Maastricht University

MH&NS school for mental health and neuroscience

MHeNs Self Assessment 2015-2020

School for Mental Health and Neuroscience - MHeNs

Faculty of Health, Medicine and Life Sciences, Maastricht University

Case studies

Case studies of areas of traditional strength of MHeNs:

1. Alzheimer Centrum Limburg – from biomarkers to partner interventions
2. Psychosis research – contributions from environmental, common and rare genetic factors
3. Gene x environment interaction research – in neurodegeneration and neurodevelopment
4. Neuromodulation – towards an integrated neurotechnology programme

1. Alzheimer Centrum Limburg – from biomarkers to partner interventions

Dementia research, coordinated by the Alzheimer Centrum Limburg (ACL), has been since long an area of research strength in MHeNs. Led by professors Frans Verhey and Marjolein de Vugt, the center is not a legal entity, but rather a thematic bundling of both clinical activities in MUMC's memory clinic and research activities of MHeNs' division 1 on neurodegenerative disorders, thus integrating health care and clinical research. ACL was officially recognized in 2001 as a leading expertise center by Dutch Alzheimer Association, for its strong reputation in clinical dementia research with an important supra-regional function and a considerable network. Since then, ACL has grown gradually, now hosting more than 50 employees working, of whom four professors (5 within soon), 3 associate profs, 5 assistant profs, 7 postdocs, and 24 PhDs. ACL has therefore the critical mass to continue supporting the full range of dementia research, including biomarkers, clinical trials and psychosocial interventions.

The mission of the ACL is to enable a better living with dementia, by 1) a better understanding of its underlying mechanisms, improving the diagnosis of dementia subtypes, 2) by searching for new means for prevention, and 3) by designing / evaluating innovative psychosocial interventions. These aims correspond with the three interrelated research lines of 1) early diagnosis and disease mechanisms; 2) neuroepidemiology and 3) psychosocial innovations. In all these three areas, ACL was able to consolidate its strong position in the last five years, both in terms of obtaining important external grants, and in delivering a considerable output of high ranked papers and PhD defenses (there were 7 successful defenses by ACL PhDs in 2018, and 8 in both 2019 and 2020). Preparations for several consortium applications are under way, such as consortia from Innovative Medicine Initiative (IMI) Alzheimer's disease and beyond, MI, the Amyloid group, The Research Consortium for Personalized Dementia Risk Reduction (RADAR), and Joint Artifical Intelligence Network (JAIN).

Early diagnosis and disease mechanisms

The main focus of our biomedical studies is the development of Alzheimer's disease, and especially in the pre-dementia stage. In this research line, the BioBank Alzheimer Center Limburg (BB ACL) study is an important infrastructure. BB ACL, led by dr Inez Ramakers and prof Frans Verhey, is an ongoing prospective cohort study, including consecutive patients from the memory clinic of the Alzheimer Center Limburg, Maastricht University Medical Center + (MUMC+). BB ACL aims to assess and examine factors related to the impact of AD on patient, caregiver and societal level, and is a relatively large, well-phenotyped, cohort study, representative of the memory clinic population. It includes a wide variety of multimodal data from currently about 1000 participants, providing unique opportunities to model patient, caregiver and societal outcomes of AD.

By pooling large amounts of data from eight European studies, Prof Pieter Jelle Visser and his team were able to analyze more than 1,500 proteins in the cerebrospinal fluid. With the protein research we were able to characterize three subtypes: one group of patients with mainly inflammation, who may be could best be treated with drugs targeting inflammation in the brain; a second group of people who have hyperactivity of the brain cells, which one might slow down with other medications; and a third subgroup with an actual state of hypoactivity which may be addressed with other pharma regimes. In addition, we know that there is a close interaction between beta-amyloid and the condition of blood vessels in the brain, which underlines the importance of living a healthy life. Through the Netherlands Consortium of Dementia Cohorts (NCDC) we combine data from nine studies in the Netherlands: we already have data from 80,000 people and up to 200.000 will be included. Maastricht ACL plays a major role in this consortium.

Another central topic in the biomarker research is the intriguing new concept of SNAP (Suspected Non-Alzheimer Pathophysiology). People with SNAP have brain damage consistent with Alzheimer's disease, but without significant accumulation of the Alzheimer's protein amyloid beta. For the time being the nosological status of SNAP is unclear (Jack...Visser, Vos, 2015- [1]), specifically whether it is a subtype Alzheimer's disease, another form of dementia, or another condition. The MCI-SNAP project led by Prof Pieter-Jelle Visser and Dr Stephanie Vos investigates the prognosis, the biological underpinnings and mechanisms of SNAP.

Another major subtheme in this ACL research line is on optimizing neuroimaging methods (3T, 7T and PET) to investigate the neuromodulatory nuclei. The group led by Dr Heidi Jacobs has developed and validated the first 7T MRI sequence to visualize the locus coeruleus in vivo (Priovoulos et al., 2018 [2]). We recently demonstrated that greater functional connectivity between the locus coeruleus and nucleus basalis of Meynert or the ventral tegmental area were associated with lower memory performance in individuals older than 40 years of age (Jacobs et al., 2018 [3]). We also combine MRI data with other data modalities (physiological data, fluid data, PET data, pupil measurements) to determine how these nuclei fit into current disease models. We recently showed that increased turnover of norepinephrine is associated with greater levels of amyloid and tau and worse cognitive performance (Jacobs et al., 2019 [4]). Currently, we work on combining our developed MRI methodologies with amyloid, tau and FDG-PET, CSF and blood measurements in healthy individuals and patients to investigate regional patterns, temporal sequences as well as examining what makes these nuclei vulnerable to pathological events. As these neuromodulatory nuclei plays an important role in cognition and behavior and are vulnerable to pathology early in life, it is our goal to delay cognitive decline as early as possible by modulating the function of these nuclei (Veni grant of Dr Heidi Jacobs).

Neuroepidemiology

The diagnostic and prognostic value of biomarkers from these research lines are further investigated in the second research line Neuroepidemiology, which is led by Dr Seb Koehler. He is member of management team of the important epidemiological study the Maastricht Study, for which he is chairing the brain section. The Maastricht Study is an extensive phenotyping study that focuses on the etiology of type 2 diabetes, its classic complications (such as cardiovascular disease and neuropathy) and its emerging comorbidities, including cognitive decline and depression. The study uses advanced MRI techniques and extensive biobanking to determine health status in a population-based cohort of 10,000 individuals and is expected to become one of the most extensive phenotyping studies in both the general population and type 2 diabetes participants world-wide [5]. Since 2016, four PhD theses from ACL PhD candidates have been finalized using data from the Maastricht Study, and two are still underway. The Maastricht Aging Study (MAAS) is second population based study, which was initiated by prof Jelle Jolles, the previous co-chair of ACL and division 1 in 1995, and is now led by dr Martin van Boxtel. MAAS is devoted to the age-related decline of memory and other cognitive functions in normal people and the factors that may be involved in this process. MAAS tries to study these factors in an integrative way. This can be achieved only by studying large numbers of normal healthy adults of all ages and by monitoring them for several years. Data in MAAS were collected in nearly 1,900 participants by means of postal surveys, questionnaires and laboratory assessments. From 2019 onwards, a 25-year follow-up will be performed in all participants. Results obtained so far have highlighted the role of specific health variables, such as diabetes, depressed mood, and exposure to neurotoxic substances that accelerate the cognitive aging process. Identified protective factors related to 'cognitive reserve' were a high level of educational attainment and both a rich social and professional environment. Cognitive abilities were strongly associated with sensory function (vision and hearing), in both cross-sectional and longitudinal studies.

Besides these populations based studies, the ACL research line is also involved in public health. In 2018, the campaign "We ourselves are the medicine" was launched to increase awareness on dementia risk reduction among inhabitants of the Province of Limburg. This campaign aimed at motivating the general public to engage in a brain-healthy lifestyle, and thus by means of an eHealth platform and a mobile app called MijnBreincoach. The MijnBreincoach eHealth platform (or app) uses the well-validated LIfestyle for BRAin health" (LIBRA) [6] score to give people insight into their own dementia risk profile and flags individual room for lifestyle improvement, consisting of 12 modifiable risk and protective factors for dementia. LIBRA was developed as part of the European InMINDD project (INnovative, Midlife INtervention for Dementia Deterrence), led by Dublin University, Ireland, in which Dr Koehler, Dr van Boxtel, Prof Verhey were leading the WP epidemiology. Dr Kay Deckers recently received the national Young Researcher Young Outstanding Researcher Award from the Dutch Alzheimer Association for his doctorate studies on the LIBRA. At present, the quick LIBRA test (kiosk version) is already available in English, Norwegian and Flemish., and other language versions will follow soon. Difference in awareness before and after the campaign was assessed by an online questionnaire in two independent samples of

more than 1200 adults. Overall, one out of five random persons in Limburg had heard of the campaign, and these people were significantly more aware of dementia risk reduction and the three campaign themes. Currently, several (inter) national parties engaged in health promotion have shown interest to adapt the campaign and/or the eHealth platform for local roll-out.

Psychosocial innovations

The psychosocial innovations research line aims to improve the quality of life for the person with dementia and their relatives by insight in daily life, wishes and needs, development/ evaluation of (eHealth) interventions, and improving implementation. This line is led by Prof Marjolein de Vugt who was appointed in 2017 as a professor of Psychosocial innovations, with Dr Lizzy Boots as the coordinator. The Alzheimer Center Limburg has acquired a strong international research position in the field of psychosocial aspects of dementia and the number of ongoing studies has increased. Subthemes in this research line are young onset dementia, technology & dementia, diagnosis & post-diagnostic care, dementia friendly society and building capacity. Traditional approaches like RCTs are being combined with new technologies such as the Experience Sampling Method (ESM), and the development of supportive apps or internet tools. An often used framework for the development and evaluation of our complex psychosocial innovations is the Medical Research Council (MRC) Framework. [7] This framework adopts an iterative view of the development and evaluation of complex interventions ranging from needs assessment, testing of feasibility and effect to implementation. The intervention called 'Partner in Balance' (PiB) was designed, developed, evaluated and implemented by ACL and is a therefore a nice example of the interventions passing through all MRC stages. PiB is a blended care self-management program (combining in vivo support from a personal coach -e.g. casemanager- and online course materials.) for spouses and other relatives of people with dementia (www.partnerinbalans.nl) in the post-diagnostic stage. During an 8-week intervention, participants follow on-line self-selected themat ic modules that match their personal needs and helps them adapt to their new caregiver role. Partner in Balance increases self-efficacy and quality of life in participants [8] and has been awarded in November 2017 the Medical Inspirator Prize, (https://www.maastrichtuniversity.nl/news/caregiver-project-partner-balance-nominated-medical-inspirator-prize) highlighting the best collaboration between researchers and end-users (people with dementia and their caregivers). PiB was recently licensed with "good indications for effectiveness" by the recognition committee "Long-term elderly care" of Vilans, (https://www.vilans.nl/artikelen/interventie-dementiezorg-partner-in-balans-officieel-erkend) thus demonstrating the societal impact of this ACL research line. Adaptations of PiB to be used by people with other diagnoses are underway, such as for partners of people with young onset dementia, frontotemporal dementia, Parkinson's disease and Huntington's disease. In addition, PiB was part of the EU Interreg project 'The senior friendly society', in which PiB was implemented across borders in Dutch, Belgian and German municipalities in the Euregion. PiB will now be adapted to the UK context by a £2 grant (https://www.uea.ac.uk/news/-/article/2-million-project-to-support-uk-dementia-carers)from the UK National Institute for Health Research (NIHR) together with the University of East Anglia and Norfolk and Suffolk NHS Foundation Trust (NSFT) in which also ACL participates.

ACL was also WP lead in the JPND RHAPSODY study to develop an eHealth program for caregivers of people diagnosed with young onset dementia (YOD), in which we collaborated with Alzheimer Nederland and the RadboudUMC Alzheimer Center in Nijmegen. The aim of this program is to provide informal careers with more information and support in day-to-day care and contains modules on causes and consequences of YOD dementia. The RHAPSODY intervention was developed in German, French, English and Portuguese and the intervention has proven effective.

A second JPND project was the European Actifcare study (Access to timely formal dementia care) for which ACL profs Marjolein de Vugt and Frans Verhey were the project leads. This project aimed in a multi-method approach at improving timely access to formal care for community-dwelling people with dementia: ActifCare combined qualitative approach with a quantitative 1 year-longitudinal cohort study conducted in eight European countries, monitoring the process of finding access to formal care in people with dementia and informal careers. HTA data on service use, quality of life and needs was also collected. The results of Actifcare were used to reveal pan European best-practices in organizing formal care.

Our focus on technology and dementia can best be illustrated by the leading role we play in the INDUCT (Interdisciplinary Network for Dementia Using Current Technology) and DISTINCT (Dementia: Intersectorial Strategy

for Training and Innovation Network for Current Technology) consortia, both funded by the EU's Horizon 2020 Marie Sk odowska-Curie Innovative Training Network (ITN). These consortia establish multidisciplinary, international training & research networks that leverages cross-sectorially the expertise of universities, industry, healthcare, and the social sector. Various international organizations, are also involved such as the World Health Organization, Alzheimer Europe and Alzheimer Disease International. In addition, ACL also plays an important role in developing training programs for early stage researchers. Apart from two PhD positions in each ITN, we are the training coordinators (WP leads) for both INDUCT and DISTINCT networks with the important aim of equipping the 15 INDUCT and 15 DISTINCT PhD candidates with the knowledge and skills necessary to pursue their careers in various international sectors. This training consists of an online module Living with Dementia: Personal perspectives, as well the organization as 5 Schools where the entire INDUCT/DINSTINCT network will come together to exchange expertise.
Further international impact is demonstrated by the close involvement in the Pan-European network for psychosocial interventions, called Interdem, in which now more than 14 EU countries participate with almost 200 participants. Prof Marjolein de Vugt is the chair elect for Interdem. Annex to Interdem is the junior training network of the Interdem Academy, which is also led by ACL (with Dr Fania Dassen as the coordinator).

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6. *See Schiepers OJG, Köhler S, Deckers K, Irving K, O'Donnell CA, van den Akker M, Verhey FRJ, Vos SJB, de Vugt ME, van Boxtel MPJ. Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. Int J Geriatr Psychiatry. 2018 Jan;33(1):167-175. And see:pubmed.ncbi.nlm.nih.gov/ ?term=köhler+libra&sort= date for all our publications on LIBRA*
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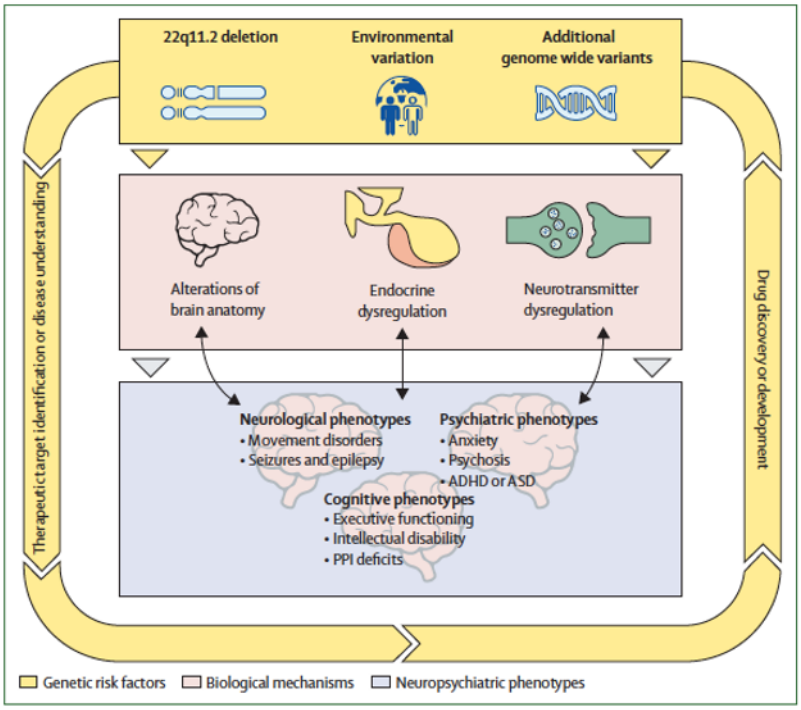
2. Psychosis research – contributions from environmental, common and rare genetic factors

Psychosis and Genetic Syndromes

Departments of Psychiatry & Neuropsychology (MHeNs); Clinical Genetics and Bio- informatics

Genetic syndromes, although individually rare, are a collectively important cause of disabling and chronic diseases in the general population, and costly to patients, families, and society. It is currently estimated that around 5% of a population is affected by a rare disease. These syndromes are often associated with several somatic and neuropsychiatric comorbidities. This implies that care for these patients is often complex, requiring a multidisciplinary clinical care approach. Since the individual syndromes are rare, most professionals are not familiar with them. Therefore, MUMC+ has initiated a specialty clinic for neuropsychiatric problems in genetic syndromes which offers advice and consultation (https://centraal.mumc.nl/sites/central/files/flyermumcgenetische_syndromen_en_psychiatrie.pdf).
Recurrent rare copy number variants (CNVs), deletions or duplications of stretches of DNA, are an important, yet understudied source of genetic variation covering 12% of the human genome, and are strong contributors to genetic syndromes. CNVs are also among the strongest known risk factors for neuropsychiatric disorders. For example, the 22q11.2 deletion syndrome (22q), a major research focus within MHeNs, is caused by a rare recurrent deletion that is usually 3 Mb long. Expression is thought to involve reduced gene dosage of the genes in the deleted region. While overall penetrance is thought to be 100% (typically, no 22q patients are found in control populations), it is incomplete for any single major clinical feature. Also, the severity of associated manifestations is variable, although the causes of this variability remain largely unexplained. Studies investigating the cause of the variability using microarray data have identified possible genome-wide modifiers for congenital heart disease and have indicated that rare structural variants additional to the 22q11.2 deletion can affect the risk of schizophrenia. A study by the International 22q Brain Behaviour Consortium (IBBC) of which Maastricht University is a member, used available psychiatric and cognitive assessments and obtained whole genome sequencing (WGS) data and found a shared genetic basis for schizophrenia and schizophrenia-related phenotypes highlighting the future potential of polygenic scores for risk stratification.



(source, Zinkstok et al 2019, Lancet Psychiatry)

Bioinformatics

There are currently two major research lines pursued by the bioinformatics group :

1. Generation of machine-readable knowledge databases on the molecular interactions that are affected in a rare genetic disorder. Together with the European Programme on Rare Diseases (EJP-RD) we established a rare disease portal on the pathway database WikiPathways (http://raredisease.wikipathways.org) [https://doi.org/10.1093/nar/gkaa1024] which holds currently 68 rare disease pathways,. These pathways are particularly useful for studying molecular downstream effects of diseases for which little prior knowledge is available and enables discovery of similarities between diseases due to overlaps in their molecular pathways. Additionally, knowing affected pathways allows searching for potential drug targets for drug repurposing.

2. Using this knowledge to analyse omics data from patients and model systems to investigate the affected molecular pathways. Omics data (e.g. transcriptomics, proteomics, metabolomics or lipidomics) generally allow a hypothesis free, respectively, hypothesis-generating research, which is especially interesting for diseases with little prior knowledge and low sample numbers. This approach allows furthermore the integration of multiple datasets, including genetic variation data to investigate e.g. multiple genetic causes for polygenic disease traits. The results are usually prioritized pathways and networks that give a holistic view on processes happening in parallel within a cell, tissue, and individual. Due to increasing levels of standardization and FAIRness (Findability, Accessibility, Interoperability and Re-usability) of data resources it is possible to integrate and pool data from different independent studies for larger sample size – an issue, rare disease research is constantly challenged with.

Brain imaging in genetic syndromes

Genetic syndromes also have an impact on brain development. Recently, researchers from MHeNs have shown that CNVs impact subcortical and cortical brain morphology and that these effects mediate the relation between CNVs and cognitive performance. In addition, we have shown that some CNVs and genetics syndromes are associated with abnormal brain and neurotransmitter function and that these changes are related to cognitive function and psychopathology.

Ongoing projects

Ongoing projects include large, international collaborative efforts on sharing and integrating phenotypic, genomic, and imaging data in Genes2MentalHealth, IBBC and ENIGMA studies. In addition, local experimental studies involving clinical trials, ultra-high field neuroimaging (^{1}H-MRS, neuromelanin), ophthalmology (OTC), ENT (audiography) and experience sampling (ESM).

Collaborations

For the studies on genetic syndromes, both national (UMCU, 's Heeren Loo, RadboudUMC) and international existing collaborations (Cardiff University, KULeuven, IBBC-CNV, MINDDS) have been further strengthened over the recent years. Collaborative grants have been obtained (NIH IBBC22q, NIH IBBC-CNV, COST MINDDS, COST EnGagE). The participation in ENIGMA CNV and ENIGMA 22q working groups has emphasized the strong international presence of MHeNs in the neuroimaging and genetics research communities. The cost action Maximising Impact of Research in Neurodevelopmental Disorders (MINDDS: https://mindds.eu/), provides strategic opportunities for European funding applications. Further, MHeNs is linked to the European network of psychiatric genetic counselling and testing (EnGagE), comprising preclinical and clinical researchers, experts on ethics and leaders in diagnostic genetic testing.

Future perspectives

Currently, the scientific interest for the bottom-up approach of research into genetic syndromes is growing and there may be opportunities for future therapeutic applications. Future perspectives with regard to CNV imaging include multiple modalities (including diffusion imaging) and cross-species comparison, y and identification of the responsible genes within the CNV region. In keeping with the traditional MHeNs agenda 'from gene to brain to behavior' these

genetic variants are ideally suited to studies that combine genetics, gene expression, imaging, clinical characterisation and behavior.

Societal impact

1. L1 Television Interview Therese van Amelsvoort : https://l1.nl/avondgasten-over-de-zeldzame-afwijking-22q11-123771
2. https://www.youtube.com/watch?v=kYaL-qG4IY0
3. https://www.youtube.com/watch?v=B5LbZWs-9DA
4. https://www.22q.org/ International 22q11.2 Family Meeting Program (July 22 – 23, 2016 – Conference; July 24, 2016 – Family Fun Day Sirmione, Italy

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3. Gene x environment interaction research – in neurodegeneration and neurodevelopment

Neuroepigenetics

Department of Psychiatry and Neuropsychology (MHeNs)

Gene x Environment Interactions and research on Neuroepigenetics

The organization of DNA into chromatin enables the cell to use powerful regulatory mechanisms broadly defined as epigenetics. Epigenetic changes are reversible and responsive to environmental influences, unlike genetic mutations, which represent rare events with permanent consequences on genes. Research on Neuroepigenetics and environmental epigenetics aims to characterize the molecular basis that underlies sensitivity to environmental exposures in (neuro) psychiatric, neurodegenerative and neurological phenotypes and disorders, with a particular interest in gene-environment (GxE) interactions and epigenetics. Neuroepigenetic research within this program examines several aspects of epigenetic regulation, such as DNA methylation at promoter sites, chromatin modifications, gene silencing induced by miRNAs, and other novel epigenetic mechanisms, for their roles in disease and dysfunction in response to environmental conditions. The ultimate goal of this program is to identify molecular and cellular pathways that are causally involved in the aetiologies of psychiatric disorders, to identify biological markers that predict disease onset and course, to determine the reversibility of neurobiological changes, and to find novel preventive and therapeutic strategies. Research on neuroepigenetics is currently focussing on mood and anxiety disorders, psychotic disorders including schizophrenia, cognitive disorders like Alzheimer's disease (AD), multiple sclerosis (MS), and epilepsy. State-of-the-art technologies (e.g. ranging from epigenome-wide association studies [EWAS] to single cell methylation profiling) are being employed to analyse epigenetic changes in single genes, signalling pathways or the entire genome. Research involves various innovative, translational projects using *in vitro* cell cultures (e.g. *in vitro* epigenetic editing), *in vivo* animal models (e.g. *in vivo* epigenetic editing), and human tissues and/or biologic samples to examine (epi)genetic modifications and to determine the precise mechanism responsible for these changes. Datasets generated by (multi-) omics approaches such as those associated with EWAS are analysed by advanced data science approaches.

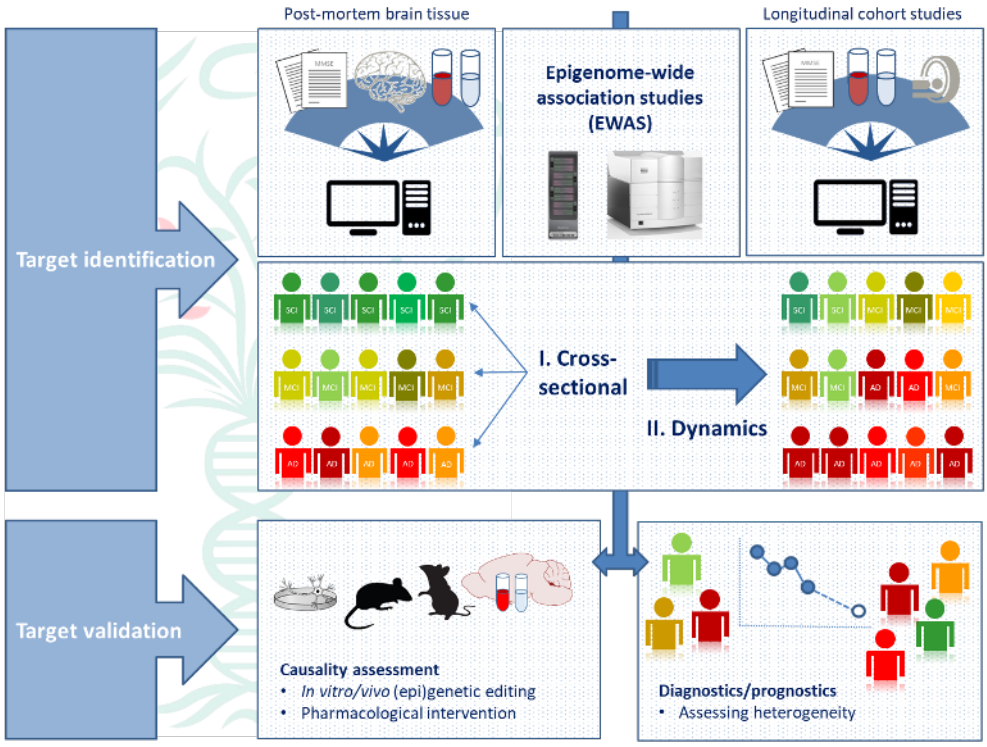
Ongoing projects

Pioneering work addressing the role of epigenetic dysregulation in aging and AD e.g. led to obtaining a European H2020/ERA-NET Co-fund scheme Joint Programme on Neurodegenerative Disease Research (JPcofuND; Dutch part funded by ZonMw/Memorabel) grant for EPI-AD, a project which addresses DNA methylation changes linking stress, depression and AD (coordinator Prof Dr Daniel van den Hove; see www.epi-ad.eu). As part of this work, we identified epigenetic differences in AD patients when compared to age-matched controls in the middle temporal gyrus, pertaining to genomic regions close to or overlapping with genes such as *OXT* (Lardenoije et al., 2019). In parallel, in an independent cohort, we examined the blood methylome in a preclinical stage. In the blood of elderly, non-demented individuals, DNA methylation in the same region of the *OXT* promoter as found in the brain was found to be associated with subsequent conversion to AD dementia. The implication of genome-wide significant differential methylation of *OXT*, encoding for oxytocin, in two independent cohorts indicates it is a promising target for future studies on early biomarkers and novel therapeutic strategies in AD. In addition, ground-breaking work on PTSD has identified first leads on identifying epigenetic signatures linked to differential susceptibility to develop mental ill-health after exposure to traumatic stress (see e.g. Rutten et al., 2017), awarded by NWO with a VENI and VIDI grant (Prof Dr Bart Rutten) and by a Marie-Curie individual fellowship (Dr Laurence de Nijs).

Collaborations

Neuroepigenetics research, which covers all divisions within MHeNs, is supported by grants from e.g. the Internationale Stichting Alzheimer Onderzoek (ISAO), Alzheimer Netherlands (AN), the European Union (e.g. EU-GEI [FP7]; EPI-AD [H2020-JPND]), NWO-VENI, NWO-VIDI, ZonMw-Memorabel, Hersenstichting Nederland, and the Transnational University Limburg (tUL). While EPI-AD officially ended in 2020, numerous consortium members (see www.epi-ad.eu) are still in

close collaboration in terms of further unravelling the role of epigenetic dysregulation in AD. In addition, based on one of the target genes identified in the EPI-AD project, i.e. *OXT*, an ongoing project (funded by AN) is examining the effects of *in vivo* epigenetic editing of *Oxt* in an AD mouse model. Work on trauma and PTSD is performed in close collaboration with numerous Dutch academic hospitals as well as with numerous international partners. Work on psychosis is performed in close collaboration with e.g. the GROUP consortium and the centres of the European Network of National Networks studying gene-environment interactions in schizophrenia (EU-GEI, www.eu-gei.eu). More recently, in close collaboration with Hasselt University (Hasselt, Belgium), work on GxE interactions and epigenetic dysregulation in MS garnered more attention as well.



Schematic illustration of research pipeline on GxE and Neuroepigenetics (using AD as a showcase).

Future perspectives

Work on this line will focus more on developmental disorders such as ADHD and associated aggression-related phenotypes. Moreover, in general, as an ongoing development, this line of work will integrate more and more with various data science and computational modelling disciplines, in particular with regards to identifying multi-omics signatures and associated drug repurposing work (e.g. linked to a ZonMw-Memorabel Fellowship recently obtained by Dr Ehsan Pishva). Along similar lines, we will work towards integrating analyses on polygenic risk scores, environmental exposures, epigenetic profiles on the onset and course of mental disorders making use of e.g. systems biology approaches. As such, we will incorporate e.g. genetic, environmental, and epigenetic risk scores in clinically applicable risk charts predicting e.g. disease onset, its course, and treatment response. Generally, this line of work will further strengthen its efforts with respect to experimental modelling, studying underlying biological processes, testing causality, identifying targets for intervention, both in silico, in vitro, and in vivo. Single cell analyses will garner more attention as well in the near future.

Scientific quality

Next to several prestigious grants obtained by key representatives of this line of work (see above for some examples), work on GxE and Neuroepigenetics within MHeNs has resulted in numerous high-impact publications in the last decade, including papers published in Molecular Psychiatry, Nature, Nature Communications, Nature Neuroscience and the New England Journal of Medicine. In addition, over the last decade, this line of work has resulted in about 20 PhD theses with more than 10 PhD candidates currently working on this topic.

Societal impact

1. Interview on stress, depression and epigenetics in Alzheimer's disease H2020/JPND (H2020/JPND grant; internet; 2016): http://www.neurodegenerationresearch.eu/views/unraveling-the-links-between-stress-depression-and-alzheimers-disease/
2. Interview ZonMw/Memorabel on stress, depression and epigenetics in Alzheimer's disease H2020/JPND (H2020/JPND grant; internet; 2016): http://www.zonmw.nl/nl/over-zonmw/inspirerend-dementieonderzoek/op-zoek-naar-de-verbanden-tussen-stress-depressie-en-alzheimer/

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4. Neuromodulation – towards an integrated neurotechnology programme

A. Brain Neuromodulation

Neuromodulation can be either pharmacological or medical device assisted. Mostly, when referring to neuromodulation, we are referring to medical devices, either non-invasive or invasive. Neuromodulation is a broad field within the domain of neurotechnology, and involves a combination of clinical disciplines (e.g. neurosurgery, neurology, psychiatry, rehabilitation medicine) and engineering disciplines (biomedical technology, neural engineering, computational neuroscience). The majority of neuromodulation projects, either clinical or research, focus on the central nervous system. Well known applications are deep brain stimulation and spinal cord stimulation. In the context of brain neuromodulation, a further distinction can be made between "brain reading" (decoding of information) and "brain writing" (stimulation or, further ahead, encoding of information). Finally, "reading" and "writing" can be combined to deliver closed-loop (or: adaptive) neuromodulation interfaces. Examples are adaptive deep brain stimulation and brain computer interfaces (BCI). This section will focus on these two applications.

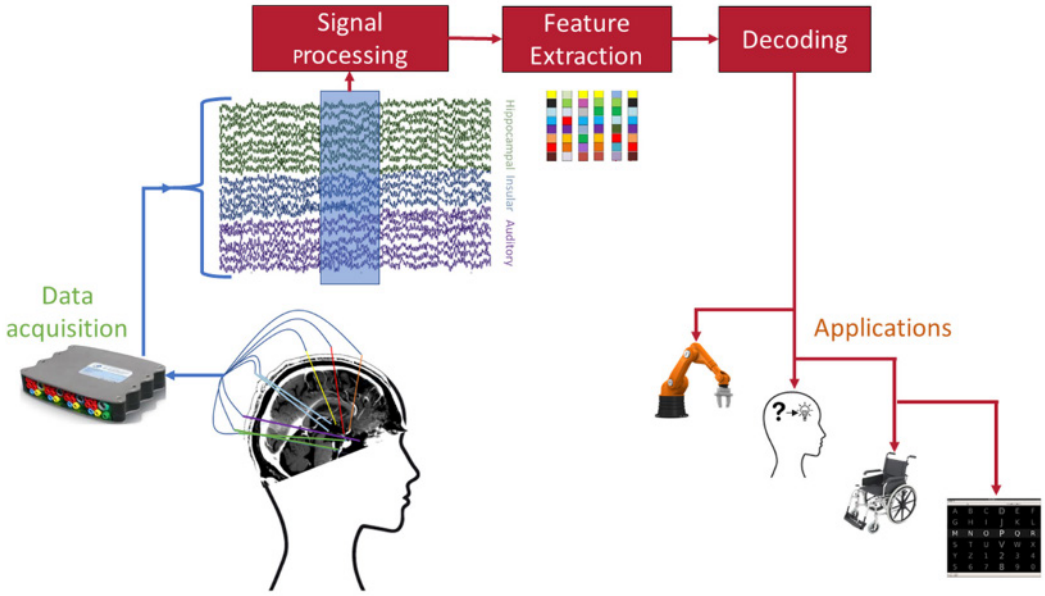
Ongoing projects

Brain writing

Adaptive deep brain stimulation (aDBS) can be obtained using either electrophysiological input (such as local field potentials in the beta band, measured from the subthalamic nucleus in patients with Parkinson disease) or external input (such as wearable sensors for motor symptoms, combined with ecological momentary assessment of non-motor symptoms). MHeNs has research projects on both approaches. *Dr M. Janssen* (neurologist and clinical neurophysiologist) is working on using electrophysiological input for aDBS in Parkinson's disease, working with Medtronic devices (the new Percept PC pulse generator) and a new company Newronika (ALphaDBS system). *Dr P. Kubben* (neurosurgeon) is working on using external feedback loops with wearable sensors and ecological measures, collaborating with Abbott. *Dr C. Herff* is involved from a neural engineering perspective with potential extensions towards BCI applications. These researchers closely collaborate to ensure maximal cross-disciplinary benefit and to avoid conflicts of interest. This project has started as a part of UTAP (funded by Weijerhorst foundation) and is now acquiring additional funding. The project has 3 PhD candidates.

Brain reading

Dr C. Herff leads the invasive BCI research line, which benefits from invasive epilepsy monitoring being performed for presurgical mapping and candidate selection for resective surgery. His VENI-awarded DESIS project on speech-decoding on stereo-EEG has been the starting point for establishing an online ("live") decoding pipeline using open-access software (Python, Lab Streaming Layer). This pipeline has been expanded towards a variety of clinical tasks (e.g. hippocampal decoding of navigation, motor decoding for robotic arm tasks) which are selected based on stereo-EEG electrode position. *Dr. P. Kubben* is coordinating the clinical aspects of this project. This project is funded by NWO (VENI), ZonMW (INTENSE cross-over grant by NEUROTECH-NL) and the CIN, resulting in 4 PhD candidates.



Stereo-EEG BCI pipeline

Collaborations

- University: Center for Integrative Neuroscience, Donders Institute/ Radboud UMC, UMC Utrecht, Virginia Commonwealth University, Uniklinik Aachen, University of Bremen, FPN, SBE
- Consortia: NEUROTECH-NL (https://neurotech-nl.com)
- industry: Abbott, Newronika, Medtronic

Future perspectives

All research projects mentioned before are in pre-clinical stage and expected to result in clinical applications within the next 5-10 years. These will focus on aDBS for Parkinson's disease, thereby exploring both feedback loops mentioned under "brain writing" as well as further improving speech decoding (in collaboration with Donders institute at Radboud UMC).

Societal impact

1. https://www.nationalgeographic.com/science/article/new-computer-brain-interface-translates-activity-into-speech
2. http://www.clinicaldatasciencebook.com
3. https://bcisociety.org/event/machine-learning-for-bci/

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B. The vestibular implant

Background

Severe and chronic hypofunction of the vestibular system, bilateral vestibulopathy, is very disabling. Patients suffer from imbalance and with each head movement they experience a sensation of dizziness and disorientation. This strongly influences their daily functioning, with big socio-economic consequences like reduced participation in social activities and society. Approximately 75% of the patients are not able to work, and they have a 30-fold increased risk of falling. This not only leads to a reduced quality of life, but also puts a socio-economic pressure on society. The estimated amount of patients suffering from severe vestibular hypofunction is approximately three million worldwide, but this is very like to be an underestimation.

The vestibular implant

Unfortunately, there is no treatment yet for loss of vestibular function. Therefore, the team from Maastricht UMC+ and the University of Geneva have built a strong collaboration to develop an artificial balance organ. This has resulted in the first surgically implanted artificial balance organs in humans in the world, and feasibility was previously demonstrated.

Until now, this team has still the biggest patient population with implanted artificial balance organs in the world (13 patients). The last couple of years, this has attracted the attention of international, national and local media, including radio, television, newspapers and social media.

The artificial balance organ is a bio-electronic prosthesis, that replaces the failing vestibular organ. Gyroscopes capture motion and these motion signals are converted by a processor into electrical pulses. These electrical pulses are then transferred by surgically implanted electrodes to the vestibular nerve. By this, the brain of the patient is able to recognize motion again.

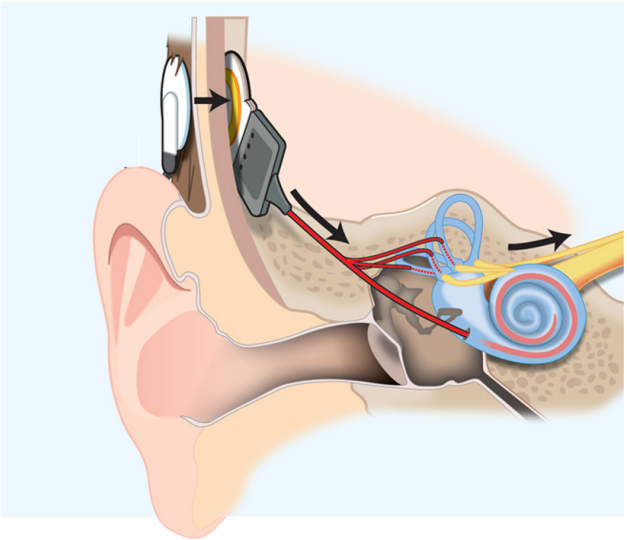
Research projects

Now that feasibility has been shown, it is important to further investigate all factors necessary to facilitate fast clinical availability on the market. The team of Maastricht UMC+ and the University of Geneva have therefore extended their collaboration with, among others, the faculty of physics of the university of Tomsk (Russian Federation), the department of otorhinolaryngology of the university of Antwerp (Belgium) and the manufacturer Med-El (Austria). This has resulted in obtaining several grants (including multiple international grants from Russia) and PhD positions with each their own specific research domain. First, the patient group is currently characterized more in detail, to develop a diagnostic pathway and implantation criteria. Core members of the team of Maastricht UMC+ have, based on results from this study, written the first opinion statement about implantation criteria for research. This was the first time that all internationally competing teams joined forces to create a common document based on consensus. Secondly, additional outcome measures are developed, including the use of Psymate (cooperation with Prof. Delespaul, Prof. Peeters, Dr. Leue and the European Dizziness network "Dizzynet"), to complement the current outcome measures with improved subjective and objective parameters. Thirdly, the surgical technique and electrode design has been fine-tuned, to improve safety and efficacy of surgery. This has led to significant alterations of electrode design and surgical technique, which will

be implemented in future trials. By this, surgical implantation can be safely performed in multiple centers in the world. Fourthly, the settings of the implant are currently being optimized (optimizing stimulation paradigm by investigating the transfer function) and tested, to ensure the most optimum stimulation by the artificial balance organ. At this moment, the VertiGO! trial (funded by ZonMw and Heinsius Houbolt Fonds) is conducted, which investigates the safety and efficacy of chronic electrical vestibular stimulation. Finally, beginning of 2021, a new trial funded by Stichting The Weijerhorst, will start. This new trial will investigate many more aspects of the vestibular implant, including the effects in patients with unilateral vestibulopathy, the effects of bilateral stimulation and the effects of etiology on efficacy of stimulation. This creates the opportunity to extend the patient group with ten additional patients, and to implant them with the newest version of the artificial balance organ.

Future

After successful completion of the studies mentioned above, we aim to have the artificial balance organ clinically available on the market within five to ten years. Maastricht UMC+ is currently the only "center of expertise" in The Netherlands for this disorder, and therefore has already many patients waiting for this treatment.



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Public engagement

1. Algemeen Dagblad (en alle dagbladen die erbij horen): "Chip in oor zorgt voor balans" 16-09-2019
2. L1 Limburg Centraal: het kunstmatig evenwichtsorgaan 20.10.2019
3. Hoormij magazine September 2020 – Uitval of mindere werking van één of twee evenwichtsorganen
4. L1 radio 02.11.2020: 1.5 miljoen euro voor ontwikkeling kunstmatig evenwichtsorgaan

Case studies

Case studies of some areas of (relatively) recent development which have already achieved broad scientific and societal impact:

5. Imaging the eye – window to the brain and mind
6. Vascular cognition – the crucial role of blood supply for brain health
7. Early recognition and intervention in mental health – reaching out to the community

5. Imaging the eye – windows to the brain and mind

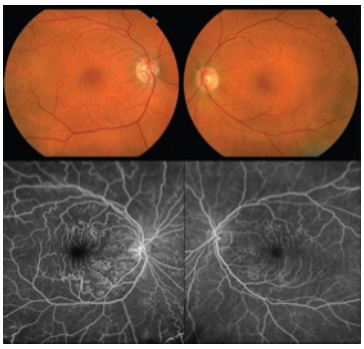
The eye has important characteristics that makes it a sensitive biomarker for brain diseases. All modalities described below are being used in the ophthalmology department and have led to important insights and breakthroughs in recent years.

First, the retina offers a unique "window" to study pathophysiological processes in the brain, as it is an extension of the central nervous system (CNS) and shares prominent similarities with the brain in terms of embryological origin, anatomical features and physiological properties. The vascular and neuronal structure in the retina can now be visualized easily and non-invasively using retinal imaging techniques, including fundus photography and optical coherence tomography (OCT), and quantified using computer-assisted analysis programs. State of art studies using these imaging techniques have demonstrated that structural and physiological abnormalities in retina are correlated with brain diseases. The former can be used to study neuronal changes, while the latter may be used to study microvasculature abnormalities. Recently, OCT image analyses showed widespread ganglion cell losses (the output neurons of the eye), retinal nerve fiber layer thinning (RNFL, ganglion cell axons) and optic nerve degeneration in AD. Fundus image analysis revealed changes in parameters such as retinal vessel calibres, fractal dimension and tortuosity in Alzheimer's disease (AD), schizophrenia and bipolar disorder.

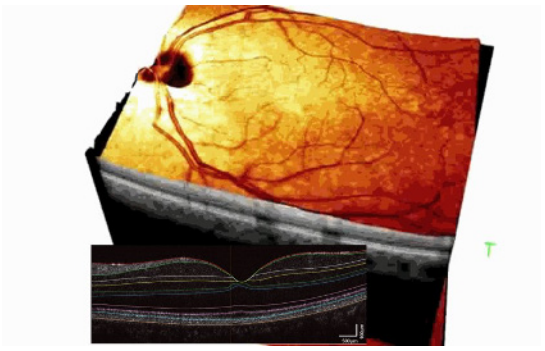
The retinal oxygen tension can be determined by spectral analysis of the light that is reflected at the retina. The possibility of the usage of retinal oximetry in AD has only been explored recently with promising results.

A widely held hypothesis concerning the pathogenesis of AD is that abnormal processing of Amyloid precursor protein results in accumulation of AβAmyloid ß in the brain, which in turn leads to neuronal dysfunction and neurodegeneration. Recent data suggest that AβAmyloid ß can also elicit cerebrovascular disease, impairing blood vessel relaxation and enhancing vasoconstriction. Direct optical imaging of Aβretinal plaques may be obtained by using multispectral imaging and retinal fluorochrome-staining.

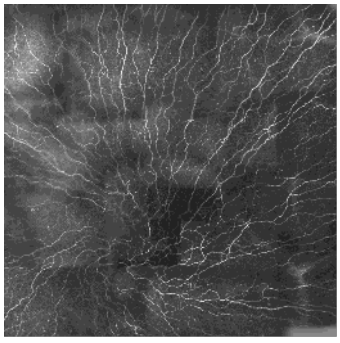
Macular Pigment Optical Density (MPOD) is a non-invasive measure of retinal carotenoids and surrogate measure of brain carotenoid concentration. Compositional analyses of centenarian brains have shown that lutein is the main carotenoid in the brain although not in plasma, indicating a preferential accumulation in neural tissues, and has been associated with disease prevention and cognitive health.



Retinal vasculature



Optical Coherence Tomography



Corneal nerve micromorphology

Tears covering the ocular surface are an important bio-fluid containing thousands of molecules, including proteins, lipids, metabolites, nucleic acids, vitamins and electrolytes. As such, tear fluid is an alternative source of biomarkers which can be collected non-invasively, painless and quickly. Recently, we demonstrated (for the very first time) the presence of soluble AD biomarkers (amyloid-beta peptides, tau and p-tau) in tear fluid of patients with cognitive impairment. Currently, validation of the potential of this non-invasive source (tear fluid) of AD biomarkers is being investigated in a large clinical trial.

Finally, in vivo confocal microscopy has established itself as a rapid and non-invasive method to image subbasal nerve plexus of the cornea. Its density has been linked with central nervous system disorders like Parkinson's disease.

Scientific quality

Marlies Gijs was awarded the prestigious Veni grant for her research proposal "Smart tears", that will study if tear biomarkers can be used for Alzheimer's disease screening and diagnosis. In the last five years more than 25 scientific publications have been published and last year Abhishek Appaji has defended his Ph.D. thesis on "Retinal vascular features as a biomarker for psychiatric disorders", a fully multi- and interdisciplinary study, encompassing psychiatry, ophthalmology, and medical image processing that evaluated new and original screening methods for mental health, which not only benefits the Dutch mental health system, but has worldwide impact also well.

Collaborations

There are several ongoing collaborations in which the eye as window to the brain and a as a biomarkers for different systemic diseases is being explored. In Maastricht we collaborate with the Maastricht Study, an extensive study to diabetes, with eye scans, blood samples, life style data and MRI scans available of 9000 subject. We also work with the Centre for Overweight Adolescent and Children's Healthcare (COACH) that focuses on healthcare and tailor-made long-term care counselling for overweight and obese children and young adults. Further, on aging and neurodegeneration we collaborate with the Alzheimer centrum Limburg. We participate in the Horizon 2020 CRUCIAL project that studies microvascular rarefaction in vascular cognitive impairment and heart failure. We have a long standing collaboration with the National Institute of Mental Health and Neuro-Sciences (NIMHANS), a premier medical institution in Bangalore, which is the apex centre for mental health and neuroscience in India.

Societal Impact

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2. Ocular Biomarkers for Alheimer's Dementia, October 2019, CORR Ophthalmic Imaging Symposium, Rotterdam (http://www.corr-rotterdam.nl/symposium)
3. Gezondheidsbeurs, October 2016 (http://www.gezondheidsbeurslimburg.nl/programma/)

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6. Vascular cognition – the crucial role of blood supply for brain health

Blood-brain barrier imaging

Authors: Alida Jacobi-Postma & Walter Backes
Department of Radiology & Nuclear Medicine

What is the blood-brain barrier?

The blood–brain barrier (BBB) is a highly selective barrier of interconnected endothelial cells. It prevents circulating blood elements from non-selectively crossing into the extracellular fluids of the central nervous system (CNS), thereby protecting the neurons. This barrier is formed by tightly connected endothelial cells by so called tight-junctions, astrocyte end-feet ensheathing the capillary, and pericytes embedded in the basement membrane.
The passage of hydrophilic molecules is limited, whereas the passage of small lipophilic substances, as are O_2 and CO_2 can diffuse along a concentration gradient. Selective transport of various nutrients, ions, and macromolecules such as glucose, water and amino acids that are crucial to neural function is regulated via transporters.

Dysfunction and breakdown of the BBB leads to leakages of toxic blood components into the CNS, cellular infiltration, and aberrant transport and clearance of molecules, contributing to neurological deficits. BBB impairment relates to neurological deficits and other pathologies in many disease states, including sporadic Alzheimer's disease, Parkinson's disease, multiple sclerosis, various forms of stroke including small-vessel-disease, traumatic brain injury, and also epilepsy.

Imaging initiative

Until recent years in vivo imaging of the BBB was mainly performed by means of nuclear imaging techniques utilizing smart pharmaceutical ligands, chemically coupled to radioactive tracers, that could actively pass the BBB. Magnetic resonance imaging (MRI) was only used to display rather coarse pathological openings of the BBB by uptake of a gadolinium based contrast agent, for instance in brain tumours, infection and active inflammatory lesions in multiple sclerosis. With the advent of more sensitive MRI techniques, especially quantitative imaging methods that focus on the time-pattern of the distribution of the contrast agent, it became possible to visualize subtler deficiencies of the impaired BBB in brain tissue without macroscopic lesions. Such a contrast agent acts as a magnetic dye and traverses the routes of surrogate small biomolecules. In the last 10 years, dynamic contrast-enhanced (DCE) MRI has become one of the most popular imaging techniques that is increasingly applied world-wide to study the breakdown of the BBB in various disorders that affect the brain, including aging.

In 2011 prof. Walter Backes, a medical physicist at the Radiology department of the Maastricht UMC+, started a novel research line on the permeability of the blood vessels of the brain, extending on previous research experiences in various

types of extracranial tissues and disorders. As the leakage of a gadolinium contrast agent in the brain was very subtle, novel image quantification methods considering noise reduction were tailored to the corresponding small and noisy MRI signals.

First results

By following the internal blood circulation and distribution of an MRI contrast agent, MRI measurements were designed to detect its leakage in brain tumours and, most importantly, in remotely located normal appearing brain tissue. After an initial demonstration providing pilot results, the Alzheimer foundations recognized the potential and granted two projects to determine the role of BBB impairment in patients with early signs of Alzheimer's disease. In this project,the first BBB impairments were noticed in these patients with the novel imaging technique. With this finding a long suspected, but yet hidden, link between vascular and intrinsic Alzheimer pathology has been demonstrated. It also explains the often seen mixed pathologies in these patients and warrants novel concepts for treatment and prevention strategies directed to the promotion of vascular health, without the visibility of overt vascular brain lesions.

Ongoing projects

Almost in parallel, research was set up in neurological patients with small-vessel-disease which yielded even more subtle BBB leakage effects. This project was granted by NWO and partly by the Health Foundation Limburg. Subsequent grants were obtained from the Alzheimer Foundation for subsequent research in neurodegenerative patients, a H2020 project on the phenomenon of microvessel rarefaction, and the call from Holland Health Foundation together with the Epilepsy Foundation.

Collaborations

For the research studies on aging and neurodegeneration is was collaborated with prof. Verhey from the Alzheimer centrum Limburg and in the initial stages with Prof Matthijs van Osch and Prof Mark van Buchem from the Leiden UMC. The small-vessel-disease research line is led by Prof Robert van Oostenbrugge and Dr Julie Staals from the Neurology department and is incorporated in the international H2020 project SVD@target, a cooperation of university medical centers in Edinburgh, Maastricht and Munich chaired by prof. Joanna Wardlaw (Edinburgh University).

Future perspectives

A currently ongoing project that started in 2019 is to further improve the detectability of the BBB breakdown by down-scaling the noise level with the use of the ultra-high field MRI systems at the Scannexus facility and the expertise of physics group at the faculty of Psychology & Neuroscience.

Currently, the scientific interest for BBB research, in particular in vivo imaging, is growing and expectations for medical applications are high. Though the encouraging results confirmed today by multiple research sites around the world, we should remain cautious as further improvement of the sensitivity and standardisation of the technique is required. After that a more widespread clinical application can be envisioned. Together with the neuroradiologist dr. Linda Jacobi novel projects are currently being explored to apply and integrate the novel methods in medically relevant projects.

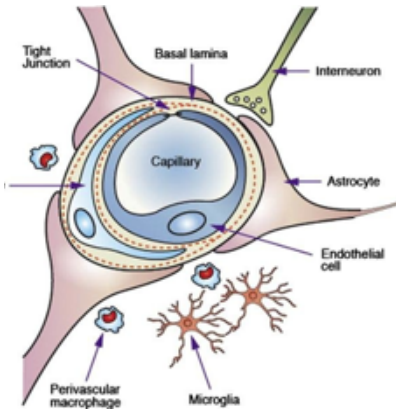
Scientific quality

The most objective event that expresses the quality of this research was the prestigious Alexander Margulis award that was offered at the annual congress of the Radiological Society of North America to prof. Backes and his team. This was obtained for the scientific excellence of the 2017 paper on the initial application of the BBB imaging technique [1]. Furthermore, the high-impact journal Neurology has devoted two editorials to the BBB work on small-vessel disease [2,3]. Till now, approximately 17 scientific publications [1-17] have emerged on the topic of BBB imaging from Maastricht, and 4 PhD thesis have been defended with 4 more PhD students working on this topic.

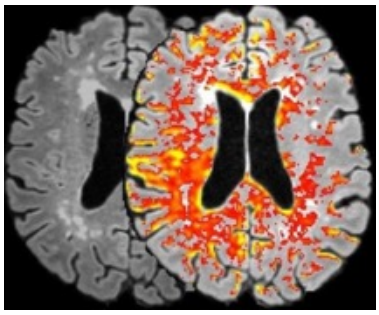
Societal impact

The press release by RSNA, entitled "Research linking blood-brian barrier leakage to Alzheimer's captures Margulis Award" (Nov 2017), lead to the following media reports:

1. NRC news paper article, "Dementie kan ontstaan door lek in bloedvaten", June 2, 2016
2. 1Limburg, news message, "Alzheimer: lekkage tussen hersenen en bloed", June 1, 2016
3. RSNA 2017, Daily Bulletin, "Walter Backes, PhD, Accepts Alexander R. Margulis Award for Scientific Excellence", Nov 28, 2017
4. Healthcare-in-Europe.com. Interview in the magazine European Hospital "Seeking leaks in the blood-brain barrier"(Vol 27, Issue 1/18, feb/march 2018, page 12-13)
5. New Scientist, "Vaccines might be able to stop Alzheimer's plaques from forming", with contribution from J.Jansen, May 31, 2016



Schematic microscopic view on the structure of the blood brain barrier.
From: A.K. Parashar & R.K. Nema in Current Research in Pharamceutical Sciences (2012;0:134-141;)



Leakage pattern of MRI contrast agent in a patient with early signs of Alzheimer's disease.

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7. Early recognition and intervention in mental health – reaching out to the community

Early recognition & intervention (@ease, SELFIE, Smartscan)

Department of Psychiatry & Neuropsychology (MHeNs)

Prevention of mental disorders is one of the top public health challenges. Innovative (personalized) solutions allowing for early detection, intervention and management are therefore needed to improve mental and socioeconomic health. Particularly adolescence forms a period of high risk for the development of serious mental disorders with approximately 75% of mental disorders emerging before the age of 25. Maastricht University has a long history of research into personalized ecological mental health assessment which can empower individuals to engage in self-management, ultimately help skill transfer to daily life and in turn reduce burden on patients, families and health care systems. Increasingly, transdiagnostic approaches are used linking clinical symptoms to neurobiology. Moreover, self-management transdiagnostic interventions aimed at improving self-esteem are currently employed in traumatized youth (https://server2.sp.unimaas.nl/selfie/). Another approach to enhance early recognition and intervention is by improving service accessibility and developing mental health reform initiatives particularly for young people where the traditional age gap around the age of 18 is often causing discontinuity of care. The emergence of transitional psychiatry teams, providing continuity of care and a holistic, transdiagnostic approach are Maastricht initiatives. Also the Dutch variant of the Australian Headspace, @ease, first opened its doors in Maastricht in 2018 (www.ease.nl).

Ongoing projects

Ongoing projects include large, experience sampling studies (esm-maastricht.nl), also in collaboration with national and international partners. In addition, novel youth mental health initiatives (everybody@ease, transition journeys) are ongoing.

Collaborations

National collaborations are taking place for the development of the Dutch variant of eHeadspace, in collaboration with AmsterdamUMC (Prof Popma, dr Nieman), and internationally as part of the International Youth Mental Health movement which developed guidelines in collaboration with the World Economic Forum and Orygen Melbourne (Prof McGorry). Also collaborations with CIMH (Prof Reininghaus) and Leuven (Prof Myin-Germeys) are continuing.

Future perspectives

Currently, the interest for cross-domain, transdiagnostic, innovative preventative and treatment approaches is increasing. Future perspectives with regard to therapeutic applications include ongoing mobile health development and (youth) mental health services reform, with active involvement of experience experts and social media.

Societal impact

Facebook: SELFIE.studie ease Nederland
Insta: selfie.studie ease_nederland
Twitter: @selfiestudie @ease_Nederland
https://www.nrc.nl/nieuws/2020/04/15/naar-de-psychiater-gaan-is-niet-cool-a3996904?utm_source=SIM&utm_medium=email&utm_campaign=Vandaag&utm_content=&utm_term=20200416
https://www.nporadio1.nl/nieuws-en-co/onderwerpen/495784-bus-luisterend-oor-jongeren-in-de-knel-deel-1
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