Amsterdam Neuroscience

Annual Report 2018

Amsterdam Neuroscience

Colophon

Datamining and newsitems: Thea Laan & Sabira Noerkhan
Monitoring and quality assessment: Arjen Brussaard & Diederik van de Beek
Cover design: Karen Folkertsma

Amsterdam UMC | locations VUmc and AMC in collaboration with
Vrije Universiteit Amsterdam & University of Amsterdam

Word from the directors

The mission of Amsterdam Neuroscience is to generate understanding of the human brain and nervous system in health and disease by integrating basic, translational and clinical research and to provide common ground for clinicians and basic scientists in the Neuroscience field in the Amsterdam area.

At Amsterdam Neuroscience we aim to bridge the gap between basic research and translational medicine by gaining deep understanding of the many brain disease mechanisms, techniques and various disciplines and research methods used nowadays in Neuroscience, and by taking advantage of our proven affinity for brain disease and clinical innovation in the field of Neurology and Psychiatry. We do this by initiating new research strategies and proof-of-concept studies for radically new approaches in the early diagnosis of brain diseases, the elucidation of the underlying mechanisms, and thus providing new routes towards therapy.

As an organization we have organized our research in a focused way along the nine translational research programs, each around specific brain and nervous system diseases, disease mechanisms, or technology innovations. We will continue to keep this focus but also want to stimulate young and promising researchers. With this purpose, over the last three years (2016-2018), 46 outstanding proof-of-concept (PoC) - and collaborative projects were funded for a total of 6.5 M€. We believe that this strategy has been meaningful and effective, and indeed the metrics and highlights of our institute are a great benchmark for the coming years.

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

Executive Summary

- With 153 principal investigators and 78 faculty & residents, 217 postdocs & research associates and currently 439 PhD students the ensemble 'community' of the alliance institute Amsterdam Neuroscience presently includes 877 investigators.
- They acquired a total of ~ 47 M€ in conditional funding during 2018. This included three Veni grants, two Vidi grants and other major grants from Dutch agencies as well as the EC (EU). In addition there was > 10 M€ from non-profit (patient oriented) organizations and also > 10 M€ funding in contracted research from biotech and pharma industry. Finally, Amsterdam Neuroscience internally funded > 2 M€ in proof of concept (PoC) projects, alliance- and innovation- projects.
- In 2018 a total of 1239 refereed articles were published with 160 papers in the highest impact journals (impact factor > 10) and another 284 with a solid impact factor (> 5 <10).
- Of these 1239 unique papers, 139 papers had 'shared' co-authorship (i.e. 'bi-location' affiliations).
- Highlights throughout 2018 included a number of appointments to full professorship (Charlotte Teunissen, Joep Killestein and Guido van Wingen), the 3rd Annual Meeting of Amsterdam Neuroscience (www.amsterdamresearch.org), 4th Transnational Neuroscience Network (TN2, www.tn2.eu) meeting and 2nd CSF Society meeting in Amsterdam.
- In 2018-2019 the group of eight (out of a total 45) graduate students of the European Neuroscience Campus Network (i.e. Erasmus Mundus Joint PhD program, ENC-Network, www.enc-network.eu under supervision of Amsterdam Neuroscience) finished their PhD projects.

Research mission

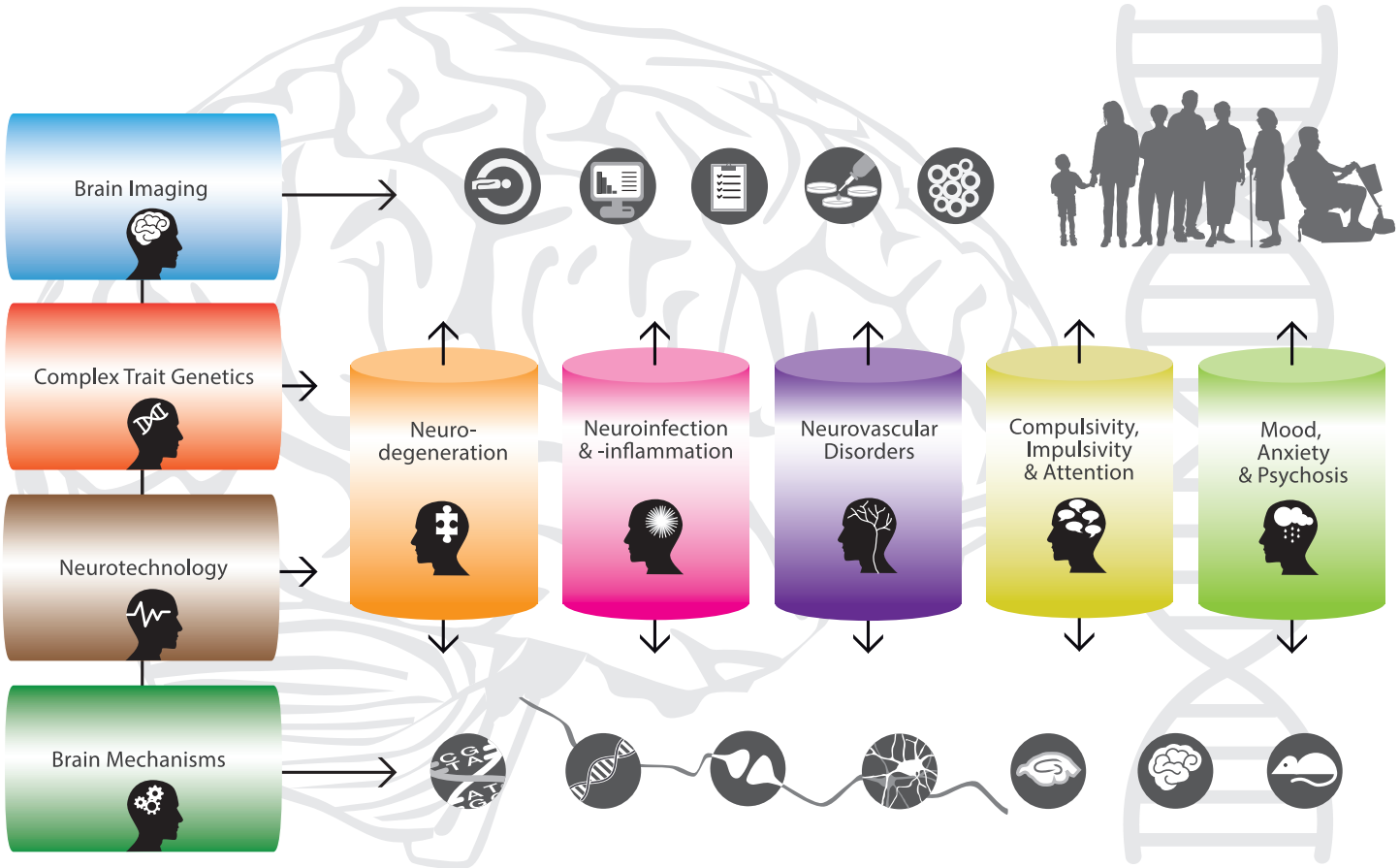
Amsterdam Neuroscience is a high-profile network research organization; the core being the collaboration between relevant departments of the merging academic medical centers and both universities in Amsterdam. The organization is aware that it needs to focus on a limited number of experimental approaches, brain functions and disease mechanisms in order to exceed. The projects within the nine programs should strengthen the link between different disciplines and urge for collaboration between different partners, i.e. irrespective of their location in the Amsterdam region.

Amsterdam Neuroscience bridges the gap between Basic Neuroscience and Translational Medicine by both gaining deep understanding of the many brain disease mechanisms, techniques and various disciplines and research methods used nowadays in Neuroscience, and by taken advantage of our proven affinity for brain disease and clinical innovation in the field of Neurology and Psychiatry. We do this by initiating new research strategies and proof-of-concept studies for radically new approaches in the early diagnosis of brain diseases, the elucidation of the underlying mechanisms, and thus providing new routes towards therapy.

Amsterdam Neuroscience aims to strengthen collaborations between investigators by focusing its research strategy on nine research programs. Five research programs focusing on specific brain and nervous system disease mechanisms are complemented by four programs focusing on innovation, that will provide proof of concept for causal relationships in brain and nervous system function mechanisms. In Amsterdam Neuroscience innovation takes place at all levels of study, from molecular to cellular studies, to circuitry and intact brain and behavior, both at the individual as well as population level.

The nine research programs outlined here act as steering committees each with over fifteen principal investigators (PIs) and faculty. Shared infrastructure and translational efforts are being realized. Graduate training and involvement of medical residents in research is being guided as an integrative approach within each of the research programs.

Research programs



Infographics of the research organization of Amsterdam. Research programs are abbreviated as follows:
Brain Imaging (bi); Complex Trait Genetics (ctg); Neurotechnology (nt); Brain Mechanisms (bm); Neurodegeneration (nd); Neuroinfection & -inflammation (nii); Neurovascular Disorders (Ndis); Compulsivity, Impulsivity & Attention (cia) and Mood, Anxiety & Psychosis (map).

Amsterdam Neuroscience

Gouvernance

Management Team

Arjen Brussaard (director)	Amsterdam UMC – location VUmc
Diederik van de Beek (co-director)	Amsterdam UMC – location AMC
Damiaan Denys	Amsterdam UMC – location AMC
Susanne la Fleur (as of 2019)	Amsterdam UMC – location AMC
Jeroen Geurts (2016-2018)	Amsterdam UMC – location VUmc
Cyriel Pennartz (2016-2017)	University of Amsterdam
Paul Lucassen (as of 2017)	University of Amsterdam
Brenda Penninx (as of 2019)	Amsterdam UMC – location VUmc
Yolande Pijnenburg (as of 2019)	Amsterdam UMC – location VUmc
Philip Scheltens (2016-2018)	Amsterdam UMC – location VUmc
Guus Smit	Vrije Universiteit Amsterdam
Taco de Vries (as of 2019)	Amsterdam UMC – location VUmc
Guido van Wingen (adviser)	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
Peter Beek	Dean Faculty of Behaviour and Movement Sciences, Vrije Universiteit Amsterdam

Program leaders

Dick Veltman	Amsterdam UMC – location VUmc
Liesbeth Reneman	Amsterdam UMC – location AMC
Huibert Mansvelder (as of 2019)	Vrije Universiteit Amsterdam
Helmut Kessels (as of 2019)	University of Amsterdam
Matthijs Verhage	Vrije Universiteit Amsterdam
Rick Schuurman (2016-2018)	Amsterdam UMC – location AMC
Johannes de Boer (2016-2018)	Vrije Universiteit Amsterdam
Susanne la Fleur (as of 2019)	Amsterdam UMC – location AMC
Marten Smidt (2016-2018)	University of Amsterdam
Danielle Posthuma	Vrije Universiteit Amsterdam
Hanne Meijers (2016-2018)	Amsterdam UMC – location AMC
Frank Jacobs (as of 2019)	University of Amsterdam
Wiesje van der Flier	Amsterdam UMC – location VUmc
Rob de Bie	Amsterdam UMC – location AMC
Joep Killestein	Amsterdam UMC – location VUmc
Diederik van de Beek (2016-2017)	Amsterdam UMC – location AMC
Matthijs Brouwer (as of 2017)	Amsterdam UMC – location AMC
Pieter Vandertop	Amsterdam UMC – location VUmc
Yvo Roos (2016-2017)	Amsterdam UMC – location AMC
Jonathan Coutinho (as of 2017)	Amsterdam UMC – location AMC
Odile van den Heuvel	Amsterdam UMC – location VUmc
Wim van den Brink (2016-2018)	Amsterdam UMC – location AMC
Judy Luigjes (as of 2019)	Amsterdam UMC – location AMC
Brenda Penninx (2016-2018)	Amsterdam UMC – location VUmc
Christiaan Vinkers (as of 2019)	Amsterdam UMC – location VUmc
Sabine Spijker	Vrije Universiteit Amsterdam

Task force members

Fleur van Rootselaar	Amsterdam UMC – location AMC
Bart van Berckel	Amsterdam UMC – location VUmc
Huibert Mansvelder (2016-2018)	Vrije Universiteit Amsterdam
Wytse Wadman (2016-2018)	University of Amsterdam
Marjo van der Knaap	Amsterdam UMC – location VUmc
Eric Reits	Amsterdam UMC – location AMC
Tinca Polderman	Vrije Universiteit Amsterdam
Frank Jacobs (2016-2018)	University of Amsterdam
Charlotte Teunissen	Amsterdam UMC – location VUmc
Henk Berendse (2016-2017)	Amsterdam UMC – location VUmc
Paul Lucassen (2016-2017)	University of Amsterdam
Lars van der Heide	University of Amsterdam
Elga de Vries	Amsterdam UMC – location VUmc
Ivo van Schaik (2016-2017)	Amsterdam UMC – location AMC
Filip Eftimov (as of 2017)	Amsterdam UMC – location AMC
Gert Kwakkel	Amsterdam UMC – location VUmc
Charles Majoie	Amsterdam UMC – location AMC
Taco de Vries	Amsterdam UMC – location VUmc
Conrado Bosman	University of Amsterdam
Liewe de Haan	Amsterdam UMC – location AMC
Aniko Korosi (as of 2017)	University of Amsterdam

Research staff

Amsterdam Neuroscience – Research Institute

Total	877		474,9		
	persons		fte - research	% - research	
Subtotal	379	1e geldstroom	166,8	35.1%	1e geldstroom
	199	2e geldstroom	136,8	28,8%	2e geldstroom
	277	3e geldstroom	156,6	33.0%	3e geldstroom
	23	4e geldstroom	14,8	3.1%	4e geldstroom

Total	439	PhD students
	persons	
Subtotals	111	1e geldstroom
	141	2e geldstroom
	170	3e geldstroom
	18	4e geldstroom

Amsterdam Neuroscience – Research Programs

	bi	ctg	nt	bm	nd	nii	ndis	cia	map
	118	83	51	244	177	137	74	132	109

	bi	ctg	nt	bm	nd	nii	ndis	cia	map
	persons								
1e geldstroom	59	37	33	109	62	59	36	68	51
2e geldstroom	25	23	10	70	37	20	18	35	20
3e geldstroom	33	24	8	59	70	51	19	29	38
4e geldstroom	2	0	1	7	9	8	1	1	1

Amsterdam Neuroscience – Research Programs

	bi	ctg	nt	bm	nd	nii	ndis	cia	map
Subtotal	40,6	32,4	18,5	108,2	82,1	66,7	31,8	54,1	39,6

	bi	ctg	nt	bm	nd	nii	ndis	cia	map
	fte - research								
1e geldstroom	16,2	10,3	9,5	35,7	21,4	23,0	12,8	26,6	13,1
2e geldstroom	11,3	11,6	5,4	39,7	22,3	12,7	9,3	15,3	8,8
3e geldstroom	12,1	10,4	3,3	29,3	34,0	26,3	9,0	11,9	17,8
4e geldstroom	1,0	0,0	0,3	3,5	4,4	4,7	0,8	0,3	0,0

NFU definition

- ”1e geldstroom”: internal funding of medical centers and universities
- “2e geldstroom”: conditional funding by intermediary public bodies and agencies (ZONMW, NWO, KNAW en EU)
- “3e geldstroom”: private funding by non-profit organizations
- “4e geldstroom”: private funding from commercial sources: contract-research and clinical research funded by biopharma industry

Note

In the ratio-conversion from personnel to the full-time-equivalent (fte) spend on research the default (HRM-SAP instructed) guidelines were applied unless otherwise instructed by the appointing institute: Full professor: 0.4 fte; Strategic professor: 0.1 fte; Associate professor: 0.4 fte; Assistant professor: 0.4; Investigator: 0.8 fte; Post doc: 0.8 fte; PhD student: 0.75 fte and a lecturer: 0 fte.

Funding

Amsterdam Neuroscience - Research Funding

	Grand total	bi	ctg	nt	bm	nd	nii	ndis	cia	map
Total	€ 46.898.432	€ 4.362.519	€ 1.779.000	€ 2.789.366	€ 9.843.349	€ 14.404.356	€ 3.570.396	€ 3.411.563	€ 2.746.192	€ 3.991.691
	Conditional funding									
	Subtotal	bi	ctg	nt	bm	nd	nii	ndis	cia	map
1e geldstroom*	€ 2.080.235	€ 558.729	€ -	€ 50.000	€ 606.444	€ -	€ 144.618	€ 649.444	€ -	€ 71.000
2e geldstroom	€ 23.627.387	€ 2.918.855	€ 909.000	€ 2.489.366	€ 4.403.671	€ 6.415.353	€ 497.536	€ 636.242	€ 1.596.619	€ 3.760.745
3e geldstroom	€ 11.118.757	€ 88.347	€ 870.000	€ 250.000	€ 3.635.224	€ 2.058.902	€ 914.082	€ 1.992.682	€ 1.149.573	€ 159.946
4e geldstroom	€ 10.072.053	€ 796.588	€ -	€ -	€ 1.198.010	€ 5.930.100	€ 2.014.160	€ 133.195	€ -	€ -

NFU definition

"1e geldstroom": Shown is internal so-called alliance funding (i.e. 2.080 k€) only; the unconditional internal funding for tenured and other personnel is estimated to be more than 45 M€ for 2018;
"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.

Research output & quality in total

Amsterdam Neuroscience - Research Output

	Total	bi	ctg	nt	bm	nd	nii	ndis	cia	map
Refereed article	1239	121	67	46	235	191	158	99	95	227
Non-Refereed article (1)	25	2	2	2	0	4	4	6	4	1
Books	1	0	0	1	0	0	0	0	0	0
Book chapters	6	0	0	0	2	0	0	0	0	4
PhD theses	99	10	4	6	41	11	6	5	13	3
Conference papers	8	3	0	0	0	0	0	1	2	2
Professional publication (2)	24	1	0	0	2	2	3	3	8	5
Publications aimed at the general public (3)	1	0	0	0	1	0	0	0	0	0
Other research output <specify> (4)	4	0	0	0	1	0	2	1	0	0
Total publications	1407	137	73	55	282	208	173	115	122	242
With impact > 10	Subtotal	bi	ctg	nt	bm	nd	nii	ndis	cia	map
Refereed articles (selected output)	160	2	23	2	30	28	21	12	13	29
With impact > 5 < 10	Subtotal	bi	ctg	nt	bm	nd	nii	ndis	cia	map
Refereed articles (selected output)	284	19	10	4	64	65	49	33	10	30

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 (professionele publicaties), 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

Of a total of 1239 refereed papers, 284 papers were with an impact factor between 5 -10 and 160 papers were above impact factor 10 or higher. In this last category at least 47 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 7 papers that published so-called perspectives and reviews in high impact journal (i.e. > 10). Another 106 papers were mainly with international collaborators.

Bi-location authorships

In 2018 there were 139 'bi-location' papers (i.e. papers in which either VUmc and/or AMC shared co-authorship with university co-authors). VUmc had co-authors on 120 of these papers (of which 50 papers shared with AMC), AMC participated on 66 bi-location papers, VU on 77 papers and UvA on 13 of the bi-location papers.

Highlights of the Annual Meeting

Research Report: The genetics of a happy life

Prof. Dr. Meike Bartels
University Research Chair Professor in Genetics and Wellbeing
Department of Biological Psychology
Netherlands Twin Register

Happiness and well-being have emerged as important study subjects within and across many fields of research. A major driving force behind this is the association with physical and mental health and its pivotal role in socioeconomic issues and economic development. With the increased interest in the importance of well-being it is critically important to understand and reveal sources of individual differences.

To understand causes of individual differences in happiness and well-being we apply behavioral genetic and molecular genetic methods. A robust estimate of the heritability of wellbeing is obtained via meta-analysis and we identified the first genome-wide significant genetic variants for wellbeing. Multivariate approaches reveal polygenicity and strong genetic correlations between different forms of wellbeing. Biological annotation uncovers differential gene-expression of genetic variants associated with wellbeing in the subiculum and the ventral tegmental area.

Research Report: Human-specific NOTCH2NL genes: Possible contributors to human's evolutionary increase in brain size

Dr. Frank Jacobs
University of Amsterdam;
Faculty of Science
Swammerdam Institute for Life Sciences

Genetic changes causing dramatic brain size expansion in human evolution have remained elusive. Notch signaling is essential for radial glia stem cell proliferation and a determinant of neuronal number in the mammalian cortex. In this talk, I will discuss our recent discoveries regarding a cluster of human-specific NOTCH-like genes called NOTCH2NL. NOTCH2NL genes emerged in the human genome as a result of a complex series of genomic structural rearrangements, with the last ones marking the birth of NOTCH2NL genes between 4 and 0.5 million years. 2 paralogs of NOTCH2NL are highly expressed in neuronal stem cells of the fetal human brain and have varying potencies to influence Notch signaling. Genetic deletion of NOTCH2NL genes in stem-cell derived human cortical organoids, as well as the association of the NOTCH2NL locus to brain size abnormalities suggests an important role for NOTCH2NL genes during normal human cortical development in vivo. Our discoveries suggest that the creation of NOTCH2NL genes during human evolution may have contributed to the rapid evolution of the larger human neocortex, but ironically, this happened at the expense of genomic instability where NOTCH2NL genes were born.

Research Report: Vulnerability and Neuroplasticity in Obsessive compulsive disorder

Prof. dr. Odile van den Heuvel
Amsterdam UMC, Location VUmc, Department of Psychiatry

Obsessive compulsive disorder (OCD) is a neurodevelopmental disorder characterized by repetitive anxiety-provoking thoughts and ritualistic behaviours. Symptoms often start at childhood and vary across different stages of development and disease. The course of disease is mostly chronic. My vision is that symptoms emanate from the inability to efficiently control emotions and behaviours, due to altered brain maturation early in life; that chronic symptoms, by the power of repetition, cause neuroplastic changes in brain function and structure during the course of the disease; and that the plasticity of the brain circuits is a powerful entry to innovate treatment, e.g. using intensive behavioural therapy combined with non-invasive rTMS-induced neuromodulation. A lifespan approach is needed to disentangle neural mechanisms involved in cause and consequence of the disorder. Age- and disease stage-specific brain markers of disease will lead to innovative prevention and treatment alternatives targeting more specifically the mechanisms of disease in the individual patient.

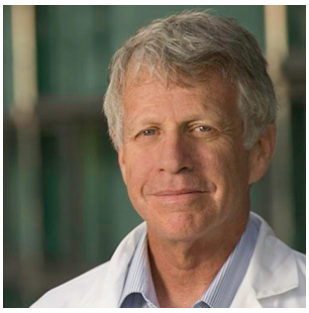
Research Report: The psychobiology of trauma

Prof. Dr. Miranda Olff
Amsterdam UMC, Location AMC, University of Amsterdam; Neurobiological Mechanisms of Prevention and Treatment in Trauma and PTSD, Arq Psychotrauma Research

After a traumatic event individuals show a cascade of stress responses that can lead to development of posttraumatic stress disorder (PTSD), a disorder currently categorized as a trauma- and stressor-related disorder in the DSM-5. Interestingly, the evolutionary short-term adaptive response to stress (e.g. with regard to the HPA-axis), are not the responses we see in PTSD patients. Lower basal cortisol output, enhanced glucocorticoid receptor function, and a proinflammatory state have been most consistently found in PTSD. The alterations become more apparent with increasing time since trauma, but may be reversible with effective treatment or even prevented with early intervention. For instance, the 'love hormone' oxytocin may be a promising novel strategy for prevention and for medication-enhanced psychotherapy (MEP) for PTSD, by influencing neural fear responses, peripheral stress responses and socio-emotional functioning. Further challenge lies in understanding how context and interindividual differences (e.g. gender) moderate clinical effects of oxytocin, and considering the complex interplay of neurobiological systems, how we can enhance the clinical application of biomarkers in screening, prevention and treatment.

Swammerdam Lecture "Inflammation" in Multiple Sclerosis is vastly different than "inflammation" in Neurodegenerative Diseases

Dr. Lawrence Steinman, MD
Stanford University School of Medicine, California USA



Although certain dogma-SOMETIMES CALLED THE AMYLOID HYPOTHESIS- portrays amyloid fibrils as drivers of neurodegenerative disease and neuroinflammation, we have found, paradoxically, that amyloid fibrils and small heat shock proteins (sHsps) like aB crystallin are therapeutic in experimental autoimmune encephalomyelitis (EAE). They reduce clinical paralysis and induce immunosuppressive pathways, diminishing inflammation. A key question was the identification of the target for these molecules. When sHsps like aA and aB crystallin and amyloid fibrils were chemically cross-linked to immune cells, a limited number of proteins were precipitated, including the α7 nicotinic acetylcholine receptor (α7 nAChR). The α7 nAChR is noteworthy among the over 20 known receptors for amyloid fibrils, because it plays a central role in a well-defined immune-suppressive pathway. Competitive binding between amyloid fibrils and α-bungarotoxin to peritoneal macrophages (MΦs) confirmed the involvement of α7 NAChR. The mechanism of immune suppression was explored, and, similar to nicotine, amyloid fibrils inhibited LPS induction of a common set of inflammatory cytokines while inducing Stat3 signaling and autophagy. Consistent with this, previous studies have established that nicotine, sHsps, and amyloid fibrils all were effective therapeutics in EAE. Interestingly, B lymphocytes were needed for the therapeutic effect. These results suggest that agonists of α7 nAChR might have therapeutic benefit for a variety of inflammatory diseases. The α7 nAChR is a key component of immune regulatory responses that suppress inflammation in a wide swathe of diseases. We might consider the amyloid hypothesis from a vastly different perspective.

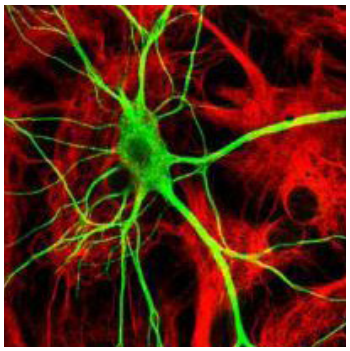
Young MS patient meets clinical investigator of Natalizumab at Annual Meeting 2018

A young general practitioner, Sofie van Nues, with a history of Multiple Sclerosis, met with clinical inventor of Natalizumab, Prof. Larry Steinman at 2018 Amsterdam Neuroscience Annual Meeting at Johan Cruijff Arena on October 5, 2018. The meeting with over 550 of registrants was well attended and perceived by many as outstanding in what has become an annual tradition by now. As Prof. Larry Steinman put it later-on by email: "The Amsterdam Neuroscience meeting was exceptional, and I shall share my perceptions with the Neuroscience team at Stanford. We ought to aspire to organize this type of meeting featuring the outstanding students, and asking them to share their progress with the entire community. The students were truly outstanding. I appreciate that they were advised and drilled by their mentors, but they are going to be the "future" in neuroscience."

Mrs. Sofie van Nues shown here on the left in the picture, and who successfully completed here medical studies and training to become GP despite suffering from Multiple Sclerosis, has been meeting with the inventor of Natalizumab, Prof. Larry Steinman (middle) and was interviewed on stage by Prof. Joep Killestein (right in picture). During a 30-minute session which was at times breath-taking Joep Killestein interrogated Sofie van Nues on her experience and storytelling being both an MD and a patient. As Larry put it later-on: "Her interview with Joep Killestein was gripping and she told her story with grace. She educated me and hundreds of others. I was inspired even after four decades of being a neurologist." Steinman who featured as the 2018 Swammerdam Key Note Speaker is well known for his efforts during four decades at Stanford, which have included the discovery and subsequent development of a monoclonal antibody to block homing to the inflamed brain, leading to Natalizumab, an approved therapeutic for two autoimmune diseases: relapsing-remitting MS and for inflammatory bowel disease.
Amsterdam Neuroscience program leader Prof. Dr. Killestein who has been treating Sofie for over ten years until now, after a staged interview with Sofie van Nues, discussed in front of hundreds of young investigators and students, her patient history and in particular several important aspects of efficacy, risks and reasons for switching medication. The careful process of 'shared decision making' where neurologist and patient team up in taking therapy decisions and titration schemes of immunotherapy-interventions lately applied under Killestein's supervision at the department of Neurology of Amsterdam UMC were elegantly discussed and outlined on stage during his Perspective Lecture.

Selection of newsitems of 2018

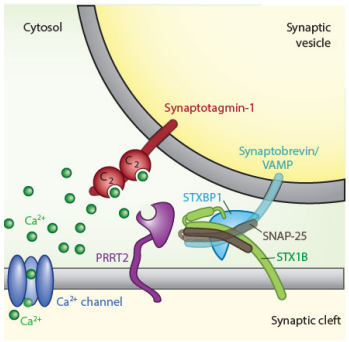
Consortium led by Huibert Mansvelder received 1 M€ EU grant



In the ERA-NET NEURON awarded research project iPS&BRAIN, Prof. dr. Huib Mansvelder (CNCR, VU) collaborates with researchers at the Pasteur Institute in Paris and the Medical University of Vienna. The consortium aims to elucidate mechanisms of nicotine addiction and schizophrenia. In both disorders, genetic variants of nicotinic acetylcholine receptors are involved that increase the disposition for both addiction as well as schizophrenia, but we do not understand how. The nicotinic receptors are involved in neuronal communication in our brain, but the role of the genetic variants is unclear. In addition to fundamental studies to investigate the communication between neurons based on these genetic variants, the consortium will use iPSCs derived from patient cells to test potential therapeutic strategies.

Consortium led by Ruud Toonen received 1 M€ EU grant

Epilepsy is a severe and disabling disease affecting about 1% of the world's population. Despite years of intense research about 30% of all epilepsies cannot be treated by available drugs. To develop new and better treatment options, a detailed knowledge of the mechanisms leading to epilepsy is urgently required. Toonen will lead the ERA-NET NEURON transnational research project "SNAREopathy" that will focus on a group of difficult-to-treat, severe epilepsies caused by mutations in genes that mediate the communication between nerve cells (synaptic transmission). The consortium unites experts in the genetics of epilepsy and neurobiologists working on synaptic transmission from the Netherlands, Germany, Italy and Norway to identify the mechanisms leading to epilepsy using several sophisticated mouse and zebrafish models, as well as human cell models derived from skin biopsies that will be transformed into human neurons (so-called iPSC-derived neurons). Based on the identified epileptic mechanisms, the consortium will use these models for drug screening to search for novel medications to better and more specifically treat the severely

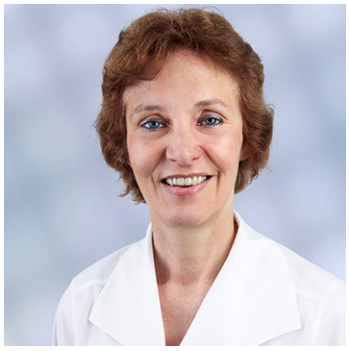


affected epilepsy patients. The interaction of SNAREs (soluble N-ethylmaleimide–sensitive factor-attachment protein receptors) and STXBP1/MUNC18-1, together with calcium binding proteins of the synaptotagmin family ensures the speed and precision of neurotransmitter release. Importantly, mutations in two central components of the SNARE-complex and one co-factor, encoded by the STX1B, STXBP1 and PRRT2 genes (See Figure), lead to a wide spectrum of seizure phenotypes and other neuropsychiatric symptoms, many of which respond poorly to available antiepileptic drugs. Interestingly, the same genes are associated with autism and schizophrenia disorders with an increased seizure comorbidity. We have identified mutations in two of the three genes, STX1B & PRRT2, in familial or sporadic forms of epilepsy. Similar to but clinically distinguishable from STX1B mutations, de novo mutations in STXBP1cause a severe, early onset epilepsy with a characteristic suppression-burst pattern in the EEG. We will now combine our knowledge of these presynaptic proteins to reach a comprehensive picture of presynaptic dysfunction in epileptic disorders and related comorbidities using animal models, patient-derived neurons and innovative in vitro and in vivo screening platforms to develop new tailored therapeutic approaches.

Charlotte Teunissen appointed as professor of Neurochemistry

Professor Charlotte Teunissen aims at developing biomarkers for neurodegenerative diseases. Her vision is to improve biological diagnosis, therapy development and monitoring of disease progression through biomarkers in body fluids, such as cerebrospinal fluid and blood. Her strategy is to address the whole workflow from identification of candidate biomarkers, assay development and finally clinical implementation, and collaborate with all relevant stakeholders in this process. Hereby, she envisions to find better solutions to address important unmet medical needs and increase our understanding of neurodegenerative and neuroinflammatory diseases. Her current major disease topics are dementias, such as Alzheimer's disease, and Multiple Sclerosis.

Major ZONMW grant for Leukodystrophy research of Marjo van der Knaap



In 2018 a project proposal entitled 'Disease Mechanisms in Vanishing White Matter: Targets for Therapy Development 'was granted by the ZONMW agency for funding.
Marjo van der Knaap (Principle Investigator at VUmc) about the research in short: "Leukodystrophies, genetic brain white matter (WM) disorders, have an overall incidence of >1:7500. Vanishing white matter (VWM) is one of the commonest. It mainly affects children, causing neurological regression with stress- (esp. fever-) provoked episodes of rapid decline, coma, and death. Cerebral WM displays profound myelin lack, scarce astrogliotic scarring, and complete disappearance of all structures. We identified the underlying defect in initiation factor eIF2B, which is indispensable for mRNA translation and a key component of the integrated stress response (ISR) in all body cells. The ISR is also one of the 3 pathways of the unfolded protein response (UPR), which is activated by overload of un- and misfolded proteins in the endoplasmic reticulum. We developed mutant mouse models replicating human VWM. We showed that WM astrocytes and oligodendrocytes are selectively affected, astrocyte pathology being primary, oligodendrocyte pathology secondary. VWM has regional variation in WM disease severity and repair potential, for which the degree of astrocyte abnormality appears responsible. We showed selective ISR activation in astrocytes and oligodendrocytes. It is unclear whether ISR activation is protective, neutral or detrimental. No therapy is currently available for VWM. We work at developing multimodal therapy, including pharmacological approaches. For this, we need to delineate roles of the ISR and astrocytes in VWM pathology and identify molecular targets to modulate ISR activation and astrocyte (dys)function to enhance repair. This proposal will answer 2 questions: (1) How does the ISR impact VWM? (2) How do VWM astrocytes determine WM disease severity and repair potential? We rely on unique VWM patient and control brain tissue and VWM mice. The project will add ground-breaking novel insight into basic roles of the ISR and astrocyte heterogeneity in VWM, with strong implications for WM pathology and physiology and therapy development."

Launch of hersenonderzoek.nl accelerates recruitement of participants in clinical trials in brain disorders

hersen onderzoek nl

For studies and trials in the field of dementia and other brain diseases, there is a major and increasing mismatch between the limited number of participants and the high number of subjects needed in studies. Recruiting participants for clinical trials is one of the major bottlenecks in research, resulting in prolonged trial duration and increase in costs. To speed up recruitment for studies, we created a Dutch registry of both older healthy (at risk) individuals and patients by means of an online platform: Hersenonderzoek.nl. This platform will connect participants and researchers in the Netherlands, and will facilitate efficient recruitment of participants for all kinds of studies. Please visit www.hersenonderzoek.nl for more info.
The platform was initiated by Amsterdam Neuroscience investigators dr. Niels Prins and prof. dr Philip Scheltens in a joint collaboration with prof. dr. Wiesje van der Flier and dr. Marissa Zwan (coordinating manager of the platform). Several sponsoring party and agencies were involved in setting this up, including Alzheimer Nederland, the Hersenstichting and most recently ZonMw through a research grant awared to Zwan c.s. Since the launch of the website presently > 10000 new participants have subscribed.

EU Horizon 2020 grant for INSIST project

Charles Majoie (Dept of Radiology, AMC), Henk Marquering (Depts of Biomedical Engineering and Physics and Radiology, AMC), Ed van Bavel (Dept of Biomedical Engineering and Physics, AMC), and Alfons Hoekstra (Dept of Computational Sciences, UvA) were awarded a 5.25 M€ Horizon 2020 grant for the INSIST project. The project started november 1, 2017 and will run for 4 years.

INSIST - IN-Silico trials for treatment of acute Ischemic Stroke.
www.insist-h2020.eu

Stroke is the number one cause of disability in the Western world and the 3rd most common cause of death. Despite new treatment options with intra-arterial thrombectomy, still 2 out of 3 patients still have a poor outcome. The main goal of INSIST is to advance treatments of ischemic stroke and its introduction in clinical practice by realizing in silico clinical stroke trials in which stroke and treatment are modeled. The investigators team being led by Prof. Dr. Charles Majoie will generate virtual populations of stroke patients, generate and validate in silico models for intra-arterial thrombectomy, thrombosis and thrombolysis, and microvascular perfusion and neurological deterioration after stroke, and integrate the in silico models to realize an in silico clinical stroke trial. In silico models and virtual populations will be combined to simulate clinical trials and validated by simulating and comparing finalized and currently running trials. The in silico models will be used to simulate clinical trials to evaluate effectiveness and safety of novel devices and medication, both for the medical device- as well as the pharmacological industry.

Wim van den Brink received the EUFAS-EAR 2018 Award

In 2018 Professor Wim van den Brink - former program leader of the Amsterdam Neuroscience research program Compulsivity, Impulsivity & Attention - has been awarded the EUFAS-EAR 2017 Award for outstanding contributions to the advancement of addiction science. Wim van den Brink is professor of Psychiatry and Addiction at the Academic Medical Center, University of Amsterdam. He is also Director of the Amsterdam Institute for Addiction Research. He received the 2018 award at the European Psychiatric Association's (EPA) 26th annual meeting in Nice.

PhD student Mats Nagel published in Nature Communications

Through genome-wide association studies (GWAS) geneticists aim to identify genetic variants that are associated with human traits, such as cognitive function, depression, or personality. Generally, identified variants have very small effects, supporting the idea that many human traits are genetically highly complex. To date researchers tend to use composite scores to measure traits in the psychological domain. These composite scores summarize information contained in multiple items or symptoms, and have proven very useful in daily practice, e.g., in directing therapeutic intervention or predicting school/job performance. However, in studying the genetics of behavior, an important question is whether the combined items or symptoms are indeed genetically similar. If not, combining them will severely dilute the genetic signal, and thus compromise our understanding of underlying genetic mechanisms. In a paper published in Nature Communications (2018), PhD student Mats Nagel, under supervision of Sophie van der Sluis (Amsterdam Neuroscience, Complex Trait Genetics) was the first to examine the genetic similarity of individual symptoms of psychological traits in a large-scale study.

Nagel M, Watanabe K, Stringer S, Posthuma D, van der Sluis S. Nat Commun. 2018 Mar 2;9(1):905. doi: 10.1038/s41467-018-03242-8.

Computer model published by PhD student Laura Han predicts older age in people with depression

People with a depression likely experience stress, both mentally and physically. Previous research has shown that depressed people are at risk for prematurely developing aging-related disorders, such as cardiovascular diseases, diabetes or cancer. "Globally, an estimated 300 million people of all ages suffer from depression, of which many feel older than they actually are", says Laura Han, researcher at GGZ inGeest and VU University Medical Center. Together with colleagues from Amsterdam and the Virginia Commonwealth University in Richmond, Laura Han under supervision

of Brenda Penninx (Amsterdam Neuroscience, Mood, Anxiety & Psychosis), researched whether depressed people are estimated to be older based on patterns on the DNA. They recently published their findings in the renowned scientific journal The American Journal of Psychiatry.

Han LKM, Aghajani M, Clark SL, Chan RF, Hattab MW, Shabalin AA, Zhao M, Kumar G, Xie LY, Jansen R, Milaneschi Y, Dean B, Aberg KA, van den Oord EJCG, Penninx BWJH. Am J Psychiatry. 2018 Aug 1;175(8):774-782. doi: 10.1176/appi.ajp.2018.17060595. Epub 2018 Apr 16.

Guido van Wingen appointed as professor of Neuroimaging in the Psychiatry

Guido van Wingen has been appointed professor Neuroimaging in the Psychiatry. His research is focused on misophonia among other things. This psychiatric disorder involves people with misophonia (meaning: hatred of sound) who experience irritation, disgust and anger, triggered by sounds from other human beings.

Nathan Marchant received Vidi grant from NWO

Nathan Marchant (Behavioral and Translational Neuroscience Group, Department of Anatomy & Neurosciences, VUmc) received a Vidi grant from NWO. This 800 k€ grant enables researchers to establish their innovative research line. This Vidi grant will enable Nathan and his team to study the underlying neurobiology of two critical aspects of Alcohol Use Disorder (AUD). The AUD clinical population is defined as people that continue to use alcohol despite the harm it is causing, however not all people that use alcohol become addicted. To study this variation, Nathan and his team will use advanced neuroscience techniques, such as chemogenetics, optogenetics, calcium imaging, and transcriptomics, to identify innovative treatment targets for restoring control of alcohol use. In parallel Nathan and his team will identify a causal role for a genetically defined sub-population of neurons in the lateral hypothalamus in encoding the alcohol memories that cause relapse during abstinence. This project may open the door for future studies aiming to suppress the expression of these tenacious memories, reducing relapse propensity.

Vidi grant awarded to Rogier Min

Rogier Min (Child Neurology, VUmc & Integrative Neurophysiology, VU) receives a Vidi grant from the Netherlands Organisation for Health Research and Development (ZonMw). This 800 k€ grant enables researchers to establish their innovative research line. With the grant, Rogier and his team will study how a disturbed balance of salts and water in the brain leads to neurological diseases. Salts and water are crucial for electrical signaling in the brain. If the precise distribution of these two ingredients is disturbed this can disrupt brain function and cause chronic white matter swelling, with serious consequences. In the heritable white matter disease MLC (Megalencephalic Leukoencephalopathy with subcortical Cysts) the balance of salts and water in the brain is disrupted because of a defect in astrocytes, supportive brain cells. However, the exact role of astrocytes in the development of this disease is unclear. Rogier and his team will use advanced microscopy and electrophysiology techniques in mouse models for MLC to visualize astrocyte dysfunction in the intact brain, with the ultimate aim to find new openings for treatment.

Veni grants for Amsterdam Neuroscience investigators

Project: The brain's response to medication: zooming in with pharmacological MRI

Dr Anouk Schrantee – Radiology and Nuclear Medicine AMC

The exact brain response to psychotropic medication is difficult to investigate using regular brain scans. In this proposal a new method will be developed to zoom in on the activation of brain cells during psychotropic drug administration. This method will advance treatment monitoring and the development of psychotropic medication.

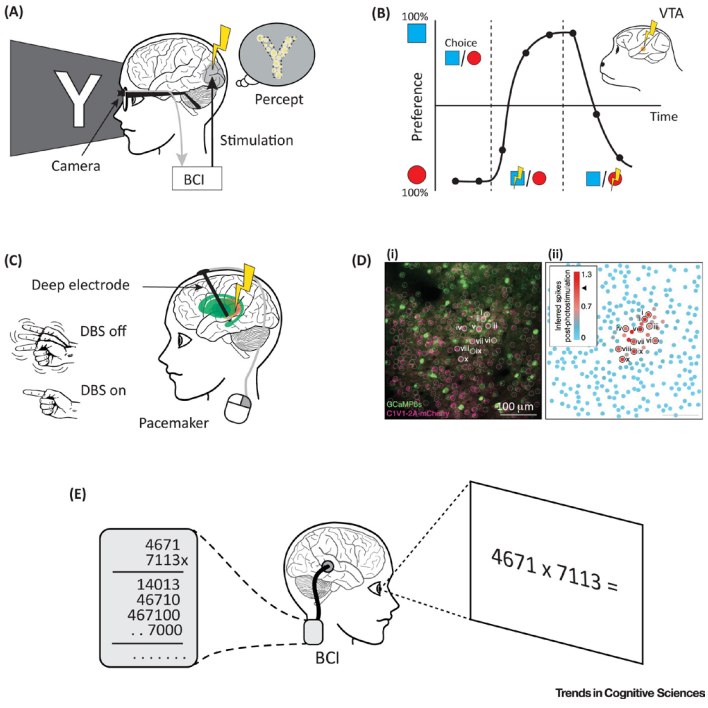
Project: What causes depression?
Dr Wouter Peyrot - VU - Psychiatry

Depression is a heterogeneous disease whose causes are poorly understood. Recently, new statistical methods were proposed to identify causal factors based on genetic data. This project investigates the reliability of these methods, and investigates whether the identified causal factors can aid in identifying clinically relevant patient subgroups.

Project: The blood-brain barrier in Vanishing white matter: filling a knowledge gap
Dr Marianna Bugiani - VUmc

Astrocytes on trial. Genetic white matter disorders destroy the brain white matter and cause handicap and death. Astrocytes (type of brain cells) maintain brain health, but little is known about their role in these disorders. My research suggests that astrocytes are central. This I will study in detail.

Mind Reading and Writing: The Future of Neurotechnology - Pieter Roelfsema and Damiaan Denys publish white paper in Trends of Cognitive Sciences



Advanced methods to record brain activity make it increasingly possible to access an individual's mental processes (i.e., to 'read their mind'). The information that is directly extracted from the brain can be used to control devices, artificial limbs, or obtain knowledge of (hidden) intentions.
Methods to stimulate the brain with electrical currents, opto-genetics, and other methods are routinely used to probe causal relations in the brain and to restore dysfunctional neural circuits. These methods can also be used to 'write to the mind' (i.e., to feed information directly into the brain).
Neurotechnologies to read from, and write to, the brain might be combined in a single individual to create 'augmented cognition' with increased processing capacity and an enhanced cognitive repertoire. This potential methodology also raises some important ethical questions.

Roelfsema PR, Denys D, Klink PC.
Trends Cogn Sci. 2018 Jul;22(7):598-610. doi: 10.1016/j.tics.2018.04.001. Epub 2018 May 2. Review.

Joep Killestein appointed as professor of Multiple Sclerosis

Professor Killestein's research focusses on developing a) dedicated clinical intervention protocols aimed at individual MS patients, b) the use of biomarkers to predict and monitor disease activity, progression and response to disease modifying therapy and c) biomarkers to predict and monitor adverse effects of disease modifying therapy in MS.
The vision of his research is perfectly embedded in the Research Program Neuroinfection and – Inflammation of Amsterdam Neuroscience, where he also acts as program leader, together with Matthijs Brouwer (location AMC).
The aim of this research program is to conduct clinical and translational research of international distinction, in parallel with compassionate and innovative care of the highest quality. The focus of the research is on multiple sclerosis and as such Prof Killestein will coordinate all MS research at the location VUmc, in particular in collaboration with the other members of MS Center Amsterdam.

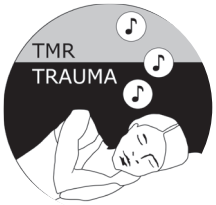
Inge Verberk published article on Plasma amyloid in SCD: the SCIENCe project in Annals of Neurology

Cerebral amyloid pathology, one of the Alzheimer's Disease pathological hallmarks, is currently identified using amyloid PET scanning of the brain or by low levels of amyloid beta in cerebrospinal fluid (CSF). The available diagnostic tools are however invasive (CSF) or expensive (PET), hampering widespread application for diagnosis, e.g. in a primary care setting, and large scale identification of individuals with an abnormal amyloid status in the context of recruitment for trials. A blood marker would qualify as an easy pre-screening tool, subsequently forwarding less individuals towards further invasive and/or expensive testing to obtain definite cerebral amyloid status. Using high-sensitive SIMOA technology amyloid and tau levels were measured in blood plasma of a group of cognitively unimpaired individuals with subjective cognitive decline. Plasma amyloid was a reasonably good predictor of amyloid status, and showed potential as pre-screener to reduce the number of lumbar punctures or PET scans. Inge Verberk, PhD student with Charlotte Teunissen (neurochemistry laboratory) and Wiesje van der Flier (Alzheimer center Amsterdam) recently published these results in Annals of Neurology.

Plasma amyloid as pre-screener for the earliest Alzheimer's pathological changes (Verberk IMW, Slot RE, Verfaillie SCJ, Heijst H, Prins ND, van Berckel BNM, Scheltens P, Teunissen CE, Van der Flier WM. Ann Neurol. 2018)

Hein van Marle received NARSAD Young Investigator Grant to treat trauma during sleep

Hein van Marle, Amsterdam UMC (location VUmc) and GGZ inGeest, received $70.000 from the Brain & Behavior Research Foundation to further support his recently started TMR-TRAUMA study. With this study van Marle aims to open up sleep as a potential treatment window in post-traumatic stress disorder



(PTSD). Recent advances show that memory consolidation can be significantly enhanced by presenting reminder cues during subsequent sleep (known as targeted memory reactivation). The study seeks to apply memory reactivation strategies during sleep in patients for the first time in an effort to increase therapy effectiveness. Van Marle will specifically test whether re-administering auditory cues that are already part of a treatment, again, during subsequent sleep, will strengthen the (re)consolidation of updated traumatic memory. To visualize the underlying reorganization of the traumatic memory in the brain, he will additionally obtain functional MRI during scripted recall of the traumatic event pre/post study. The US-based Brain & Behavior Research Foundation annually awards 200 grants worldwide to early-career scientists, who pursue innovative mental health research. As 1 of 2 Dutch recipients, van Marle was awarded in the category Next-Generation Therapies.

European (JPND) grant for Wiesje van der Flier, Ingrid van Maurik and colleagues from Sweden en France

Project title: ADDITION | Total budget: 1.1ME; Amsterdam 420 kE
Short description of the project: ADDITION will study disease trajectories, care pathways and time to key events along the full disease course of AD, by combining cohorts with different strengths and adding newly collected data on patient relevant outcomes. Second, ADDITION will study the long term cost-effectiveness, economic and societal impact of interventions aimed at improving care outcomes (today) and changing the course of disease (tomorrow). Amsterdam will be responsible for the work package that models disease progression. If successful, results from ADDITION will contribute to strengthening patient competence in decision-making by providing accurate prognostic information across the entire disease course, and to enabling rational societal decisions on new preventive, therapeutic and care strategies for AD. The EU Joint Programme – Neurodegenerative Disease Research (JPND) is the largest global research initiative aimed at tackling the challenge of neurodegenerative diseases, in particular Alzheimer's.

Professor Gert Kwakkel of Amsterdam UMC awarded prestigious American Award

The Outstanding Neurorehabilitation Clinician-Scientist (ONCS) Award has been presented to Gert Kwakkel, Professor of Neurorehabilitation attached to Amsterdam UMC. The award was awarded by the scientific committee of the American Society of Neurorehabilitation and it is a recognition of Prof. Kwakkel's research into the mechanisms of neurological recovery of the brain in relation to the return of functions and skills in patients who have had a stroke.
In 2018, Prof. Kwakkel – a distinguished Task force member of Amsterdam Neuroscience and also head of acquired brain injury research at Reade Rehabilitation Center in Amsterdam - travelled to San Diego, California to accept the award. He is very happy and surprised to receive the ONCS Award: "This award almost always goes to an American scientist and rarely to investigators who have a Chair outside the United States. I see it as international recognition of our work in the field of neurorehabilitation."
Since the mid-1990s Prof. Kwakkel's research has been primarily focused on recovery after stroke. A stroke can be due to a bleed or an infarction in the brain, infarction being far and away the most common cause. In recent years Prof. Kwakkel has demonstrated that intensive rehabilitation after stroke accelerates the return to independence. In addition, he has developed prediction models on the return of arm-hand function, walking ability and activities of daily life after a stroke. Prof. Kwakkel has been involved in the development of the current multidisciplinary guidelines post stroke, as well as in a number of international consensus agreements on stroke management.

Volkswagen Brain Van"Thanks to an advanced ERC award from the European Commission in 2012, Amsterdam UMC together with the Technical University of Delft, were able to build a Volkswagen Brain Van containing the equipment for our serial measurements in time. This enabled us to travel to patients at prearranged times".
Each year, approximately 42,000 Dutch people will have a stroke for the first time, of which approximately twenty percent die within one year after stroke. As a consequence, the prevalence of stroke is about 478,000 people. However, this number also includes those patients who suffered from a so-called transient ischemic attack. Stroke is the main cause of invalidity. Prof. Kwakkel: "Recovery following stroke is uncertain, which makes predicting the outcome important. This is not only important for the patient, but also for determining the further discharge policy (going home with or without help, rehabilitation center or nursing home). If recovery can be more accurately estimated, then the collaboration within the rehabilitation services can also be better organized and by extension, we will know who will benefit most from which type of therapy. This is what makes our prognostic research valuable.

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