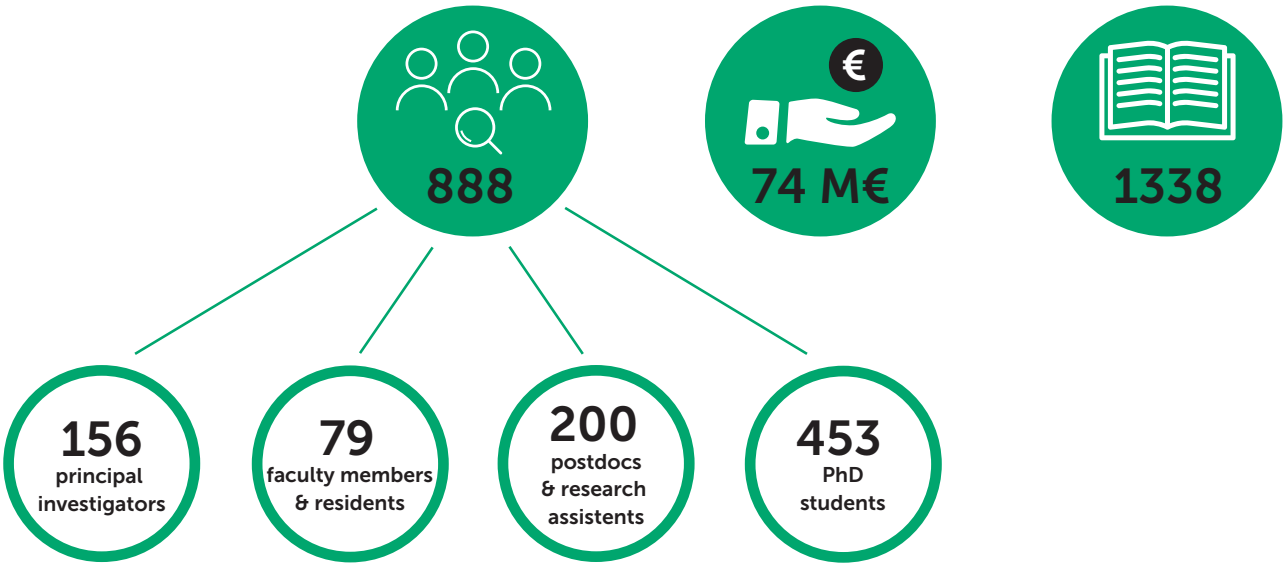
Executive Summary

- The collective 'community' of the Amsterdam Neuroscience research institute is currently made up of 888 investigators. This includes 156 principal investigators, 79 faculty members & residents, 200 postdocs & research associates, and 453 PhD students.
- Over the course of 2019, Amsterdam Neuroscience investigators acquired a total of circa 74 million euros in conditional funding. This included a Veni grant, three Vidi grants, and one Vici grant, as well as other major grants from Dutch agencies and the European Commission (EC), including one ERC advanced grant. Moreover, the Amsterdam Neursocience affiliates were involved in acquiring an NWA grant (1.8 million euros) for Precision Psychiatry, a Gravitation grant (approx. 20 million euros) for Complex Trait Genetics & Neuroscience, and an NWO Crossover grant (approx. 14 million euros) for NeuroTech-NL research.
- This also included more than 20 million euros from non-profit (patient-oriented) organizations and more than 20 million euros funding in contracted research from the biotechnology and pharma industry. Finally, in 2019 Amsterdam Neuroscience internally funded 2.5 million euros in proof of concept (PoC) projects, alliance projects, and innovation projects, which extend until the end of 2021.
- In 2019, a total of 1,338 refereed articles were published with 175 papers in the highest impact journals (impact factor > 10), and another 317 with a solid impact factor (> 5 < 10).
- Of these 1,338 unique papers, 150 had 'shared' co-authorship (i.e. 'bilocation' affiliations). Additionally, an extensive co-authorship network analysis revealed profound connections throughout, and also between, the different research programs of Amsterdam Neuroscience.
- Highlights throughout 2019 included Martijn van den Heuvel being appointed as University Research Chair (URC) professor, the Gravitation grant for the Brainscapes consortium being awarded to Danielle Posthuma c.s., Pieter Roelfsema c.s. receiving the NWO grant for the NeuroTech-NL consortium, Hilgo Bruining c.s. receiving the NWA consortium grant, and many more collaborative efforts as also show-cased during the 4th Annual Meeting of Amsterdam Neuroscience, held on 4 October, 2019.
- In 2019, the last group of 8 (out of a total of 45) graduate students of the European Neuroscience Campus Network (i.e. Erasmus Mundus Joint PhD program, ENC-Network, under supervision of Amsterdam Neuroscience) finished their PhD projects.



About Amsterdam Neuroscience

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

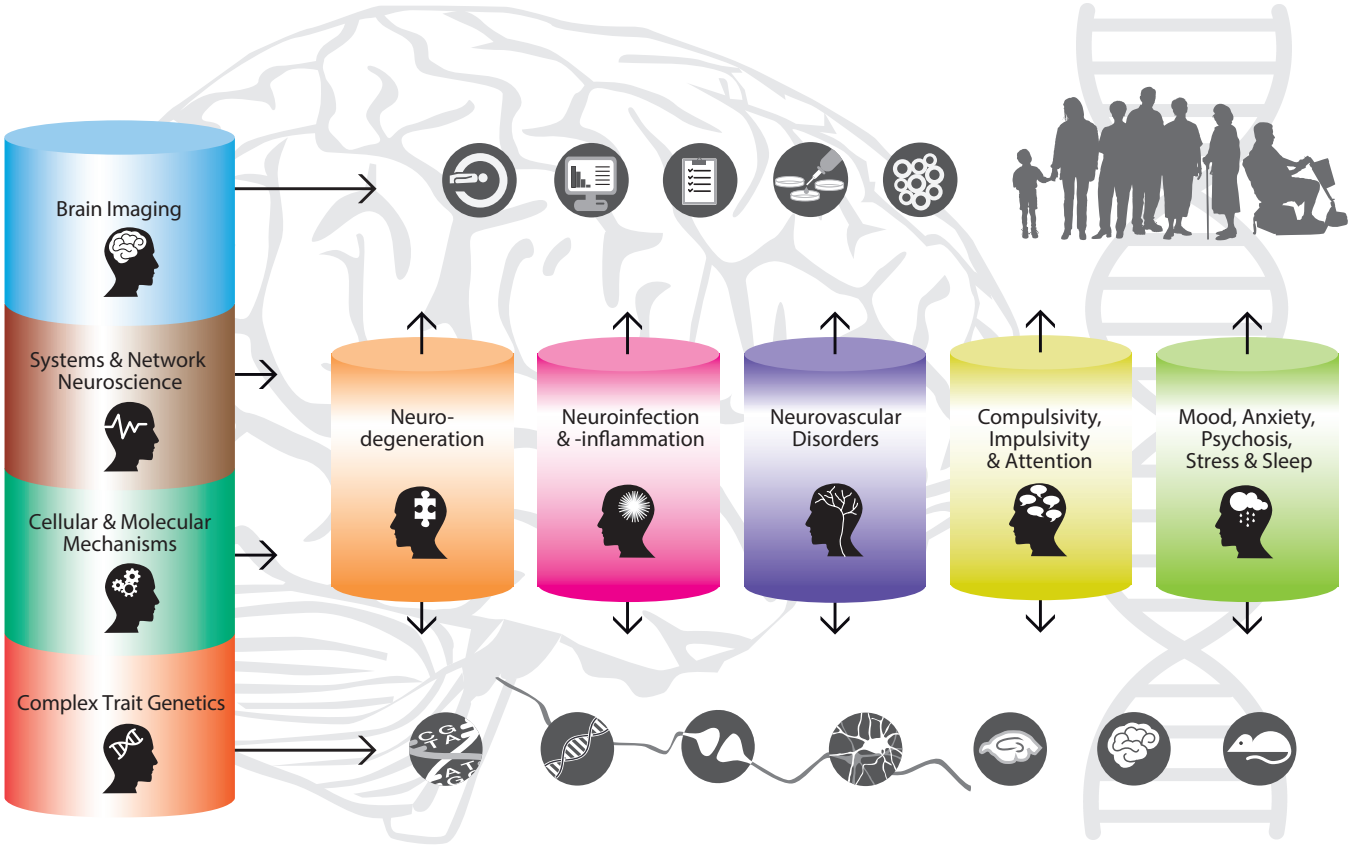
To enable translational neuroscience research, we develop and translate neuroscience knowledge into applications for patients. Amsterdam Neuroscience focuses on scientific excellence, young talent and innovation in four cross-disciplinary research programs. In addition, there are five clinical research 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.

Research programs



Infographics of the research organization of Amsterdam Neuroscience in the period 2019-2021. Research programs are abbreviated as follows: 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), and Mood, Anxiety, Psychosis, Stress & Sleep (mapss).

Amsterdam Neuroscience

Gouvernance

Management team

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

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

Peter Vandertop	Amsterdam UMC – location VUmc
Jonathan Coutinho	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
Judy Luigjes	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 of the Association of Universities in the Netherlands (VSNU), the Netherlands Organisation for Scientific Research (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; 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 888 investigators. This includes 156 principal investigators, 79 faculty members & residents, 200 postdocs & research associates, and 453 PhD students. Of the 453 PhD students currently employed, 52 of them started their project in 2019.

Amsterdam Neuroscience – Research programs

Shown here are 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	122	61	252	73	190	147	84	145	98

PhD students only	**Persons**								
	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Subtotal	58	20	145	33	81	86	50	84	44

Funding

Amsterdam Neuroscience – Research funding

Shown here is the grand total, the subtotals per type of funding as well categorized per research program of newly acquired funding for the institute. In this table funding that is unique to each particular research program is quoted. Double affilations are not shown.

	Grand total	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Total	€ 76,429,394	€ 9,152,036	€ 5,122,629	€ 10,134,647	€ 6,908,639	€ 16,026,305	€ 16,822,569	€ 2,833,940	€ 4,130,124	€ 5,298,505

Conditional funding

	Subtotal	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
1e geldstroom	€ 2,475,000	€ 275,000	€ 275,000	€ 275,000	€ 275,000	€ 275,000	€ 275,000	€ 275,000	€ 275,000	€ 275,000
2e geldstroom	€ 33,050,876	€ 1,954,261	€ 4,552,594	€ 6,104,601	€ 6,047,038	€ 2,615,253	€ 4,952,669	€ 1,116,100	€ 3,255,691	€ 2,452,669
3e geldstroom	€ 20,617,131	€ 607,957	€ 235,598	€ 1,813,915	€ 355,159	€ 8,946,905	€ 5,778,114	€ 521,858	€ 584,133	€ 1,773,493
4e geldstroom	€ 20,286,387	€ 6,314,818	€ 59,436	€ 1,941,132	€ 231,442	€ 4,189,147	€ 5,816,787	€ 920,982	€ 15,300	€ 797,344

NFU definition

- ”1e geldstroom”: Shown is internal so-called alliance funding (i.e. 2,475 k€) only; the unconditional internal funding for tenured and other personnel is estimated to be > 50 M€ for 2019;
- “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 in total

Amsterdam Neuroscience – Research output

Shown here are the metrics for all types of publications. Double affiliations are not shown, i.e. each publication in this table is only affiliated with one research program.

	Total	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Refereed article	1338	157	33	205	92	234	190	127	101	199
Non-Refereed article (1)	50	3	0	9	2	9	10	5	6	6
Books	0	0	0	0	0	0	0	0	0	0
Book chapters	23	4	0	10	3	2	0	1	1	2
PhD theses	83	8	7	9	4	15	18	6	6	10
Conference papers	13	7	0	0	0	3	0	1	2	0
Professional publication (2)	71	1	2	4	1	15	7	4	17	20
Publications aimed at the general public (3)	2	0	0	0	0	1	0	0	0	1
Other research output (4)	11	1	1	1	0	5	1	0	1	1
Total publications	1591	181	43	238	102	284	226	144	134	239
With impact > 10	Subtotal	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Rsfereed articles (selected output)	175	7	6	32	27	41	20	7	15	20
With impact > 5 < 10)	Subtotal	bi	snn	cmm	ctg	nd	nii	ndis	cia	mapss
Rsfereed articles (selected output)	317	27	10	61	24	53	62	25	21	34

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 sector (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 1,338 refereed papers were written in 2019 by Amsterdam Neuroscience researchers. Out of this, total 317 papers were published in international journals with an impact factor of between 5 - 10, and 175 papers were in journals with an impact factor of 10 or higher. Of the latter category, at least 38 papers were original research papers in the center of our core strategy and with first and last authors coming from our organization. There were an additional 18 papers that were published as so-called perspectives and reviews in high-impact journals (i.e. > 10), with corresponding authors from our institute. Another 119 papers were mainly produced together with international collaborators and consortia.

Bilocation authorships

In 2019, there were at least 150 'bilocation' papers (i.e. papers in which either VUmc and/or AMC shared co-authorship with university co-authors) written by Amsterdam Neuroscience researchers. VUmc had co-authors on 141 of these papers, while AMC participated on 59 bilocation papers. With regards to the universities' contribution to these bilocation papers, the VU contributed to 63 and the UvA contributed to 6.

Highlights of the 2019 Annual Meeting

Research report: Cognitive rehabilitation in multiple sclerosis: is there a window of opportunity?

Dr. Hanneke Hulst
Departments of Anatomy and Neurosciences, Amsterdam UMC & MS Center Amsterdam

Cognitive problems occur in up to 70% of the patients with multiple sclerosis (MS) which are highly debilitating and an important cause of unemployment and disconnection from society. The first results of studies using non-pharmacological interventions to improve cognitive functioning in MS patients report mild to moderate effects. However, these effects might be confounded by the large heterogeneity of the patient population in terms of brain characteristics (lesion load, atrophy, brain network characteristics/disturbances; i.e. not all patients might be able to benefit equally from such interventions and there may even be a limited window of opportunity). An essential step in the field of cognitive rehabilitation in MS is therefore the search for (neurobiological) markers that allow us to identify patients that will be responsive to cognitive rehabilitation. Ultimately, this will pave the way for personalized (cognitive) medicine in MS and perhaps even a shift from treatment towards secondary prevention

Research report: Confidence estimation in compulsive disorders

Dr. Judy Luigjes
Department of Psychiatry, Amsterdam UMC & University of Amsterdam

Compulsive behavior consists of repetitive self-defeating acts with devastating consequences. Obsessive-compulsive disorder (OCD) and gambling disorder (GD) are characterized by compulsive behaviour with both opposing (taking risk in GD; avoiding risk in OCD) and overlapping aspects (persistence despite devastating consequences). Interestingly, both disorders have been associated with an aberrant sense confidence albeit in an opposite direction: under-confidence in OCD and over-confidence in GD, which may explain both the shared and opposing characteristics of the behaviors. Recent studies suggest that confidence—an intuitive feeling about the probability of being correct—could be key in optimally adapting one's behaviour. Using a decision-making task where participants rate their decision confidence we investigated whether and how confidence of OCD and GD patients deviates from each other and healthy controls. Characterizing the mechanisms of confidence in OCD and GD will elucidate mechanisms related to compulsivity and may lead to new avenues for treatment.

Research report: Early-life stress increases vulnerability to develop cognitive dysfunction: a focus on inflammation and nutrition

Dr. Aniko Korosi
University of Amsterdam, Swammerdam Institute for Life Sciences | CNS division

Early-life stress (ES) is associated with increased vulnerability to cognitive impairments later in life. We investigate the role of a synergistic effect of stress, nutrition and the neuroimmune system in this early-life induced programming. We use a mouse model of chronic ES of limited nesting and bedding material during first postnatal week and study the brain structure and function under basal and challenged conditions (i.e. LPS, amyloid accumulation). Because of the key role of early nutrition during brain development we propose that an early dietary enriched with essential fatty acids might protect against ES-induced functional deficits. We show that ES leads to cognitive impairments associated with primed microglia with exaggerated response to LPS or amyloid accumulation. With an early dietary intervention with fatty acid we were able to prevent ES-induced cognitive decline mediated by modulation of microglia. These studies give new insights for the development of dietary interventions for vulnerable populations.

Research report: Cognitively healthy centenarians are genetically protected against aging associated diseases

Dr. Henne Holstege
Amsterdam UMC: Alzheimer Center and Department of Clinical Genetics
Delft University of Technology: Department of Intelligent Systems, Bioinformatics Lab

Although the prevalence of dementia increases exponentially with age, some people reach ages well over 100 years enjoying great mental health. This indicates that cognitive decline is not inevitable. To identify the molecular characteristics associated with resilience to cognitive decline we designed the 100-plus Study, an on-going prospective cohort study comprising cognitively healthy centenarians from a homogeneous Dutch population. Currently the cohort includes almost 370 cognitively healthy centenarians.
Preliminary findings indicated that siblings from the centenarians live on average 5-10 years longer compared to their birth cohort-peers. Also, the incidence of cognitive decline in siblings is negligible, indicating a strongly heritable, overlapping etiology of retained cognitive health and longevity. Indeed, the genomes of centenarians are depleted with risk alleles associated with age related diseases such as dementia, cardiovascular diseases and diabetes. Moreover, the genomes of the centenarians are enriched with genetic variants that are protective against disease. Specifically, exploring the effect of the protective heritable component is of value, as this discloses the molecular etiology underlying the delay or escape from age-associated cognitive decline. This may ultimately reveal an entry point for novel therapeutic targets that offer resilience to cognitive decline.

Swammerdam lecture "Mental and neurological diseases: success in the genetics reveals great challenges for translational neurobiology and therapeutics"

Prof. Dr. Steven E. Hyman
Director of the Stanley Center for Psychiatric Research at Broad Institute of MIT and Harvard, a core member of the Broad, and Harvard University Distinguished Service Professor of Stem Cell and Regenerative Biology.

Mental disorders represent a significant and growing public health problem worldwide, yet new treatment discovery has lagged other fields of medicine based on lack of insight into disease mechanisms. This lack reflects the complexity of the human brain and its inaccessibility for direct study in life. Further, animal models have limited translational utility for mental disorders because of significant evolutionary divergence from humans in brain structure and function, especially in the cerebral cortex, and in such other features as regulatory genomic regions that play critical roles in brain development and risk of mental illness. This bleak picture is now changing as a result of rapid advances in computing, computational methods, and multiple relevant areas of technology. Since the beginning of this century we have gained powerful tools for genomics, cellular reprogramming, genome engineering, and investigation of neural circuit function and behavior. Large collaborative, unbiased genetic studies of mental disorders have yielded clues to pathogenesis that are being studied biologically in both human cellular models and animals.
Despite this progress, very significant challenges remain. Mental disorders are highly polygenic with overlapping patterns of genetic risk across multiple disorders and healthy cognitive and behavioral phenotypes. In addition, no current experimental model systems, whether cellular or using living animals, fully serve the purpose of translation. Nonetheless, promising new approaches are coalescing in which human genetics poses disease relevant questions for basic neuroscience.
Translational hypotheses that emerge should, when possible, be tested in humans, human cellular models, or human samples. To illustrate, results from schizophrenia genetics implicate Complement Factor 4A (C4A) and many synaptic proteins in disease risk, suggesting the hypothesis that excessive synaptic pruning mediated by microglia during the typical adolescent period of onset represents a pathogenic mechanism. GWAS results for late onset Alzheimer's disease (AD) indicates that more than half of common risk variants implicate microglia directly. As a result of these genetic findings in schizophrenia and late onset AD, new basic science efforts to characterize microglia are under way in animals, human postmortem tissue, and microglia derived from human induced pluripotent cells.
In both diseases (AD research is more advanced) fluid biomarker studies are investigating complement proteins, microglial proteins and synaptic proteins. In parallel discoveries of common and rare DNA variants associated with schizophrenia have implicated many synaptic proteins, thus motivating new efforts to localize and characterize the functions of their proteins in both animals and human cellular models, as illustrated by the synaptic gene ontology project, SynGo. There is a long way to go before such discoveries lead to new effective therapies, but the last decade has seen real and durable progress in the neurobiology of once mysterious psychiatric disorders.

Interview with Jetske van der Schaar by Philip Scheltens

Jetske van der Schaar is a writer, entrepreneur, publicist and corporate speaker. She writes columns, articles and reviews and currently is working on her second novel. She also carries a rare gene variant of PSEN1, which is a cause of familial (dominantly inherited) Alzheimer 's disease (AD). This will inevitably lead to symptoms when she will be in her early fifties. During the Annual Meeting 2019 Jetske van der Schaar was inteviewed on stage by Prof. Dr. Philip Scheltens, prof of Neurology and director of the Alzheimer Center Amsterdam, Amsterdam UMC.

Van der Schaar's grandfather, uncle and mother all died with early onset AD. In 2014 she consulted a clinical geneticist to get screened herself and got confirmation on her genetic status. In 2016 she came to the Alzheimer Center Amsterdam to know more about the disease and the possibilities to join research. One year later, on October 12, 2017, she was invited by Philip Scheltens to appear on national television (PAUW) and share her story. During the interview, she spoke for the first time about the disease and how it had affected her family and her own life. Since then she has become an ambassador for families with members suffering from dominantly inherited AD and a public figure both in the Netherlands and beyond.

In 2018 she featured as a major speaker during the international Dominant Inherited Alzheimer Network (DIAN) conference in Chicago, where scientists and DIAN family partners meet up at the DIAN-satellite meeting of the Alzheimer Association International Conference (AAIC). Jetske van der Schaar agreed to be interviewed by Philip Scheltens on stage during our Annual Meeting because she is passionate about the public debate on the disease and wants to be an active stakeholder in research as well. During the interview she will share her thoughts and insights on the taboo and stigma that surrounds this disease and how she thinks active participation of 'patients' will benefit research.

Selection of newsitems of 2019

Novel genetic risk factors discovered for Alzheimer's disease

Postdocs Iris Jansen and Jeanne Savage from the teams of Danielle Posthuma (CNCR-CTG) and Wiesje van der Flier (Alzheimer Centrum Amsterdam) find novel genetic risk factors for Alzheimer's dementia, published in Nature Genetics.

A large-scale international study discovered novel genetic risk loci for Alzheimer's disease. Combining genetic data on a large-scale and in a non-conventional manner resulted in the discovery of multiple novel genetic factors and biological mechanisms that contribute to the pathogenesis of the disease. The study was led by Danielle Posthuma from the VU University in Amsterdam, Ole Andreassen from the University of Oslo and Stephan Ripke from the Broad Institute in Boston, and was carried out as part of an initiative of the Psychiatric Genomics Consortium.

Genetic defects within the immune system and lipid components
The current study is the largest genetic study of AD so far, including over 455,000 individuals. The study included clinical diagnoses to define the patient group, but also included a group of people where parental AD status was considered. For all individuals, genetic information was available which allowed to scan the genome for possible genetic risk factors. This combined analysis yielded 29 genome-wide significant loci for AD, including 9 novel genetic loci. Results imply that genetic defects in genes involved in the immune system and components associated to lipids, contribute to the risk for AD.

Microglia and lipid components
"Specifically, using single cell gene expression patterns, we show that genetic changes in genes that are expressed in microglia cells, are associated with increased risk for AD. Microglial cells are an important part of the immune system of the brain. This finding suggests that we should widen our focus to also include microglia models when performing functional research in AD, in addition to the conventional approach of neuronal models", says Danielle Posthuma.

Iris Jansen, shared first author of the publication continues: "We additionally detect genetic changes in proteins that are involved in lipid components. This link has already been described for the APOE gene, the strongest genetic risk factor for AD, but our results show that other lipid proteins might also be genetically affected. This observation strengthens the hypothesis that AD pathogenesis involves an interplay between inflammation and lipids, as lipid changes might harm immune responses of microglia, thereby affecting the vascular health of the brain."

CNCR CTGLAB

Early start with Parkinson's disease medication proves safe for the long-term

A study led by the Amsterdam UMC showed that an early start of a commonly used drug to treat Parkinson's disease has no negative impact on the patient's long-term outcome. The results of the study were published today in the New England Journal of Medicine.

Research leader Professor of Neurological Movement Disorders Rob de Bie led the study, which evaluated levodopa, the most commonly-used drug for Parkinson's. Until now, little research had been conducted to investigate potential long-term effects of the drug, which has been used to treat the disease for nearly half a century.

"There has been a longstanding concern that starting levodopa early could accelerate the disease or have other long-term adverse consequences." said de Bie "Therefore physicians have often withheld the drug early in the disease and delayed starting it until the patients experienced more overt disability."

Over the past six years, more than 400 patients who were in the early stages of Parkinson's were enrolled in the study. The patients were divided into two groups: one group was immediately prescribed levodopa, while the other half received placebo. After 40 weeks, all patients received levodopa and were monitored for an additional 40 weeks. At the end of the 80 weeks, all patients experienced similar benefits to using the drug and those who had started the medication earlier did not experience more side-effects related to longer use.

"In short, starting the medication earlier does not mean patients will experience more long-term side-effects", says De Bie. "In fact, the advantage to beginning the medication sooner is that you can treat the disease earlier and improve patients' quality of life right at the time of diagnosis."

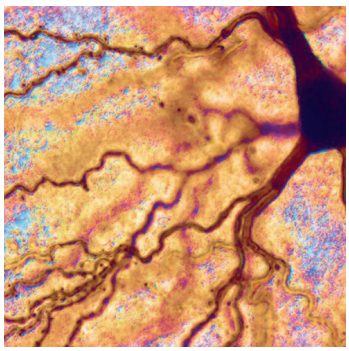
For more information on the study design, visit leapamc.nl. The research was made possible with the support of ZonMw, Stichting ParkinsonFonds, Stichting Parkinson Nederland and Parkinson Vereniging (patients' association).

Faster and larger neurons make smarter brains

The properties of individual brain cells have been linked to intelligence for the first time. Natalia Goriounova reports in eLife.

What makes some people smarter than others? Our brain works through the activity of its almost 100 billion brain cells that each act as a small chip: they collect, process and pass on information in the form of electrical signals. Especially in brain areas that integrate different types of information, such as frontal and temporal lobes, brain cells have larger dendrites - long branches specialized to collect signals. Theoretical studies predict that larger dendrites help cells to initiate electrical signals faster.

In a collaboration with neurosurgeons and clinical psychologists at VUmc and SEIN, neuroscientists at the VU Amsterdam (CNCR, Faculty of Science) tested whether smarter brains are equipped with faster and larger cells. They studied 46 people who needed surgery for brain tumors or epilepsy. Each took an IQ test before the operation. To access the diseased part deep in the brain, the surgeon also removed small undamaged samples of temporal lobe. These samples still contained living cells and their electrical signals – action potentials- were measured in the lab. The experiments showed that cells from people with a higher IQ have larger dendrites and faster action potentials especially when the neurons need to work hard. Computer models were then used to understand how these findings can lead to more efficient information transfer in human neurons.

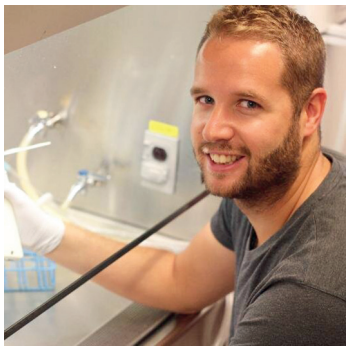


Traditionally, research on human intelligence has focused on three main strategies: to study brain structure and function, to find genes associated with intelligence and to study the connection between our mind and behavior. This study is the first to take the single-cell perspective and link cell properties to human intelligence. The findings could help connect separate approaches, and explain how genes for intelligence lead to thicker cortices and faster reaction times in people with higher IQ.

Finally, since our brain has almost 100 billion neurons, even small differences at the level of a single cell shoud be multiplied by this astronomical number. A small step for a single neuron, a giant leap for the computational power of the brain.

An HIV-drug to correct cholesterol metabolism in Alzheimer's disease

Rik van der Kant and colleagues report that accumulation of cholesterol in Alzheimer's disease (AD) neurons drives early Tau- and Amyloid pathology, and can be reversed by existing cholesterol-targeting drugs. Published in Cell Stem Cell.



Using induced pluripotent stem cell-derived (iPSC) neurons from AD patients, Rik van der Kant reports that cholesteryl esters (CE) — the storage product for excess cholesterol within cells — act as regulators of tau. Through screening of more than 1,600 Food and Drug Administration-approved drugs they found that low doses of the anti-HIV drug efavirenz lowered CE through activation of the neuronal enzyme "CYP46A1", thereby reducing tau in the AD-patient neurons.

The accumulation of amyloid beta (Aβ) plaques and tangles of a protein called tau in the brain are hallmarks of Alzheimer's disease (AD). Much effort has focused on the former, with many attempts made to prevent, slow or even reverse the presence of Aβ, and thus ameliorate the development of AD. To date, results have been mixed. In a new paper, published in the January 24, 2019 online issue of Cell Stem Cell, Rik van der Kant in collaboration with the University of California San Diego School of Medicine, focused on the alternative therapeutic target: tau.

Using induced pluripotent stem cell-derived (iPSC) neurons from AD patients, the researchers report that cholesteryl esters (CE) — the storage product for excess cholesterol within cells — act as regulators of tau. Importantly, through screening of more than 1,600 Food and Drug Administration-approved drugs they found that low doses of the anti-HIV drug efavirenz lowered CE through activation of the neuronal enzyme "CYP46A1", thereby reducing tau in the AD-patient neurons.

The findings reveal that CE inhibit the proteasomal degradation of pTau, causing it to accumulate in the neurons of AD patients. Drugs that reduced CE also reduced pTau levels in all AD neurons tested. The researchers also confirmed previous reports that CE drive the formation of amyloid. However, while the effect of CE on amyloid was highly correlated with the effect of CE on pTau, the study found the effect of CE on both pathologies were mediated by two independent downstream pathways. "These findings show

that cholesterol metabolism is upstream of both amyloid and tau pathology and provide a novel new drug target for the treatment of AD" says Rik van der Kant.

When the smoke is gone

Jentien Vermeulen and co-authors recently published two articles on smoking in relation to cognitive functioning and symptoms among patients with psychosis in The American Journal of Psychiatry and The Lancet Psychiatry.

Design

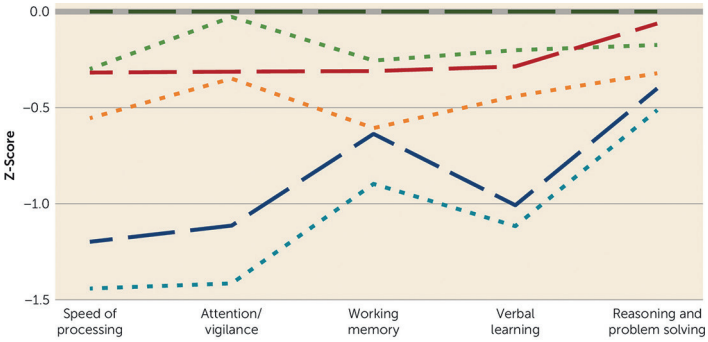
A prospective, longitudinal cohort study of patients with non-affective psychosis (N=1,094), their siblings (N=1,047), and healthy control subjects (N=579) was conducted. Participants were interviewed about smoking and tested with a cognitive battery after 3 and 6 years. Furthermore, participants self-rated level of symptoms and quality of life.

Results

At baseline, 66.6% of the patients smoked, compared with 38.3% of the siblings and 25.2% of the control subjects. Smokers showed poorer cognitive performance, higher symptom levels and inferior quality of life compared to non-smokers. Starting to smoke or smoking more cigarettes per day was not associated with long-term improvement of cognition or symptoms. Moreover, quitting smoking was associated with an improvement of speed of processing and starting to smoke was associated with more symptoms in patients.

Clinical implications

The findings suggest an absence of cognitive improvement or symptomatic relief by starting to smoke or increasing the number of cigarettes per day, indicating no support for the self-medication hypothesis that smoking has a beneficial impact on these outcomes in patients with a psychotic disorder. This should encourage clinicians to help patients to quit smoking, which may improve patients' processing speed.



Brain cells involved in insomnia identified

Amsterdam Statistical Genetics professor Danielle Posthuma (VU Amsterdam/ Amsterdam UMC) and Neurophysiology professor Eus Van Someren (Netherlands Institute for Neuroscience/Amsterdam UMC) assembled a large group of scientists and cohorts, including the UKBiobank and US-based company 23andMe to find out where in the brain insomnia risk genes exert their effect. Together, they were the first to assemble DNA and sleep data provided by no less than 1.3 million people - the largest genetic dataset ever.

The researchers identified 956 genes in which variants contributed to the risk of insomnia. They then extensively investigated which biological processes, cell types and brain areas utilize these genes. They found that part of these genes had an important role in the functionality of axons, which are the long protrusions of brain cells that allow them to communicate with each other. Another significant part of the insomnia risk genes was active in specific cell types of parts of the frontal cortex and the subcortical nuclei of the brain. These brain areas had also recently been marked as suspect in brain imaging studies of people suffering from insomnia. The findings thus seem consistent.

Specific cell types involved in insomnia

"Our study shows that insomnia, like so many other neuropsychiatric disorders, is influenced by 100's of genes, each of small effect. These genes by themselves are not that interesting to look at. What counts is their combined effect on the risk of insomnia. We investigated that with a new method, which enabled us to identify specific types of brain cells, like the so-called medium spiny neurons." says Danielle Posthuma. Philip Jansen, first author of the paper, continues: "It is fascinating that we can nowadays start to understand what happens at the micro-level of molecules and cells in the brain, just because we can assemble so many data at the macro-level, worldwide".

Insomnia is genetically more related to psychiatric disorders than to other sleep traits

The researchers compared risk genes of insomnia with those of other traits and disorders. Surprisingly, they found little overlap with genes involved in individual differences in other sleep traits, like being a morning- or evening-type. Instead there was a strong genetic similarity with depression and anxiety. "A very important finding, because we have always searched for causes of insomnia in the brain circuits that regulate sleep. We have to shift our attention to the circuits that regulate emotion, stress and tension" says Van Someren.

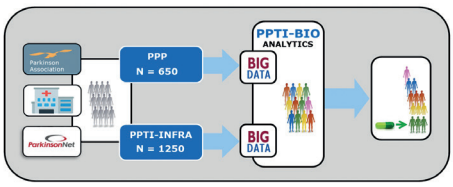
Diederik van de Beek acquires Vici grant for pioneering new treatment for bacterial meningitis

Prof. D. (Diederik) van de Beek, neurologist, principal investigator and well known for his role as co-director of Amsterdam Neuroscience got awarded with a 1.5 M€ grant for his Vici research proposal. The main topic of his research focusses on bacterial meningitis, which is a life-threatening brain infection. He and his team are investigating novel targets of treatment that have been identified and against which therapies have to be developed. We congratulate him and his team on this achievement.

National consortium for Parkinson Personalized Therapeutics Initiative

A national consortium entitled as PPTI-INFRA was awarded with 1.5 M€ ZonMw funding. The consortium is lead by Prof. Bob van Hilten (LUMC), Dr. Wilma van de Berg (VUmc) and Prof. Marcel Reinders (TU Delft). This gouvernemental funding will run for a period of five years and will be matched by industrial partners with an additional 2.4 M€ (combined cash and in-kind funding). These external stakeholders include F. Hoffman-La Roche Ltd., AbbVie, H. Lundbeck A/S, ParkinsonNet, de Parkinson Vereniging, het Parelsnoer Instituut, stichting Centre for Human Drug Research, het PHARMO Instituut, de Hersenstichting, Stichting Alkemade-Keuls.

The aim of the Parkinson Personalized Therapeutics Initiative (PPTI) is to personalize treatment in PD through the identification of biological signatures to personalize and optimize tolerability of current medical treatment, and to stratify patients for future trials aiming to alter disease progression. To achieve this, the researchers will follow 1250 PD patients for three years. They annually collect clinical, biospecimen and kinematic data, as a basis for 'big data' analytics to identify biological signatures underlying clinical heterogeneity. The consortium capitalizes on intellectual synergy of clinical and scientific experts, in collaboration with ParkinsonNet, the Dutch Parkinson's Disease Association, Parelsnoer Institute, PHARMO Institute, and commercial and non-commercial partners. This proposal aligns with the "Personalized Parkinson Project (PPP)", executed by Radboudumc among 650 patients. The knowledge, biobank and multisource dataset generated in PPTI can offer a breakthrough in research and patient care by providing tools for personalization and optimization of current and future treatment paradigms.



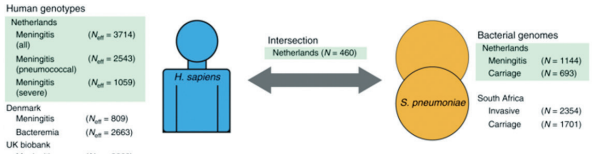
Posthuma receives ERC Advanced Grant to bridge genetics and neurobiology

Danielle Posthuma, professor of Complex Trait Genetics at Vrije Universiteit Amsterdam and Amsterdam UMC location VUmc, and holder of a University Research Chair, will receive the prestigious European Research Council (ERC) Advanced Grant. This is the largest personal research grant in Europe.

In 2013 Posthuma already received a large Dutch personal research grant (VICI). With this new grant of 2.5 million euros, she will develop novel methods and experimental set-ups that can bridge the gap between genetics and neurosciences, applied to brain-related traits. Posthuma will conduct her research at the Center for Neurogenomics and Cognitive Research, at the Beta Faculty of the VU University Amsterdam. She is looking forward to working with a multidisciplinary team of bioinformatics, statisticians and neurobiologists.

Joint sequencing of human and pathogen genomes reveals the genetics of pneumococcal meningitis

An international consortium led by Diederik van de Beek has published a genome-wide associations study of human and pathogen in Nature Communications. Genetic variation of host and pathogen is known to play a role in invasive pneumococcal disease, though to what extent is unknown. The Amsterdam Neuroscience team now show that human variation explains almost half of variation in susceptibility to pneumococcal meningitis and one-third of variation in severity, identifying variants in CCDC33 associated with susceptibility. Pneumococcal genetic variation explains a large amount of invasive potential (70%), but has no effect on severity. They identify pneumococcal genes involved in invasiveness including pspC and zmpD, and perform the first ever human-bacteria interaction analysis. These genes are potential candidates for the development of more broadly-acting pneumococcal vaccines

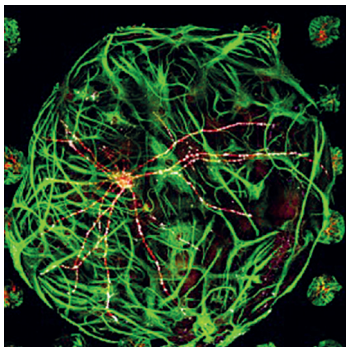


Amsterdam Neuroscience

Novel method to assess synaptic transmission in single human neurons

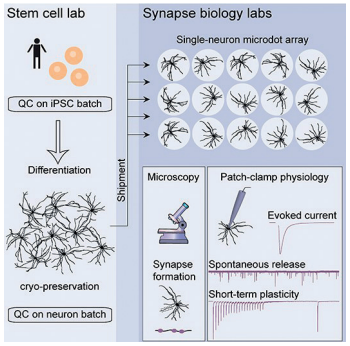
Dr. Marieke Meijer and a team of FGA/CNCR researchers, together with iPSC-experts from the University of Bonn, published a novel method to study synapse formation and function in individual iPSC-derived human neurons in Cell Reports.

In this multisite study by Meijer et al., the authors adapt a reduced model system (autaptic cultures) to the unique requirements of iPSC-derived human neurons. These neurons are cultured individually on glia microdot arrays and exhibit robust evoked synaptic transmission and plasticity features such as synaptic facilitation, depression and synaptic recovery.



Using this method, the authors were able to provide a quantitative assessment of relevant parameters of synapse development and function in iPSC-derived neurons at single-cell resolution. The authors validated their approach for GABA and glutamatergic human neurons, and developed a pipeline that generated large batches of cryopreserved neurons suitable for multi-site studies. Furthermore, the methodology can be leveraged for drug development and disease modeling, which will provide a strong asset in future collaborations with industry.

This standardized single-neuron model allows us to study synaptic transmission in iPSC-derived human neurons, also on a patient-own genomic background, which will facilitate the study of synaptic dysfunction in brain diseases. “Genes we study out of fundamental interest are being identified as disease-causing in neurodevelopmental disorders. These are genes we understand very well, and are ideal to strengthen our link with the clinic and to provide in-depth mechanistic understanding of these disorders,” says Marieke Meijer.



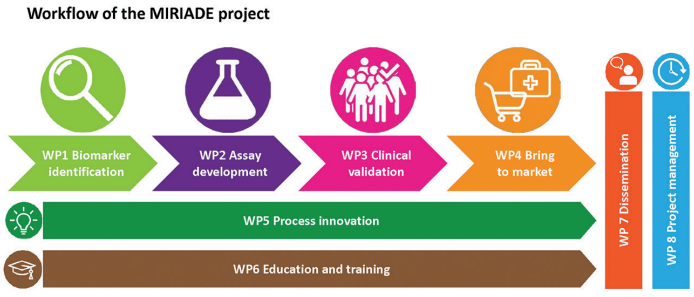
Marc Engelen received a Vidi grant from NWO

Marc Engelen (Pediatric) neurology, Amsterdam UMC) received a Vidi grant from NWO. This grant of 800,000 Euro enables researchers to establish a new innovative research line.

The Vidi grant will enable the adrenoleukodystrophy (ALD) research group to develop new surrogate outcome measures for clinical trials in adrenoleukodystrophy and possibly other neurodegenerative diseases affecting the spinal cord. Specifically, quantitative MRI (DTI, MTI, NODDI), optical coherence tomography and force plate analysis of locomotion are promising candidates. Furthermore, by using the PEROX biobank linked to the patient cohort they will search for biomarkers that predict disease severity and progression. For this, they will analyze plasma and CSF with lipidomics and other techniques.

MIRIADE – Marie Curie ITN grant of 15 PhD students acquired by Eline Willemse and Charlotte Teunissen

The Marie Curie International Training Network project “MIRIADE” has been awarded for funding by the EU! The PI of this project is Charlotte Teunissen, and Eline Willemse is the co-PI (Neurochemistry lab, dept of Clinical Chemistry AUMC). MIRIADE is an international, mainly EU, consortium of leading biomarker labs and companies, embedded in the Society of Neurochemistry and Clinical CSF analysis. A total of 15 PhD students (distributed across the consortium) will be trained as excellent biomarker development experts – the professionals of the future. Focus of the scientific activities is on differential dementia biomarkers.



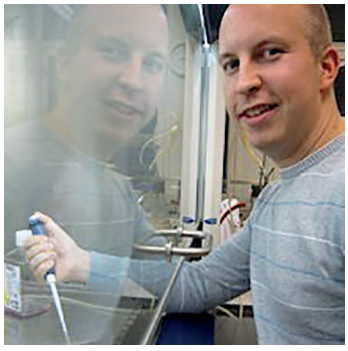
Linda Douw receives a Vidi grant from NWO for BrainLayer

Linda Douw was awarded a Vidi grant for her research on her research project entitled BrainLayer. Linda is assistant professor and affiliated with the Department of Anatomy and Neuroscience at location VUmc. She brinks the gap between brain imaging and cognitive impairment in patients coming from different disease indications by applying a multi-layer network analysis approach.

Cognitive deterioration in lesional brain disease, such as cerebrovascular accidents, multiple sclerosis and glioma, weighs heavily on patients, their caregivers and society, particularly since curative treatment is unavailable. Variation in cognitive decline is large: some patients suffer from progressive deterioration, while others do not, despite comparable disease parameters. Using concepts from graph theory, cognition is increasingly seen as a combination of segregation and integration occurring in the brain network. In the project BrainLayer Linda Douw aims to elucidate individual resilience and adaptivity of the brain network in the context of lesional brain disease, thereby allowing for more accurate understanding and possibly prediction of cognitive decline.

Gijs Kooij acquires Vidi grant and fellowship grant to resolve chronic neuro-inflammation

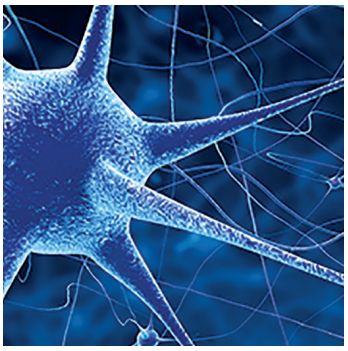
Chronic inflammation occurs if the natural process to restrain inflammation (resolution) is not functioning properly. Dr. Gijs Kooij receives a 800 k€ Vidi grant from NWO and a 465 k€ fellowship grant from the Dutch MS research foundation to unravel how this natural protection mechanism works in order to exploit it in the combat against chronic inflammatory disorders like multiple sclerosis (MS).



Inflammation is a host-protective response when properly orchestrated. Beside immune checkpoints, the inflammatory cascade boasts an additional checkpoint, driven by chemical lipid mediators that induce resolution of inflammation. These novel autacoids, called specialized pro-resolving lipid mediators (SPMs), not only inhibit the inflammatory response, they also actively terminate it, leading to the restoration of tissue homeostasis. Novel sensitive detection methods (i.e. lipidomics) have set the stage to identify and decode these SPMs, which opens new perspectives on the pathogenesis of chronic (unresolved) inflammatory diseases, leading to a novel pharmacological approach. Gijs has recently shown that in the chronic neuro-inflammatory disorder MS, the machinery of protective resolution is severely disturbed, which in turn contributes to disease progression. The goal of his research supported by the two new grants is to provide novel diagnostic, prognostic and therapeutic opportunities for MS and other chronic (neuro-)inflammatory diseases based on resolution pharmacology.

Amsterdam researchers take lead in expert-curated knowledge database of the synapse

SYNGO, a collaboration of 15 expert labs worldwide and the Gene Ontology (GO) Consortium, released a public knowledge base called Syngo, which aims to represent the current scientific knowledge about synapses in structured frameworks, called ontologies. The release of SYNGO 1.0 is supported by the first scientific publication in the leading journal Neuron, with CNCR colleagues in Frank Koopmans and Pim van Nierop as first and second author, and Guus Smit and Matthijs Verhage als corresponding authors.



1112 synaptic genes

SYNGO 1.0 is releasing 2922 ontology-based descriptions of 1112 unique synaptic genes, compiling published experimental information about the localization and function of the gene-products at synapses, according to standardized principles. This compiled information is both human-readable and machine-readable. SYNGO is fully integrated in the GO knowledgebase, the world's largest source of information on the functions of genes.

Exceptionally well conserved

In their paper published in Neuron, the authors use SYNGO 1.0 to show that synaptic genes are exceptionally well conserved in evolution and much less tolerant to mutations than other (brain-expressed) genes. The authors also show that many synaptic genes are significantly overrepresented among gene variation associated with intelligence, educational attainment, ADHD, autism and bipolar disorder. Synaptic genes are also strongly overrepresented among de novo variants associated with neurodevelopmental disorders including schizophrenia.

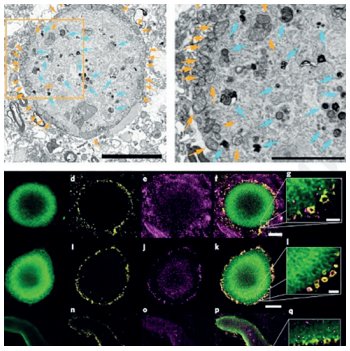
Dutch National Research Agenda (NWA) grant on precision psychiatry

Together with clinician Hilgo Bruining and researchers from Utrecht, Nijmegen and Twente, CNCR researchers Verhage, Cornelisse, Meijer (FGA) and Linkenkaer-Hansen (INF) received a €1,8M grant to improve personalized medicine for children with autism.

The prevalence of autism in children is increasing but effective treatment is lacking. This is because different forms of autism exist with different (biological) underlying causes. In this project new methods will be developed to identify biological causes for autism and to find the best matching therapies, by analyzing specific brain characteristics of each individual child. A novel EEG biomarker, developed by the team of Linkenkaer-Hansen, will be used to group children with ASD based on the balance between excitation and inhibition in their brain. The team of Cornelisse and Verhage will analyze the excitation/inhibition balance at the cellular level in in-vitro networks of neurons from the same children. They will make use of advanced stem cell technology, that was recently established at FGA , to generate human neurons from a skin sample from the same individuals that were analyzed by EEG. This will allow to measure synaptic and cellular phenotypes for each individual and to test the effect of different FDA approved drugs on these phenotypes. For each individual the two most effective drugs will be subsequently tested in a clinical trial. In collaboration with FGA, the Twente group will develop a lab-on-a-chip approach to increase the throughput of these cellular assays. By combining clinical diagnosis with novel EEG analysis and measurements in cultured neurons in every individual child, the multi-disciplinary team hopes to determine the optimal treatment before it is prescribed. This approach will lead to improved personalized medicine with a higher chance on success and less side effects, which might be applied to other brain disorders in the future.

Parkinson plaques are different than expected

An international team of researchers, including Dr. Wilma van de Berg from Amsterdam UMC | Amsterdam Neuroscience and Prof. Henning Stahlberg from the Biozentrum, University of Basel, challenges the conventional understanding of the cause of Parkinson's disease. The researchers have shown that the plaques in the brain's neurons, characteristic of Parkinson's disease, are comprised of a membranous medley rather than protein fibrils. The recently published study in "Nature Neuroscience" raises new questions about the development of Parkinson's disease.



"We used correlative light and electron microscopy to take a closer look at the postmortem substantia nigra of patients with Parkinson's disease and discovered that the Lewy bodies consist mainly of membrane fragments from mitochondria and other organelles, but have in most cases no or only negligible quantities of protein fibrils," say Van de Berg and Stahlberg. "This discovery was unexpected for us and the entire research field. We identified these plaques by their high concentration of the protein alpha-synuclein, but this is obviously not present in the form of fibrils."

Currently, the researchers do not know yet where and in what form the protein alpha-suynuclein is hidden amongst the membrane fragments and how it is involved to plaque formation. However, their work indicates that the model of alpha-synuclein fibrils as a cause and mechanism of certain forms of Parkinson's disease should be questioned. "It seems that the search for the origin of the disease has often chased the wrong target," explain Van de Berg and Stahlberg. With their work, the researchers raise many new questions regarding the role of the plaques in the development of Parkinson's disease. The insights into such cell structures also provide important clues for preventing the formation and spreading of plaques in the brain.

REM sleep silences the siren of the brain

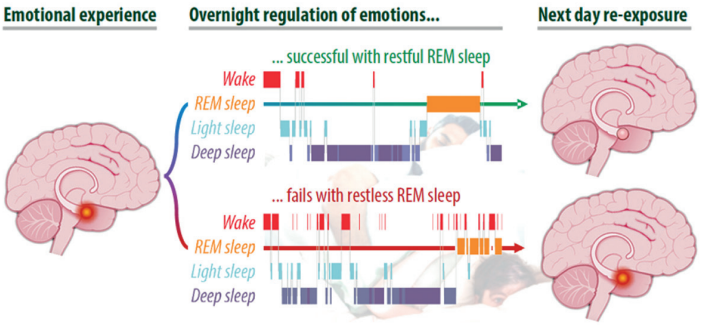
Is restless REM sleep a risk for many mental disorders? Researchers Rick Wassing and Eus van Someren from the Netherlands Institute for Neuroscience and Amsterdam Neuroscience discovered why you will be better able to bear tomorrow what you are distressed about today. And why that can go wrong.

Neuronal connections weaken and strengthen

During sleep, 'memory traces' of experiences from the past day are spontaneously played back, like a movie. Among all remnants of the day, a specific memory trace can be activated by presenting the same odor as the one that was present during the experience while awake. Meanwhile, memory traces are adjusted during sleep: some connections between brain cells are strengthened, others are weakened. Restless REM sleep disturbs these nocturnal adjustments that are essential for recovery and adaptation to distress.

Transdiagnostic importance

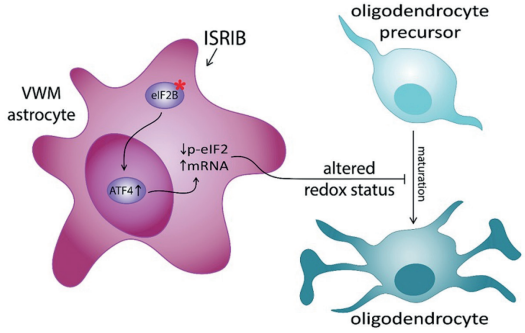
The findings can be of great importance for about two-thirds of all people with a mental disorder, as both restless REM sleep and



a hyperactive amygdala are the hallmarks of post-traumatic stress disorder (PTSD), anxiety disorders, depression and insomnia. Authors Rick Wassing, Frans Schalkwijk and Eus van Someren predict that treatment of restless REM sleep could transdiagnostically help to process emotional memories overnight and give them a better place in the brain.

Vanishing white matter: deregulated integrated stress response as therapy target

Vanishing white matter (VWM) is a fatal, stress-sensitive leukodystrophy that mainly affects children and is currently without treatment. VWM is caused by recessive mutations in eukaryotic initiation factor 2B (eIF2B) that is crucial for initiation of mRNA translation and its regulation during the integrated stress response (ISR).



Mutations reduce eIF2B activity. VWM pathomechanisms remain unclear. In contrast with the housekeeping function of eIF2B, astrocytes are selectively affected in VWM. One study objective was to test our hypothesis that in the brain translation of specific mRNAs is altered by eIF2B mutations, impacting primarily astrocytes. The second objective was to investigate whether modulation of eIF2B activity could ameliorate this altered translation and improve the disease. Mice with biallelic missense mutations in eIF2B that recapitulate human VWM were used to screen for mRNAs with altered translation in brain using polysomal profiling. Findings were verified in brain tissue from VWM patients using qPCR and immunohistochemistry. The compound ISRIB (for "ISR inhibitor") was administered to VWM mice to increase eIF2B activity. Its effect on translation, neuropathology, and clinical signs was assessed. In brains of VWM compared to wild-type mice we observed the most prominent changes in translation concerning ISR mRNAs; their expression levels correlated with disease severity. We substantiated these findings in VWM patients' brains. ISRIB normalized expression of mRNA markers, ameliorated brain white matter pathology and improved motor skills in VWM mice. The present findings show that ISR deregulation is central in VWM pathomechanisms and a viable target for therapy.

Huge genetic study provides insight into pleiotropy and shared genetic architectures across hundreds of human traits

PhD student Kyoko Watanabe (CNCR-CTG) analyzed the results of more than 500 genome-wide studies for over 500 human traits, to provide novel insight into how our genome is linked to trait variation. The study is published in Nature Genetics and all results are available through a novel central database called 'gwasATLAS'.

In this new study, the team, led by Danielle Posthuma of the VU University Amsterdam and Amsterdam UMC, systematically analyzed the results of virtually all published GWAS results. "Our study provides insight into fundamental questions on the extent of pleiotropy across the genome, the nature of risk variants and the genetic architecture of complex traits." says Kyoko Watanabe, a PhD student in the group of Posthuma and the first author on the study.

Many genes influence multiple traits

'Pleiotropy' refers to the observation that one gene can influence multiple traits. "Many traits are known to be influenced by hundreds of genes, and given that we have a finite number of genes in our genome, it has been hypothesized that pleiotropy is ubiquitous in our genome. In the current study we quantified this, by analyzing the results of well-powered GWAS studies for more than 500 different traits," explains Posthuma.

The finding that the majority of genes are influencing multiple traits suggests that strategies such as gene-editing for complex traits based on GWAS results can be risky. "One problem is that GWAS results do not provide causal variants, but provide a range of variants that might include the causal variant. A second problem is that to influence one trait via gene-editing, one would need to edit hundreds of variants in hundreds of genes, and since these genes may not only influence the targeted trait, unintended effects on hundreds of other traits may occur," says Posthuma.

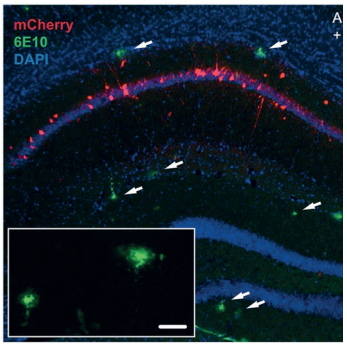
Trait-specific genes are most interesting for drug development

"The study suggests that genes associated with multiple traits tend to have more general biological functions, indicating that the bulk of genes is involved in a general susceptibility to trait variation and

variation in risk to disease," says Watanabe. The study also found several genes which were specific to one disease or trait. "These genes are highly informative for that particular trait, and therefore the most interesting targets for functional follow-up studies and drug developments", says Posthuma.

Hyperactive interneurons contribute to Alzheimer's disease

A new study by PhD student Sara Hijazi (MCN) shows that reducing the activity of interneurons in the hippocampus restores memory and delays Alzheimer's disease progression in mice. The study is published in Molecular Psychiatry.



A key question in the field is which neurons are primarily affected and responsible for early network impairments in Alzheimer's disease. Exciting new data now reveal a crucial role for hippocampal parvalbumin interneurons. This new study by PhD student Sara Hijazi (MCN) shows that parvalbumin interneurons are transiently hyperexcitable at an early, prepathological disease stage in APP/PS1 mice, a commonly used mouse model of Alzheimer's disease. This hyperexcitability was shown to be dependent on soluble beta-amyloid, the peptide that is considered to be the trigger of the disease. Specifically, adding beta-amyloid to healthy brain slices selectively induced hyperexcitability of parvalbumin interneurons, whereas decreasing beta-amyloid levels in vivo using a specific BACE1 inhibitor complete restored their excitability properties.

The authors used chemogenetics to specifically reduce the excitability of hippocampal parvalbumin interneurons and test the effects thereof on network function and behavior in young APP/PS1 mice. Restoring the activity of parvalbumin interneurons not only prevented memory loss immediately after treatment, but it also had long-lasting beneficial effects on memory performance, restored inhibitory and excitatory transmission in the hippocampus and attenuated the deposition of amyloid plaques. "These long-lasting effects of manipulating interneuron activity really came as a surprise to us," Sara Hijazi explains. "They show that targeting impaired neuronal networks, or specifically interneurons within these networks, offers exciting new possibilities for the treatment of Alzheimer's disease in its early stages."

Gravitation funding for Complex Traits Genetics program

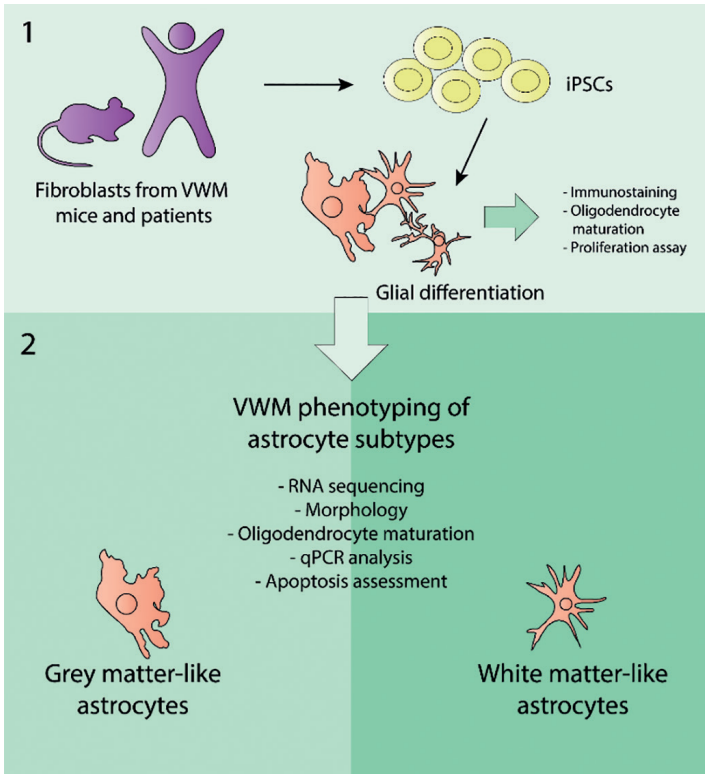
On Friday Aug 30 2019, the Dutch Research Council (NWO) announced which consortia receive a ~ 20 million Euro Gravitation Award. The Ministry of Education, Culture and Science provides this type of funding for long-term (10 year) multidisciplinary projects, with the ambition to stimulate world-leading Dutch research that could potentially lead to international breakthroughs. The research is to be carried out by consortia of various Dutch universities, academic hospitals and research institutes. One of the recipients of such a grant is Danielle Posthuma, with her peergroup including Guus Smit and Huibert Mansvelder, from the Center for Neurogenomics and Cognitive Research (CNCR) and all affiliated with Amsterdam Neuroscience.

Professor of Complex Trait Genetics Danielle Posthuma coordinates the research project BRAINSCAPES. The aim of BRAINSCAPES is to map in detail the biological mechanisms underlying brain diseases ('brainscaping'). The scientists involved in this research want to build an innovative bridge between genetics and neurobiology by making smart use of the wealth of results from the current genetic revolution, the availability of large biological datasets at the single cell level and the application of the very latest techniques from neurobiology. Posthuma works with a team of researchers from VU Amsterdam, Amsterdam UMC, LUMC, TU Delft, UMCU and Hubrecht Institute.

New iPSC –based model systems identify astrocyte subtypes vulnerability in neural disease

A new study by PhD students Prisca Leferink, Stephanie Dooves and Anne Hillen identified disease-specific pathways in astrocytic subtypes derived from patient stem cells. This study is published in Annals of Neurology.

Astrocytes have long been viewed as supportive cells of the brain, but over the last decade it has become clear that they play an important role in most, if not all, brain diseases. The authors developed a method to generate astrocytic subtypes from human and mouse induced pluripotent stem cells (iPSC). They used these iPSCs to show that a certain astrocytic subtype is more affected in the rare and severe genetic disorder Vanishing White Matter (VWM), for example presenting expression changes in genes involved in the immune system and extracellular matrix. Com-



parative studies between human and mouse cultures revealed human-specific disease mechanisms, such as neuronal and mitochondrial functioning. This study underscores the importance of considering astrocyte subtype vulnerability in neurological disease, influencing in vitro disease modeling outcomes, and targeting the correct cellular subtypes in therapeutic approaches.

Alzheimer's biomarkers in daily practice

Biomarker-based risk predictions of dementia in people with mild cognitive impairment are highly relevant for care planning and to select patients for treatment when disease-modifying drugs become available. Alzheimer Center Amsterdam investigators Ingrid van Maurik c.s. and Wiesje van der Flier, head of research for Neurodegeneration and program leader in Amsterdam Neuroscience aimed to establish robust prediction models of disease progression in people at risk of dementia and their modelling study published in the Lancet Neurology.

In this modelling study, they included people with mild cognitive impairment (MCI) from single-centre and multicentre cohorts in Europe and North America: the European Medical Information Framework for Alzheimer's Disease (EMIF-AD; n=883), Alzheimer's Disease Neuroimaging Initiative (ADNI; n=829), Amsterdam Dementia Cohort (ADC; n=666), and the Swedish BioFINDER study (n=233).

In the Lancet Neurology article risk models are described that are robust across cohorts, which adds to their potential clinical applicability. The models could aid clinicians in the interpretation of CSF biomarker and hippocampal volume results in individuals with MCI, and help research and clinical settings to prepare for a future of precision medicine in Alzheimer's disease. Future research should focus on the clinical utility of the models, particularly if their use affects participants' understanding, emotional wellbeing, and behaviour.

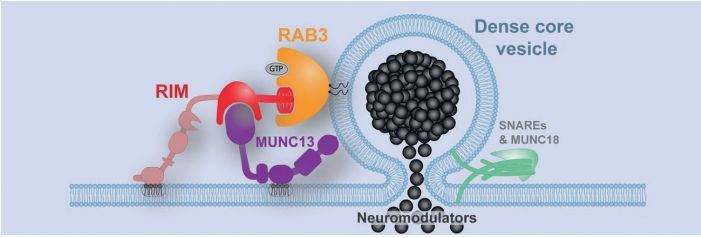
Grant to understand and improve depression related to childhood trauma

Christiaan Vinkers was awarded a grant by Stichting tot Steun VCVGZ (500kE) to investigate an innovative treatment for depression using trauma therapy that specifically aims to reverse the consequences of abuse or neglect during childhood in a single-blind randomized trial. There is increasing evidence that depression related to childhood trauma (abuse or neglect before the age of 18) is clinically distinct with symptoms earlier in life that are more severe and recurrent. As childhood trauma has a prevalence of 25% in depressed patients, there is a large and unmet need for novel therapeutic strategies in this group.

Christiaan Vinkers will examine evidence-based trauma therapy (EMDR or trauma-focused cognitive behavioral therapy) and compare it to regular depression treatment in adult patients with depression and childhood trauma. Moreover, the project also aims to mechanistically understand how trauma therapies exert its effects at the level of the brain.

New study reveals essential molecules for neuromodulator secretion

Claudia Persoon (CNCR-FGA) and colleagues identified RAB3 and RIM1/2 as essential factors for neuromodulator secretion from dense core vesicles in mammalian neurons. This study was published in Neuron.



This new study by Claudia Persoon, Rein Hoogstraten and Joris Nassal identifies RAB3 and RIM1/2 as essential proteins for neuromodulator release from dense core vesicles (DCVs) in mammalian neurons. The crucial role of RAB3 in this process shows the first distinct feature of DCV secretion compared to synaptic vesicle secretion, and identifies the essential function of RAB3 proteins. Neuropeptides, neurotrophins and other signaling molecules (together neuromodulators) are secreted from DCVs and control many physiological functions as brain development, synaptic plasticity, circadian rhythm, behavior and emotions. Defects in neuromodulator signaling are associated with multiple psychiatric disorders, obesity and diabetes, but the mechanisms of neuromodulator secretion by DCVs is largely unknown. Inactivation of all four RAB3 genes resulted in an almost complete loss of DCV exocytosis, which was restored by re-expression of RAB3A. Conditional inactivation of RIM1/2 genes, known interactors of RAB3, resulted in an even greater loss of DCV exocytosis. The N-terminus of RIM1, which interacts with RAB3 and MUNC13, was sufficient to fully restore DCV fusion and travelled together with DCVs in a RAB3-dependent manner. Together, these data show that RIMs are essential interacting partners of RAB3 and organize DCV fusion by positioning MUNC13 and recruiting DCVs via RAB3.

Netherlands Autism Register of the Vrije Universiteit Amsterdam obtains grant of 1,5 million euro

The grant was awarded by ZonMw-NWO, based on a collaborative initiative of main applicant/project leader dr. Sander Begeer (VU), project leader dr. Tinca Polderman (VU), and co-applicants dr. Erik van der Burg (VU), Prof. dr. Annemieke van Straten (VU), Prof. dr. Heleen Riper (VU), Prof. dr. Bhisma Chakrabarti (University of Reading), Prof. dr. Hilde Geurts (University of Amsterdam), and MSc. Maria Hibma (Netherlands Autism Association).

Nederlands Autisme Register

Individuals with Autism Spectrum Disorder (ASD) are characterized by impaired social skills, inflexibility and high rates of co-occurring disorders. The NAR is a unique database, founded in 2013 by the Netherlands Autism Association and the VU. Goal of the NAR is to follow individuals with ASD over time, to investigate how adequate care can improve their functioning, enhance their quality of life, and reduce societal costs.

The ZonMw grant allows to extend and enrich the NAR in the coming eight years with genetic data, online neuropsychological tests, and online interventions. Main applicant Sander Begeer: “Currently, we lack knowledge on how to support people with ASD, in particular adults, in a personalized way. Following NAR participants over time, combined with information on genetic risk, neuropsychological functioning, and intervention effects, will provide crucial insights regarding the needs of people with ASD during the life span.”

Amsterdam UMC, location VUmc - first stem cell therapy study starts in Dutch MS patients

Prof. Joep Killestein, Prof. Bernard Uitdehaag & Prof. Sonja Zweegman of Amsterdam UMC are joining in a large international study aimed at testing the effect of stem cell therapy on the course of the disease in Multiple sclerosis (MS). In this study, stem cell therapy is compared with multiple effective MS treatments (alemtuzumab, cladribine or ocrelizumab). In the next two years, ten people with MS will undergo stem cell treatment at Amsterdam UMC. Stem cell therapy is currently neither reimbursed nor performed for MS in the Netherlands. To obtain reimbursement for stem cell therapy in the Netherlands, scientific research is needed in which the effectiveness and safety of stem cell therapy is directly compared with effective treatments for MS.

Large consortium grant for long term cohort studies on early recognition and treatment of psychiatric disorders

A large 96 moth consortium under guidance of dr. Mirjam van Zuiden of the psychiatry department of Amsterdam UMC (AMC) received a ZonMw grant of 1,5 million euros for long term cohort studies on early recognition and treatment of psychiatric disorders.

One in thirteen Dutch adults develop lifetime posttraumatic stress disorder (PTSD), as a result of traumatic events involving (threatened) death, injury or violated physical integrity. Women have a 1.5 to 2-fold increased risk for PTSD following trauma exposure compared to men. Only the first weeks post-trauma provide a unique window of opportunity for preventive interventions to reduce prevalence of long-term PTSD, related adverse outcomes and societal costs, including mental health care use. Importantly, these interventions are only beneficial if delivered as indicated preventive intervention to individuals at high risk for long-term PTSD. Previous research elucidated many risk and protective factors for PTSD, from demographic, socio-economic, psychiatric, psychosocial, biological, trauma history and environmental domains. Existing prognostic screening instruments, however, fail to adequately predict long-term PTSD when applied early post-trauma. The main outcome of this eight-year consortium project will be a sex-specific prognostic screening instrument derived with machine learning methods to accurately predict which recently trauma-exposed individuals are at risk for long-term PTSD. Hereby we can target indicated preventive interventions to individuals who are most in need of help and will benefit from intervention, thus preventing major suffering and adverse outcome.

Pieter Roelfsema receives NWO grant of 14.3 million euros for the development of brain implants

Professor Pieter Roelfsema receives a grant of €14.3 million from the Netherlands Organization for Scientific Research (NWO) for the development of brain implants. It is one of the five projects that have been awarded funding from the NWO Crossover program. Pieter Roelfsema is director of the Netherlands Institute for Neuroscience and is affiliated with Amsterdam Neuroscience through his appointment as strategy professor in the department of Integrative Neurophysiology and a member of the Systems & Network Neuroscience research program.

The INTENSE (Innovative NeuroTEchNology for SociEty) project of the NeuroTech-NL consortium with Pieter Roelfsema as head will develop brain implants to improve the lives of people who are blind, deaf or paralyzed, or who have epilepsy. The research combines the greatly increased knowledge about our brains with new possibilities within neurotechnology. With this, the researchers want to come up with new solutions and activities.

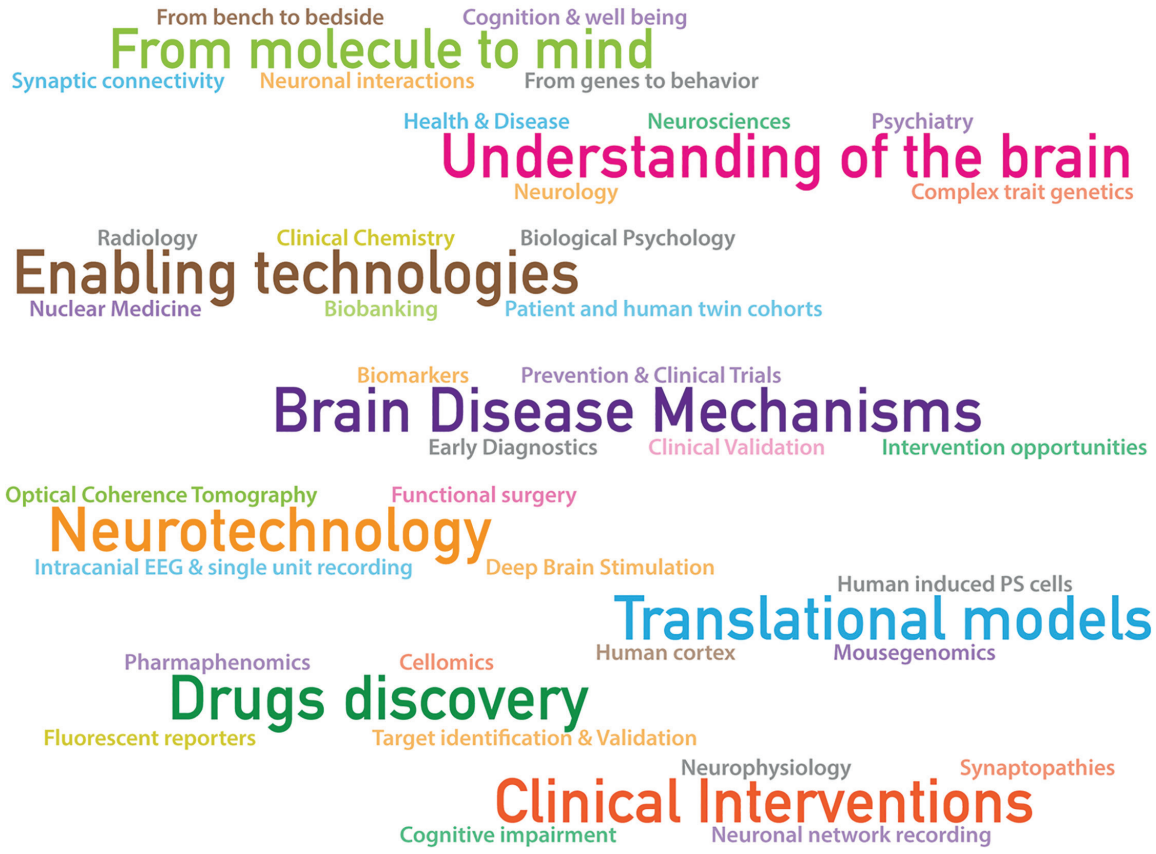
Martijn van den Heuvel appointed as URC professor

Martijn van den Heuvel - neuroscientist at the Center for Neurogenomics and Cognitive Research (CNCR) is appointed as professor in the University Research Chair (URC) program. With his scientific work at the Complex Trait Genetics program of Amsterdam Neuroscience Van den Heuvel bridges the field of neuroscience, imaging genetics and translational medicine.

One of the pioneers in the field of 'connectomics'

With his highly passionate and driven personality Van den Heuvel can be seen as one of the pioneers in the field of 'connectomics', the arena that studies the human brain from a network perspective. At the CNCR he is team leader of the connectomics research team and focusses on linking brain disconnectivity effects in diseases to changes in cell biology and genetics. With a track record of more than 150 publications and an h-index of at least 51 he can be taken seriously. In addition to this, Van den Heuvel is often described as an entertaining speaker and teacher with a big smile and good communication skills. He coordinated parts of the cognitive neuroscience track at his previous university (University of Utrecht) and he is currently also involved in neuroscience courses for bachelor students at the VU and the Master of Neuroscience program of Amsterdam Neuroscience.

Amsterdam Neuroscience



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Amsterdam Neuroscience