Amsterdam Neuroscience

Annual Report 2017

Amsterdam Neuroscience

Colophon

Data mining and collection of the data: Thea Laan & Sabira Noerkhan
Monitoring and quality assessment: Arjen Brussaard & Diederik van de Beek
Design: Karen Folkertsma

Word from the directors

In 2017 Amsterdam Neuroscience has continued to improve understanding of the human brain and nervous system in health and disease by executing integrated basic, translational and clinical research. Our research institute provides common ground for clinicians and basic scientists in the Amsterdam area, which has resulted in outstanding neuroscience research, great papers and important societal impact.

We have organized our research in a focused way along nine translational research programs, each around specific brain and nervous system diseases, disease mechanisms, or technology innovations. We will continue to keep our focus but also stimulate young and promising research, contributing to generating deep understanding of brain mechanisms at all levels of study, from molecular, to cellular studies, to circuitry and intact brain and behavior. We want to translate latest scientific insights into novel diagnostics, new interventions and clinical trials. With this purpose, 46 outstanding proof-of-concepts and collaborative projects were funded for a total of 6 M€ over a 3-year period. We look forward to the results of these projects.

Enclosed the second annual report. We followed the SEP-evaluation protocol of the VSNU; for funding categorization we used NFU-criteria. The facts and figures are a benchmark for the coming years and important for our midterm review that will take place in 2019. Perhaps even more important is the story telling of our researchers. Hence, we have presented an outline of remarkable events and highlights of our institute.

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

Executive Summary

- With 135 principal investigators in addition to faculty, residents, postdocs and including 479 PhD students the ensemble 'community' of the alliance institute Amsterdam Neuroscience presently includes 1025 investigators.
- They acquired a total of > 49 M€ in conditional funding during 2017. This included two VIDI grants and two ERC grants. In addition, in 2017 Amsterdam Neuroscience invested ~ 3.5 M€ in proof of concept project, alliance and innovation projects.
- In 2017 a total of 1321 refereed articles were published with 129 papers in the highest impact journals (impact factor > 10) and another 331 with a solid impact factor (> 5 <10)
- Of these 1321 unique papers, 141 papers had 'shared' co-authorship (i.e. 'bi-location' affiliations).
- The nine research programs are all vital in their research output and research quality, despite differences in their historical trajectories.
- Highlights included a number of appointments to full professorship (Charlotte Teunissen, Eric Reits and Rob de Bie), inaugural lectures (Liesbeth Reneman), the 2nd Annual Meeting of Amsterdam Neuroscience and the coordination of 3rd Translational Neuroscience Network (TN2) meeting.

Management Team, Program Leaders and Task Force

Arjen Brussaard - Scientific director & chair
Diederik van de Beek - co-director
Philip Scheltens - Member
Guus Smit --Member
Jeroen Geurts - Member
Paul Lucassen - Member
Damiaan Denys - Member (not shown)

Fleur van Rootselaar

Taskforce members

Liesbeth Reneman

Brain Imaging

Bart van Berckel

Program Leaders

Dick Veltman

Hanne Meijers

Program Leaders

Complex Trait Genetics

Tinca Polderman

Danielle Posthuma

Taskforce members

Frank Jacobs

Amsterdam Neuroscience

Neurodegeneration

Rob de Bie

Program Leaders

Wiesje van der Flier

Charlotte Teunissen

Taskforce members

Paul Lucassen

Neuroinfection & -inflammation

Matthijs Brouwer

Program Leaders

Elga de Vries

Taskforce members

Filip Eftimov

Joep Killestein

Neurovascular disorders

Peter Vandertop

Program Leaders

Yvo Roos

Gert Kwakkel

Charles Majoie

Taskforce members

Amsterdam Neuroscience

Research mission

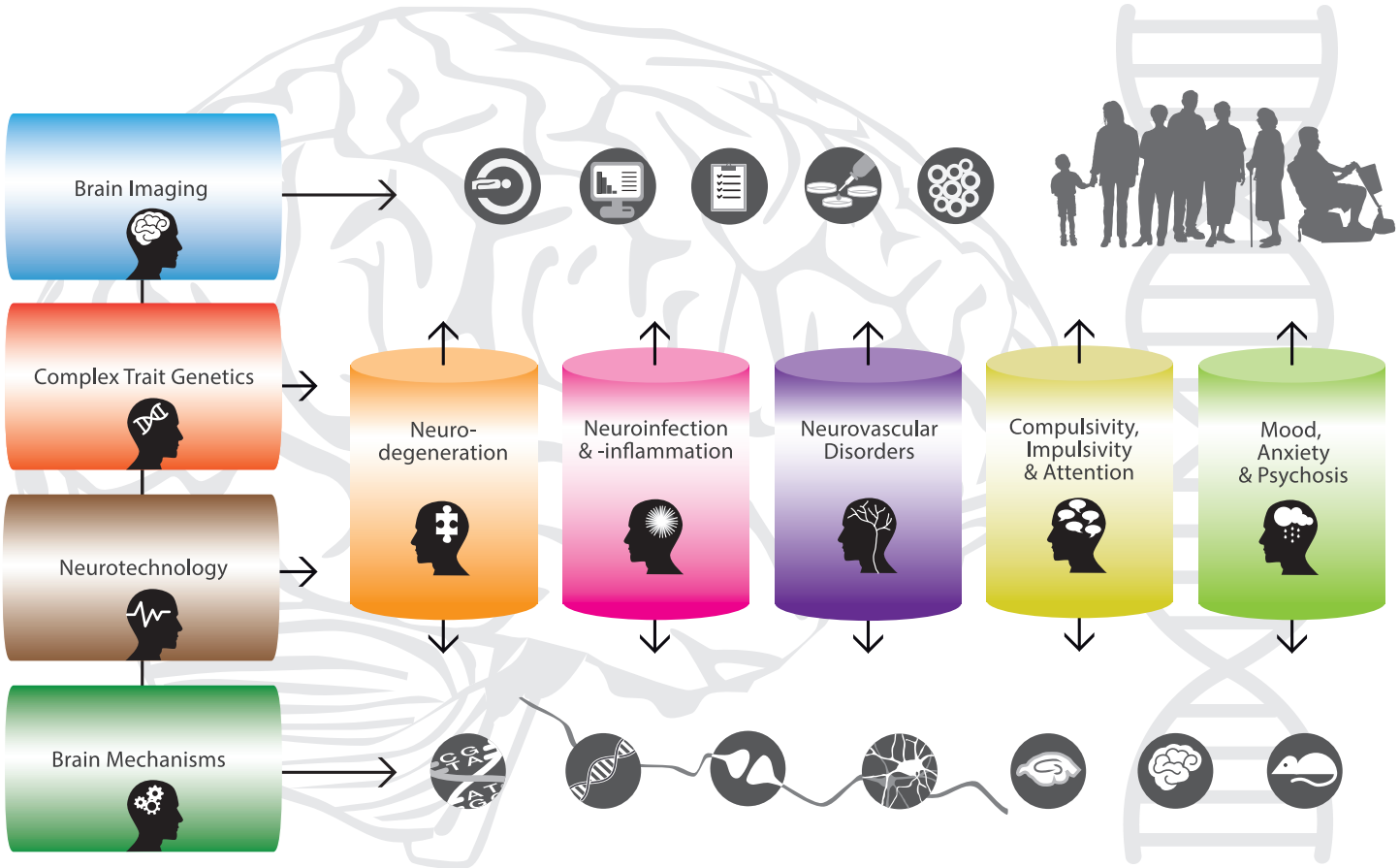
Amsterdam Neuroscience is a high-profile network research organization; the core being the collaboration between relevant departments of the merging academic medical centers and both universities in Amsterdam. The organization is aware that it needs to focus on a limited number of experimental approaches, 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 (irrespective of their location).

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 below act as steering committees with each over fifteen scientists and Principal Investigators (PIs). Shared infrastructure and translational efforts will be realized. Graduate training and residents will be guided with integrative feedback 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); Compulsivity, Impulsivity & Attention (cia) and Mood, Anxiety & Psychosis (map).

Research staff

Amsterdam Neuroscience - Research Personnel

Total	1025		498,7		
	persons		fte - research	% - research	
Subtotal	446	1e geldstroom	171,9	43,5%	1e geldstroom
	231	2e geldstroom	141,9	22,5%	2e geldstroom
	302	3e geldstroom	157,6	29,5%	3e geldstroom
	46	4e geldstroom	27,2	4,5%	4e geldstroom

Total	479	PhD students
	persons	
Subtotals	120	1e geldstroom
	160	2e geldstroom
	171	3e geldstroom
	28	4e geldstroom

Amsterdam Neuroscience - Research Personnel

bi	ctg	nt	bm	nd	nii	ndis	cia	map
114	80	62	261	182	149	64	128	114

	bi	ctg	nt	bm	ndeg	nii	ndis	cia	map
	persons								
1e geldstroom	54	40	40	111	66	53	33	60	49
2e geldstroom	21	18	9	66	39	29	12	36	30
3e geldstroom	31	22	11	71	62	57	17	30	35
4e geldstroom	8		2	13	15	10	2	2	

Amsterdam Neuroscience - Research Personnel

bi	ctg	nt	bm	nd	nii	ndis	cia	map
48,8	37,8	36,0	138,9	84,2	78,7	39,3	74,7	44,5

	bi	ctg	nt	bm	ndeg	nii	ndis	cia	map
	fte - research								
1e geldstroom	17,9	14,2	22,8	47,5	21,8	23,1	17,5	29,4	13,3
2e geldstroom	12,8	11,2	5,3	43,2	21,3	21,5	9,1	24,2	13,7
3e geldstroom	13,3	12,4	6,5	41,4	32,2	27,5	11,2	19,6	17,6
4e geldstroom	4,9		1,5	6,9	8,9	6,6	1,5	1,5	

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 time spent on research, we used the following (HRM-SAP instructed) guidelines: 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 funding	€ 49.405.912	€ 2.166.034	€ 2.946.900	€ 2.212.411	€ 11.563.334	€ 11.248.013	€ 4.920.118	€ 5.185.212	€ 1.566.186	€ 3.593.696
1e geldstroom*	€ 3.546.691	€ 464.937	€ -	€ 193.525	€ 490.000	€ 17.769	€ 682.128	€ 884.964	€ 52.186	€ 236.182
2e geldstroom	€ 27.725.790	€ 1.534.227	€ 2.433.400	€ 2.000.140	€ 6.411.959	€ 6.118.984	€ 1.797.643	€ 2.947.309	€ 1.489.000	€ 2.993.127
3e geldstroom	€ 10.514.423	€ -	€ 513.500	€ -	€ 3.475.306	€ 3.877.056	€ 1.161.511	€ 1.337.939	€ -	€ 149.111
4e geldstroom	€ 7.619.008	€ 166.870	€ -	€ 18.746	€ 3.394.795	€ 1.773.522	€ 1.784.799	€ 15.000	€ -	€ 215.276

NFU definition:

- "1e geldstroom": Shown is internal socalled alliance funding (i.e. 3.547 k€) only; the unconditional internal funding for tenured and other personnel is estimated to be > 42 M€ for 2017;
- "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.

Research output & quality in total

Amsterdam Neuroscience - Research Output

	Total	bi	ctg	nt	bm	ndeg	nii	ndis	cia	map
Refereed article	1321	257	171	61	345	239	221	133	181	254
Non-Refereed article (1)	5	0	0	0	0	0	0	0	0	0
Books	0	0	0	0	0	0	0	0	0	0
Book chapters	15	2	1	0	5	1	0	4	3	5
PhD theses	78	19	7	1	23	8	7	7	17	9
Conference papers	3	3	0	0	0	0	0	0	0	0
Professional publication (2)	38	3	3	0	5	6	8	3	9	9
Publications aimed at the general public (3)	5	0	0	0	0	1	1	0	2	2
Other research output (4)	40	13	5	3	5	7	8	16	4	3
Total publications	1501	297	188	65	384	263	245	163	217	284
With impact > 10	Subtotal	bi	ctg	nt	bm	ndeg	nii	ndis	cia	map
Rsfereed articles (selected output)	129	15	33	8	34	18	18	8	16	32

With impact > 5 < 10)	Subtotal	bi	ctg	nt	bm	ndeg	nii	ndis	cia	map
Rsfereed articles (selected output)	331	68	40	16	104	76	66	31	36	56

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 1321 refereed papers, 329 papers were with an impact factor between 5 -10 and 129 papers were at impact factor 10 or higher. In this last category at least 23 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 15 papers that published perspectives in high impact journal (i.e. > 10). Another 92 papers were mainly with international collaborators.

The short list of 2017 papers with the highest impact included:

- Hammerschlag et al. Nature Genetics (group of Posthuma)
- Sniekers et al. Nature Genetics (group of Posthuma)
- Bonder et al. Nature Genetics (group of Boomsma)
- Petzold et al. Lancet Neurology (Petzold group)
- Riga et al. Science Translational Medicine (group of Spijker)
- Tielbeek et al. JAMA Psychiatry (group of Posthuma)
- Milaneschi et al. JAMA Psychiatry (group of Penninx)
- Boedhoe et al. American Journal Psychiatry (group of Van der Werf & Van den Heuvel)
- Schmaal et al. Molecular Psychiatry (group of Veltman)
- Enqi et al. Nature Communications (group of Verhage)
- Jansen et al. Genome Biology (group of Bochdanovits)
- Verduijn et al. Biological Psychiatry (group of Penninx)
- Power et al. Biological Psychiatry (group of Smit & Penninx)
- Simons et al. Brain (group of Wolf & Van der Knaap)
- Mishra et al. Brain (group of Penninx)
- Meichen et al. Brain (group of Stam)
- Maurik et al. JAMA Neurology (group of Van der Flier & Scheltens)
- Berg et al. NEJM (group of Roos)
- Gomes et al. PLoS Medicine (group of Van der Brink)
- Bos et al. Nature Communications (group of Pennartz)

Bi-location authorships

We are proud of our 141 socalled '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 114 of these papers (of which 28 papers shared with AMC), AMC participated on 60 bi-location papers, VU on 92 papers and UvA on 16 of the bi-location papers.

Annual Meeting 2017 – an impression

We had a great 2nd Annual Meeting of Amsterdam Neuroscience. A 650+ audience attended the 2017 Annual Meeting. And we did go our way in doing some trendwatching and we discussed the 'future of Neuroscience' from different points of perspective. We were put straight by four Amsterdam Neuroscience team leaders (Ruud Toonen, Eric Reits, Jonathan Coutinho and Tinca Polderman) during the research reports. Then the 'real' heroes - of course - were the PhD students and postdocs that featured during the Pecha Kucha session and all those that were presenting their work at the poster market.

Swammerdam lecturer Matteo Carandini impressed with his work on recordings of the visual cortex and hippocampus in living mice while the animal was navigating in virtual reality on a rotating balloon. But then towards the end of the program the Neuro-tech session grabbed our full attention and emotions due to the excellent presentations by Pieter Roelfsema and Rob de Bie and the remarkeble demonstration by Job Hof (as seen in the picture here) and the very touching storytelling by Jens Naumann (see on youtube). Job Hof is a patient with Essential Tremor, and he was very generous in willing to show onstage the effect of turning 'off' his Deep Brain Stimulation (DBS) device that was placed last summer at the AMC by Rick Schuurman and Rob de Bie. Next Jens Naumann told us his mind grabbing story of how he became blind-ed at the age of 20, then found (some) relief by having had the first generation of visual cortex protheses implanted around the year 2000, which after 4 years stopped working. Pieter Roelfsema subsequently explained to the audience his new NeuroTech-NL endeavour which amongst others is aiming for the next generation of electrode probes aimed at both brain reading and writing.

Thereafter the party was 'on' and it was selfie time. Best quotes of the day: "This was the reason why I always wanted to study Neurosciences (Diederik van de Beek)" and "See you next year, same time, same place (Arjen Brussaard)".

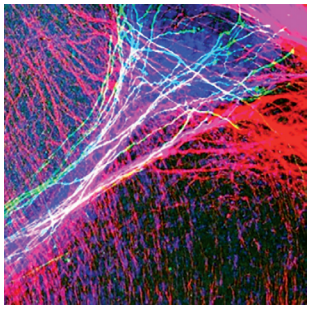
Photos by Rien Dekker

Research reports & lectures at the Annual Meeting 2017

Modeling brain disorders with patient-derived neurons

Ruud Toonen, PhD, Department Functional Genomics of the Center for Neurogenomics Cognitive Research, Vrije Universiteit Amsterdam

Induced human pluripotent stem cells (iPSC) are a powerful new tool to unravel brain disorder mechanisms. Current rodent disease models have increased our understanding of pathology but may not fully recapitulate the spectrum of disruptions associated with human neuropathology. iPSC derived neurons are generated from patient's blood sample or skin biopsy and provide an unlimited resource for disease modelling, drug screening potentially to regenerate damaged neurons in the future. Importantly, iPSCs offer the opportunity to discover early and primary disease mechanisms like synaptic communication defects. At the Functional Genomics department, two of the most important secretory pathways for synaptic communication are studied in standardized micro-networks of iPSC-derived neurons and in chimeric mouse models in which human iPCS-derived neurons incorporate and function in existing neuronal networks. In this presentation, Ruud Toonen gave an overview of his recent findings in these model systems and provided an outlook of future directions in modelling brain disorders using iPSC-derived human neurons.



Reduced recognition and degradation of aggregation-prone proteins in neurodegenerative disorders

Eric Reits, PhD, Protein Degradation and Aggregation & head core facility Cellular Imaging, Department Medical Biology, AMC, University of Amsterdam

Various neurodegenerative disorders including Alzheimer's and Huntington's Disease are hallmarked by the accumulation and aggregation of disease-related proteins. This is the result of aging-related reductions in protein degradation, but also in cell-type specific differences in the recognition and degradation of disease-related proteins that are often commonly expressed. Using a variety of unique assays we showed cell-type specific differences in their capacity to deal with these hazardous proteins and aim to manipulate the protein degradation machinery as a therapeutic strategy to improve clearance of these proteins prior to aggregation.

Developments in the treatment of acute ischemic stroke

Jonathan Coutinho, MD, PhD, Department of Neurology, Academic Medical Center, Amsterdam

Until recently, intravenous thrombolysis was the only proven therapy for treatment of acute ischemic stroke (AIS). Early 2015 the Dutch Mr Clean trial showed that adjunctive endovascular treatment (EVT) with a stent retriever improved functional outcome of patients with AIS and a proximal arterial occlusion. Various other trials have since then confirmed the results of Mr Clean and EVT is now standard-of-care for these patients. Without a doubt, the introduction of EVT marks a giant leap forward in the care of AIS patients. Still, despite EVT, about half of patients with AIS and a large vessel occlusion has a poor outcome despite achieving successful recanalization of the major arteries. This statistic exemplifies the need for additional adjunctive therapies for these patients, such as neuroprotective drugs. In addition, advanced triage methods are required to ensure that the right patient is presented in the right hospital within a minimal timeframe. In his talk, Jonathan Coutihno provided an overview of the revolutionary chances that have taken place in treatment of AIS, as well as provide an insight into possible new therapies on the horizon.

Twin studies as a tool to investigate individual differences

Tinca Polderman, Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam

Scientists have always been intrigued by individual differences in personality, cognition, health and disease. With a huge meta-analysis of twin data, and two follow-up studies we aimed to systematically examine the question: "What is the

contribution of environmental and genetic variation (i.e., heritability) to trait variation?" The meta-analysis was performed on heritability estimates that were extracted from all published twin studies of the past 50 years (N 2,748 studies), presenting data on 17,804 traits, of in total 14.5 million twin pairs. All investigated traits were heritable, varying from 15 to 71%. Across all traits the contribution of genetic and environmental effects to trait variation was "fifty-fifty". While for some traits heritability differed across age, sex differences were virtually absent. Lastly, we show for eight psychiatric disorders substantial heritability estimates that converge when using the twin data, a large Swedish sibling study, and a genetic case-control design.

Swammerdam Lecture: From vision to navigation: a journey across mouse cortex

Matteo Carandini, University College London

Vision provides crucial signals to guide navigation, and guiding navigation is one of vision's main functions. The transformation of visual signals into estimates of position, however, is not understood. To study this transformation we recorded from large populations of neurons in the cortex of mice that navigated in environments in virtual reality. Contrary to textbook expectations, Prof. Carandini and his group found that neurons as early as primary visual cortex exhibit preferences for spatial position. These preferences strengthen as signals proceed towards parietal cortex, where responses become entirely related to navigation, coding for combinations of the animal's position and heading direction. Navigation signals in visual cortex correlate strongly with signals in hippocampus, where cells have well-known preferences for spatial position, and are closely related to the animal's subjective estimate of location. Signals related to navigation, therefore, appear remarkably early in the visual system, and are intimately related to the animal's own estimate of position in the world.

NeuroTech-demonstration session at the Annual Meeting 2017

Pieter Roelfsema (Netherlands Institute Neuroscience & VU), Rick Schuurman (AMC) & Rob de Bie (AMC)

There is an urgent need for the development of new methods to improve the quality of life of patients and to ameliorate or cure brain disease. Fortunately, the rapidly growing field of neurotechnology promises to deliver innovative solutions to brain disease, grounded in our rapidly increasing understanding of the workings of the brain. Advances in neurotechnology are driven by developments in neuroscience, in combination with advances in the fields of molecular biology, microelectronics, wireless technology, neuroimaging and computer science. The field of neurotechnology will undergo substantial growth in the coming decades and depend on close cooperation between scientists and industry partners.

Neurotechnology was highlighted by the "OECD science, technology and innovation outlook 2016"[1] as one of the ten most promising and disruptive key technologies for the future. However, in spite of all these advances, a coordinated effort to rapidly translate these technologies into new treatments has been lacking. The one hour NeuroTech session during the Annual Meeting of Amsterdam Neuroscience showed trends in the field introduced by Pieter Roelfsema and commented on by Rob de Bie (in collaboration with Rick Schuurman). Next there was story telling by Jens Naumann who in the past had a visual cortex implant and a patient demonstration of a patient suffering from Essential Tremor but being treated with Deep Brain Stimulation.

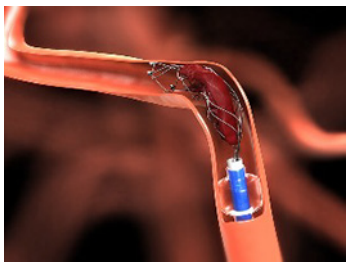
Other highlights of 2017

The 100-plus Study includes its 300th centenarian participant

In 2017 the socalled 100-plus cohort reached a size that allows Henne Holstege and her team to investigate the features that may have allowed these extraordinary people to remain healthy during their extreme aging. Indeed, we are generating some first findings.

Together organized the first 100-plus Mini-Symposium on April 12, 2017. Several scientific researchers who are involved in the study presented their ongoing work and discussed further collaborations. The 100-plus is an extreme group in the Dutch population which may provide answers to specific research questions outside the direct scope of our own research. Since VUmc is currently in close contact with our centenarian research population, we would like to ensure that we are not missing any opportunities to obtain important data from this group that may be of high value to the research of others.

International team under supervision of AMC reports on Two-Year Outcome after Endovascular Treatment for Acute Ischemic Stroke (Mr Clean study) in New England Journal of Medicine



Background

Several trials involving patients with acute ischemic stroke have shown better functional outcomes with endovascular treatment than with conventional treatment at 90 days after initiation of treatment. However, results on long-term clinical outcomes are lacking.

Methods

We assessed clinical outcomes 2 years after patients were randomly assigned to receive either endovascular treatment (intervention group) or conventional treatment (control group) for acute ischemic stroke. The primary outcome was the score on the modified Rankin scale at 2 years; this scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). Secondary outcomes included all-cause mortality and the quality of life at 2 years, as measured by means of a health utility index that is based on the European Quality of Life–5 Dimensions questionnaire (scores range from −0.329 to 1, with higher scores indicating better health).

Results

Of the 500 patients who underwent randomization in the original trial, 2-year data for this extended follow-up trial were available for 391 patients (78.2%) and information on death was available for 459 patients (91.8%). The distribution of outcomes on the modified Rankin scale favored endovascular treatment over conventional treatment (adjusted common odds ratio, 1.68; 95% confidence interval [CI], 1.15 to 2.45; P = 0.007). The mean quality-of-life score was 0.48 among patients randomly assigned to endovascular treatment as compared with 0.38 among patients randomly assigned to conventional treatment (mean difference, 0.10; 95% CI, 0.03 to 0.16; P = 0.006). The cumulative 2-year mortality rate was 26.0% in the intervention group and 31.0% in the control group (adjusted hazard ratio, 0.9; 95% CI, 0.6 to 1.2; P = 0.46).

Conclusions

In this extended follow-up trial, the beneficial effect of endovascular treatment on functional outcome at 2 years in patients with acute ischemic stroke was similar to that reported at 90 days in the original trial. (Funded by the Netherlands Organisation for Health Research and Development and others; MR CLEAN Current Controlled Trials number, ISRCTN10888758, and Netherlands Trial Register number, NTR1804, and MR CLEAN extended follow-up trial Netherlands Trial Register number, NTR5073.)

Original article: *Lucie A. van den Berg et al. Two-Year Outcome after Endovascular Treatment for Acute Ischemic Stroke (2017). N Engl J Med 2017; 376:1341-1349*

Scientists find new genetic roots for intelligence

An international research team led by Danielle Posthuma from the Vrije Universiteit Amsterdam, The Netherlands, has made a major advance in understanding the genetic underpinnings of intelligence. Using a large dataset of more than 78,000 individuals with information on DNA genotypes and intelligence scores, the team discovered novel genes and biological routes for intelligence.

Intelligence is one of the most investigated traits in humans and higher intelligence is associated with important economic and health-related life outcomes. Despite high heritability estimates of 45% in childhood and 80% in adulthood, only a handful of genes had previously been associated with intelligence and for most of these genes the findings were not reliable. The study [http://dx.doi.org/10.1038/ng.3869], published in the journal Nature Genetics, uncovered 52 genes for intelligence, of which 40 were completely new discoveries. Most of these genes are predominantly expressed in brain tissue.

"These results are very exciting as they provide very robust associations with intelligence. The genes we detect are involved in the regulation of cell development, and are specifically important in synapse formation, axon guidance and neuronal differentiation. These findings for the first time provide clear clues towards the underlying biological mechanisms of intelligence", says Danielle Posthuma, Principal Investigator of the study.

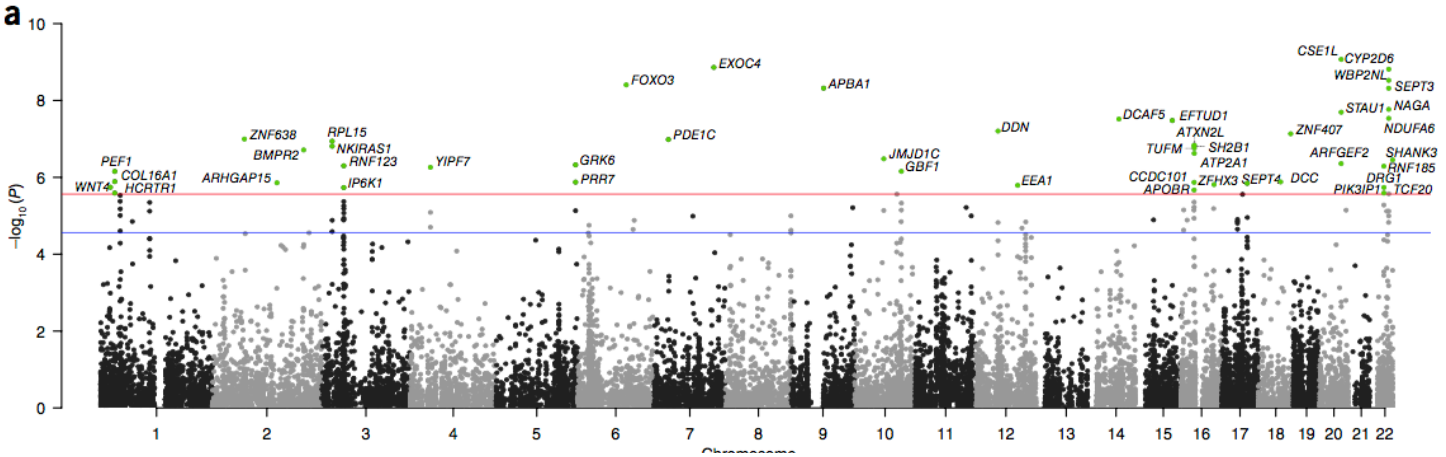
The study also showed that the genetic influences on intelligence are highly correlated with genetic influences on educational attainment, and also, albeit less strongly, with smoking cessation, intracranial volume, head circumference in infancy, autism spectrum disorder and height. Inverse genetic correlations were reported with Alzheimer's disease, depressive symptoms, smoking history, schizophrenia, waist-to-hip ratio, body mass index, and waist circumference.

"These genetic correlations shed light on common biological pathways for intelligence and other traits. Seven genes for intelligence are also associated with schizophrenia; nine genes also with body mass index, and four genes were also associated with obesity. These three traits show a negative correlation with intelligence", says Suzanne Sniekers, first author of the study and postdoc in the lab of Posthuma. "So, a variant of gene with a positive effect on intelligence, has a negative effect on schizophrenia, body mass index or obesity."

Future studies will need to clarify the exact role of these genes in intelligence in order to obtain a more complete picture of how genetic differences lead to differences in intelligence. "The current genetic results explain up to 5% of the total variance in intelligence. Although this is quite a large amount of variance for a trait as intelligence, there is still a long road to go: given the high heritability of intelligence, many more genetic effects are expected to be important, and these can only be detected in even larger samples", says Danielle Posthuma.

The study is published in Nature Genetics, May 22, 2017. www.nature.com/articles/ng.3869.
Article in The New York Times, Science section (May 22, 2017). www.nytimes.com/2017/05/22/science/52-genes-human-intelligence.html.

Figure below: Gene-based genome-wide analysis for intelligence Green dots represent significantly associated genes.
Source: http://dx.doi.org/10.1038/ng.3869



Two VIDI awards for excellent proposals

On May 30, it was announced that Odile van den Heuvel (location VUmc) and Matthijs Brouwer (location AMC) each were awarded with a VIDI grant to execute their projects in coming years. Hence Amsterdam Neuroscience acquired 2 out of the 14 VIDI grants awared by ZON MW this year. We congratulate them on this achievements.

Odile A. van den Heuvel, psychiatrist and professor of Neuropsychiatry at the Department of Psychiatry and the Department of Anatomy & Neurosciences (VUmc) will use the VIDI grant of €800,000 for an ambitious lifespan project on obsessive-compulsive disorder (OCD) focusing on the interaction between brain, behaviour and environment.

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. The hypotheses underlying this research proposal are: 1) that symptoms emanate from the inability to efficiently control emotions and behaviours, due to altered maturation of the prefrontal cortex early in life; 2) that chronic symptoms, by the power of repetition, cause neuroplastic changes in brain function and structure during the course of the disease; and 3) that the plasticity of the brain circuits is a powerful entry to innovate treatment.

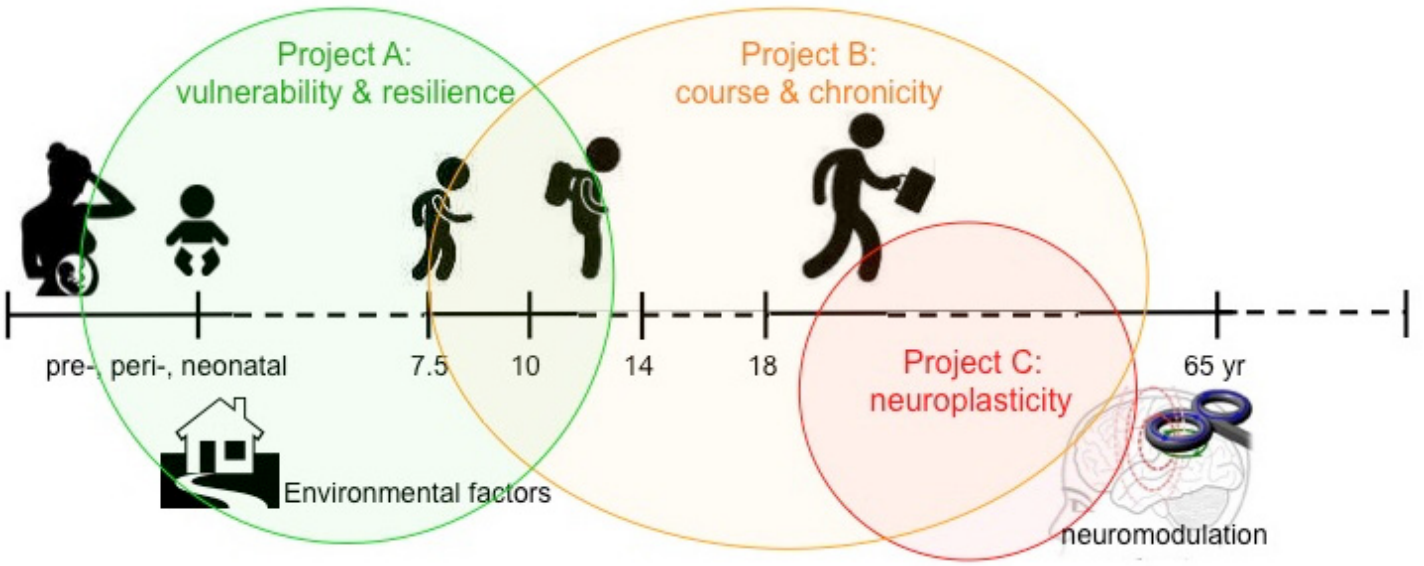
The proposal is based on the vision that the field of neurodevelopmental disorders, such as OCD, warrant a lifespan approach to disentangle neural mechanisms involved in cause and consequence of the disorder.

The proposal includes 3 interrelated projects. 1) To uncover vulnerability (and resilience) to disease and the effects of pre/peri/neonatal environmental factors on brain maturation, project A (in collaboration with the Generation R Study in Rotterdam) will focus on neurodevelopment in normal school-aged children. 2) To establish age and disease stage-specific markers of disease, in project B variation in subcortical volume across the lifespan (age 10 to 55) will be related to fluctuations in the concentration of glutamate, the most important player in brain plasticity. 3) To improve cognitive control and the response to behavioural therapy in chronic OCD patients, project C invests in the development of non-invasive rTMS-induced neuromodulation of the brain circuits, by comparing the mechanisms of action of two stimulation protocols.

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.

Matthijs Brouwer, neurologist and senior investigator at the Department of Neurology (AMC) will use the VIDI grant of €800,000 on research aimed at revealing the causes of brain inflammation. With currently available diagnostic tests, it's difficult for doctors to quickly identify the correct diagnosis in patients suspected of an infection of the brain. In this project he will evaluate new diagnos-

Figure below: Project-infographics of VIDI grant of Odile van den Heuvel (2017)



tic tests to identify the cause of disease and speed up time to treatment in a large group of patients.

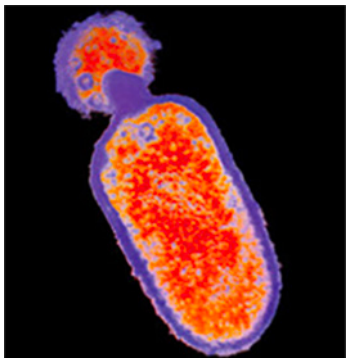
Encephalitis is a severe inflammation of the brain that can be caused by viruses, bacteria and other microorganisms, or autoimmune disease. The incidence of encephalitis is 5 per 100.000 population per year, the associated case-fatality rate is high (10-20%), and half of surviving patients have neurological or cognitive deficits. The epidemiology is changing due to emerging pathogens, such as tick-born encephalitis.

The current diagnostic methods for encephalitis are insufficient. In a recent prospective pilot study he found that a cause-specific diagnosis was made in only 50% of encephalitis patients. We need better diagnostic methods to improve treatment and prognosis of patients with encephalitis.

The aim of his Vidi project is to improve the cause-specific diagnosis of encephalitis.

In a prospective multicentre surveillance study he will include 4000 suspected encephalitis patients through my existing research network on neurological infectious diseases. He will initiate a pathogen discovery programme using ground-breaking sequencing techniques aimed at identifying new causes of encephalitis. Furthermore, he will go beyond the state-of-the art by using cerebrospinal fluid (CSF) mRNA biosignature analysis to differentiate benign from life-threatening causes of encephalitis. To this end he will set up a surveillance programme collecting clinical data, blood and CSF samples. In addition to the pathogen discovery programme and mRNA biosignatures, he will analyse the diagnostic accuracy of biomarkers, multiplex PCRs and anti-neuronal antibodies.

Matthijs Brouwer: “With my Vidi project I reach for an increase in the proportion of patients with a cause-specific diagnosis from 50% to 70%. Pathogen discovery sequencing will enable us to redefine encephalitis and lead to an array of new research possibilities.”



New Alzheimer’s Drug Shows Safety, Hints of Efficacy in Phase 2a

A first-in-class Alzheimer’s therapeutic met its primary endpoint in a Phase 2a trial, according to topline results released by the drug’s sponsor, Probiodrug in Halle, Germany. The compound, PQ912, inhibits an enzyme that produces pyroglutamate Aβ, a particularly sticky form of the peptide that may give rise to amyloid plaques. The main goal of the Phase 2a SAPHIR trial was to determine the safety and tolerability of a high dose of PQ912 over a three-month period. The compound appeared safe, though some participants had trouble tolerating it, with gastrointestinal and skin reactions that faded over time. The researchers did not expect to see a clinical effect in this short time frame, so they were pleasantly surprised to see brain electrical rhythms normalize in the treatment group; this measure suggests more coordinated synapse function. Participants taking PQ912 also bested controls on one of seven neuropsychology tasks. Biomarkers of synapse health and inflammation moved in the hoped-for direction in the treatment group, as well. “These preliminary results encourage us to go on to a longer study with more endpoints,” said Philip Scheltens at VU University Medical Center, Amsterdam, who was the principal investigator on the study.

The story around pyroGlu Aβ, which forms when Aβ loses its first two amino acids and the enzyme glutaminyl cyclase (QC) links up the ends of the exposed glutamate residue to make a circle, has been building for a decade. Independent studies have found that pyroGlu Aβ correlates with disease severity and abounds in amyloid plaques in both AD animal models and postmortem brains. Some researchers suggest it may seed plaques, though that is not universally accepted. Oligomers of pyroGlu Aβ appear particularly neurotoxic and can corrupt normal Aβ42.

Researchers at Probiodrug developed their QC inhibitor PQ912 to turn down production of pyroGlu Aβ. In the present Phase 2a trial, the researchers wanted find out how well a high dose would be tolerated over longer treatment periods, Lues said. The researchers recruited 120 people with biomarker evidence of AD at 21 sites in seven European countries. Participants were at early stages of the disease, with a mean MMSE of 25.5. The trial enrolled only people who were not taking acetylcholinesterase inhibitors or memantine. This was done to minimize noise in the data and better detect any signal on cognitive testing and brainwave

activity, Lues noted. Scheltens said this requirement made recruitment difficult at first, but as the trial progressed, positive word of mouth allowed the researchers to attract more patients than the original goal. Participants were randomized to receive either 800 mg twice daily of PQ912 or placebo for 12 weeks.

On the exploratory measures, the researchers saw a highly significant (p=0.002) effect on brainwave activity, as measured by EEG. In early AD, theta rhythms peak while alpha power wanes. In the PQ912 treatment arm, both measures became more normal, with theta power decreasing and alpha rising. The results fit with the hypothesis that pyroGlu Aβ oligomers poison synapses, and that their absence allows brain function to normalize, Lues noted. The researchers are still analyzing fMRI data to find out if functional connectivity changed in the participants. In keeping with the EEG results, people on PQ912 performed better on the One Card Back test, which measures working memory, compared to their baseline performance. The placebo group remained stable on this measure. The treatment group also had a trend toward improvement on a test of attention, but no difference from placebo on five other measures. The CSF also provided signals that PQ912 was hitting its target. QC was inhibited by 92 percent in patients on drug, in agreement with Phase 1 data for this dose. Levels of pyroGlu Aβ oligomers in CSF appeared to drop, but Lues noted that this data should be interpreted cautiously, since levels in the CSF are so low that they are at the limit of detection for the assay. Additional analysis from the SAPHIR trial will be presented at the 2017 Clinical Trials on Alzheimer's Disease conference in Boston in November.

The researchers plan to test several doses in future trials, and for longer time periods, Lues said. Animal studies show that inhibiting QC by 60 percent is sufficient for cognitive benefits. This level of inhibition can be achieved with a dose of 150 or 200 mg twice daily in people, she noted. "That makes us confident we can lower the dose," Lues told Alzforum. In future trials, participants will be allowed to take acetylcholinesterase inhibitors. The phase 2b study in Europe will start in Q4 of 2019 and coordinating PI is Philip Scheltens.

Diederik van de Beek winner AMC Societal Impact award 2017

The award was presented by Professor Hans (J.A.) Romijn, chair of the AMC Executive Board, and recognizes the societal impact of research. Diederik van de Beek got the award for his practice changing work in neurological infections. Not only did he develop new protocols and made these available to the community, he and his team also run pivotal phase 3 studies, execute a neuroinfection residency program and excel in scientific research on bacterial meningitis. After publishing a landmark RCT, he participated in national and international guidelines, and performed implementation studies. This new treatment for bacterial meningitis that has halved the mortality rate of this devastating disease.

TN2 meeting

The Translational Neuroscience Network (TN2) is coordinated from the director's office of Amsterdam Neuroscience and – adjacent to the Annual Meeting for all affiliated Amsterdam based investigators in our fields – TN2 aims to bring together fundamental and clinical researchers in the field of Translational Neuroscience from all over the Netherlands and beyond.

Each year the TN2 conference covers one or several disease indications in either the field of Neurology or of Psychiatry – i.e. in alternating years – thereby providing opportunities for academia and industrial partners to explore new collaborations in plenary sessions, potentially leading to translation of novel disease mechanisms into effective drug therapies, neurotechnologies and disease-monitoring diagnostic tools.

The scientific strategy of Translational Neuroscience is often bidirectional in nature, encompassing both bench-to-bedside factors, which aim to increase the efficiency by which new therapeutic strategies developed through basic research are tested clinically, and bedside-to-bench factors, which provide feedback about the efficacy of the clinical application of new treatments and how they can be improved.

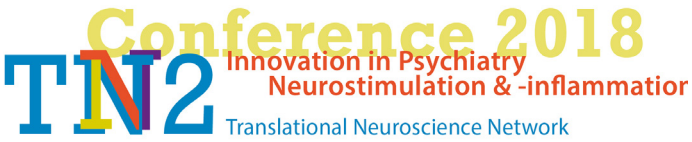
The third TN2 conference was organized as a satellite conference of the Annual Meeting of Amsterdam Neuroscience (VUmc and AMC) which took place in October 2017. Also this TN2 conference was of interest to translational neuroscientists of all academic levels, but by paid registration only.

The 2017 TN2 conference featured a plenary keynote lecture by Prof. dr. Josep Dalmau from the University of Barcelona with ground-breaking work on the pathogenesis of immune-mediated neurological disorders. Following this opening lecture two subsequent parallel symposium-programs were organized, one on Neurodegeneration and one on Neuroinfection & -inflammation.

Towards the end of the day, all registrants attended a plenary session with perspectives from Key Opinion Leaders from industry followed by a sponsored reception with sky-box views on the Ajax-soccer stadium.

Coming up

In 2018 the TN2 conference is shaped around the theme of 'Innovation in Psychiatry' with a particular focus on Neurostimulation & -inflammation. See here for the program and registration: www.tn2.eu/conference-2018/



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Fluorescent reporters
Target identification & Validation

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Synaptopathies
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