9th Annual MHeNs Research Day 2016

November 30th, 2016
Annual Research Day
School for Mental Health and Neuroscience

November 30th, 2016

Venue
Maastricht School of Management,
Maastricht, The Netherlands
Dear colleagues,

It is my pleasure and privilege to invite you to our 9th Annual Research Day of the School for Mental Health and Neuroscience, which will be held on Wednesday November 30th, 2016.

Theme for this year is:

**The Building Bridges Strategy or BRIDGES**

*From gene to passion do we understand how the brain works?*

We will welcome Prof. dr. Rianne Letschert, the Rector Magnificus, and we will have some interesting, cross-over divisions/translational lectures. A keynote speaker has been invited and PhD students will get the opportunity to give presentations in the form of elevator pitches and poster presentations. During these poster presentations the latest scientific work will be presented and at the end of the day prizes for the best posters will be awarded. All talks and discussions will be held in English.

For the support staff (OBP) a separate workshop “29 Ideas Killers” will be organized during a part of the day.

This day is not only scientifically interesting, but we also hope to offer you the opportunity to get to know each other better.

**Prof. dr. Nanne De Vries**

*Director School for Mental Health & Neuroscience a.i.*
PROGRAMME

Location: Maastricht School of Management, Endepolsdomein 150, Maastricht, Conference Hall

08.30 – 08.50 Welcome and registration (coffee/tea) - Business Lounge

09.00 – 09.05 Introduction Prof. dr. Nanne de Vries, director School MHeNs i.a.

09.05 – 09.20 What should a lawyer know about mental health when working in international tribunals?
Prof. dr. Rianne Letschert, Rector Magnificus Maastricht University

09.20 – 09.30 PhD Information, Dr. Martin van Boxtel, PhD coordinator

Chairman: Niels Janssen, PhD student

09.30 – 10.00 Elevator Pitches PhD students

Majed Aldehri: Fornix DBS enhances long-term spatial memory independent of hippocampal neuroplasticity

Christian Bertens: Non-invasive detection of ketorolac tromethamine in eyes analyzed with Raman spectroscopy and quantified by HPLC

Marina Damas: Autoimmune encephalitis, are we using the right techniques?

Elles Douven: Differences in cognitive profile between post-stroke depression and apathy: The CASPER study

Esther van Duin: Reward Learning and dopamine release in adults with 22q11DS

Nikos Priovoulos: Locus Coeruleus imaging at ultra-high field MRI

Chairman: Prof. dr. Bert Joosten

10.00 – 10.15 CO2 exposure as a translational cross-species experimental model for panic
Dr. Daniel van den Hove, Prof. dr. Koen Schruers

10.15 – 10.30 Identifying autoimmunity in neuropsychiatric disease and other rare disease forms
Prof. dr. Thérèse van Amelsvoort, Dr. Rob Rouhi, Dr. Pilar Martinez Martinez

10.30 – 11.00 Coffee Break - Business Lounge

Chairman: Dr. Pilar Martinez Martinez

11.00 – 11.15 Amyloid imaging
Dr. Pieter Jelle Visser, Dr. Mario Losen

11.15 – 11.30 Translational Research: Genetics and Postoperative Pain
Nynke van den Hoogen, PhD student, Dr. Jo Vanoevelen

11.30 – 11.45 An experience sampling intervention in depression and dementia
Dr. Marjolein de Vugt, Dr. Claudia Simons

Location: UNS 40 Onderwijsplein

11.45 – 12.45 Poster Session 1

Location: UNS 40 Drielandenpunt

12.45 – 13.45 Lunch

Location: Maastricht School of Management

13.30 – 16.15 Support staff workshop: “29 Ideas Killers”
Location: UNS 40 Onderwijsplein

13.45 – 14.45  **Poster Session 2**

Location: Maastricht School of Management, Endepolsdomein 150, Maastricht

Chairman: Dr. Lies Goossens

14.45 – 15.15  **Elevator Pitches PhD students**

Daniel Kreiter: *Investigating the use of experience sampling method and mood networks in a n=1 study of a bipolar patient*

Laurence de Nijs: *miRNA in susceptibility to traumatic stress*

Liselot Kerpershoeck: *Factors associated with the utilization and non-utilization of formal care services in Europe*

Tamar van Veenendaal: *High field imaging of neurometabolite networks in epilepsy*

Magdalena Weidner: *Brain serotonin and the mediation of early life stress*

Gusta van Zwieten: *Tinnitus suppression with high frequency stimulation of the rat medial geniculate body*

15.15 – 15.45  **Coffee Break - Business Lounge**

Chairman: Prof. dr. Nanne De Vries

15.45 – 16.30  **Keynote lecture: Neuroimaging and genetics – paradigms for integration across mental health and clinical neurosciences**

Prof. dr. David Linden

16.30 – 17.00  **Poster / Elevator Pitch awards + closing**

17.00 – 18.00  **Drinks - Business Lounge**
INVITED SPEAKERS
Nanne de Vries (1956) was trained as a social psychologist. After having occupied positions in Groningen, Maastricht, Groningen and Amsterdam, in 2000 he came to Maastricht to his present professorship as chair in Health Promotion. Until 2012 he was the head of that department, coordinating the research program and the bachelor and master programs. He also served as the Director of CAPHRI, School for Public Health and Primary Care and MHeNs, School for Mental Health and Neuroscience. His research focuses on theory-based development and evaluation of interventions in public health, with a special focus on nutrition and physical activity and on intersectoral collaboration. This work has resulted in about 200 scientific papers and chapters. Also, he supervised 50 PhD-students and advised to many Master and Bachelor theses. He has been a member of many research committees (most importantly ZonMW, the Dutch Organisation for Health Research and Innovation; MaGW, national science foundation for social and behavioural sciences; Dutch Mental Health Association) and editorial and advisory boards. At present he serves as vice-dean of the Faculty of Medicine, Health and Life Sciences, and board member of the Maastricht University Medical Center +.
Professor Rianne Letschert (1976) studied International Law at Tilburg University, the University of Amsterdam and the University of Montpellier. She obtained her PhD at Tilburg University for her thesis entitled ‘The impact of minority rights mechanisms’ (2005), which focused on competing international organisations that make policy and legislation to promote the rights of national minorities.

Letschert was appointed professor in March 2011, when she accepted the new chair in Victimology and International Law at Tilburg University. From April to August 2010 she was a visiting research fellow at the Lauterpacht Centre for International Law at the University of Cambridge and research fellow at Clare Hall in Cambridge, where she is a lifelong member. In 2014 she was a visiting professor at the University of Barcelona. She has written and edited various books, and published articles in national and international scholarly journals.

Professor Letschert received a Vidi grant from the Netherlands Organisation for Scientific Research (NWO) in May 2015 for her research on the impact of international tribunals on societies and people who are confronted with serious violations of human rights and international crime. She is an expert consultant for the Special Tribunal for Lebanon on victims’ issues. In addition to her role as professor, she was director of the International Victimology Institute Tilburg (INTERVICT). She became a member of The Young Academy of the Royal Netherlands Academy of Arts and Sciences (KNAW) in 2012, and was appointed as its chair in April 2015.

Professor Letschert was appointed Rector Magnificus of Maastricht University on 1 September 2016.
**CO2 exposure as a translational cross-species experimental model for panic**

*Dr. Daniel van den Hove, Prof. dr. Koen Schruers*

The way people react to threat depends on the perceived distance between the subject and the threat. Inappropriately long or intense responses can ultimately lead to psychopathology. This lecture will elaborate on the behaviour and neurobiology of defensive responses and how to study this in humans and other species in order to better understand the mechanisms of affective disorders.

*Dr. Daniël van den Hove*

Daniel van den Hove is an Associate professor at Maastricht University, as well as at the University of Würzburg (Germany). During his PhD at Maastricht University, he focused on the relationship between prenatal maternal stress and adult psychopathology. His main interest was directed towards the biological mechanisms that may explain the increased prevalence of affective disorders in prenatally stressed subjects. Further, in this respect, he has been investigating the effects of fetal and neonatal antidepressant exposure on offspring development.

Currently, as a collaboration between the various division within MHeNs and the Department of Psychiatry and Psychotherapy at the University of Würzburg in Germany, he is investigating the role of gene x environment (GxE) interactions, and their underlying epigenetic mechanisms, in the pathophysiology of psychiatric and neurodegenerative disorders like depression, panic disorder and Alzheimer’s disease. Along this line, he and others have launched an initiative at Maastricht University, which is referred to as ‘Translational Neuropsychiatry’ (TNP), bringing together all divisions within MHeNS in a collaborate approach to further investigate the neurobiology of psychiatric disorders in a translational setting. In addition, presently, he’s heading the Neuroepigenetics group within division 3 of MHeNs (see https://mhens.mumc.maastrichtuniversity.nl/neuroepigenetics). Since recently, he’s also coordinating the European H2020/JPND (ZonMw-Memorabel) project EPI-AD (www.EPI-AD.eu) on the role of epigenetic dysregulation in the pathophysiology of Alzheimer’s disease. As from 2007, he has been supervising 19 PhD students and has acquired over €2.7 million in funding as a PI.
Koen Schruers is a psychiatrist and professor at FHML. His research interest focuses on the neurobiology of emotion and affective disorders, with a particular interest in learning mechanisms and translational models.
Identifying autoimmunity in neuropsychiatric disease and other rare disease forms

Prof. dr. Therese van Amelsvoort, Dr. Rob Rouhl, Dr. Pilar Martinez Martinez

Summary: Psychotic syndromes such as schizophrenia are disorders with far-reaching effects on health, which have consequences for daily life of patients and their families. More than 1% of the population has a psychotic disorder, with often a first onset between 15 and 30 years of age. Treatment of psychotic disorders is still mainly symptomatic since the pathogenesis of these diseases is heterogeneous; genetic and environmental factors play a role that is still poorly understood. In a small subgroup of patients, there are strong indications that autoantibodies are responsible for causing a psychotic episode suggesting an autoimmune disease as the underlying cause.

Objective: The aim of this study is to establish the prevalence of autoantibodies against neuronal surface proteins in an early onset psychotic patient’s cohort. This will improve the diagnosis of this specific patient group and would be an important achievement because, fortunately, a standard immunosuppressive treatment is available, which has been successfully applied in other autoimmune diseases. In this way, patients could benefit by standard immunosuppressive treatment in the clinic. Additionally, we would like to determine predictors of positive test results in order to immediately refine diagnostic workup and increase yield of the test in future. This might be achieved by the (co-morbid, unnoticed?) neurologic symptoms.

Hypotheses: We hypothesize that autoantibodies against neuronal surface antigens are involved in the pathogenesis of a subgroup of patients with a primary psychotic disorder and that immunosuppressive therapy would be an effective way to treat these patients. At present, the use of clinical laboratory assays to establish whether patients with a psychotic disorder have an autoimmune disease is non-existent, apart from a few research centers in the world where patients’ material is screened for antibodies. Therefore, it is likely that the underlying autoimmune disease goes unrecognized in this patients’ subgroup.

Study design: This is an observational study with no pharmacological intervention performed in the azM. Patient sera and cerebrospinal fluid (CSF) will be screened for autoantibodies presence using cell-based and immunofluorescence assays. All participants will receive a neuropsychological battery of tests as well.

Study population: We propose to screen 300 stable ill young adult patients, preferably with an early onset psychotic disorder (less than 5 years). The range of patient inclusion ranges from 18 to 60 years. All patients will be mentally competent to assess participation.

Main study parameters/endpoints:
- Prevalence of autoantibodies against various neuronal surface antigens in blood and CSF
- Neurocognitive function, psychopathology, including presence of psychosis
- Autoantibody pathological mechanisms
- Blood brain barrier (BBB) integrity analysis
Prof. dr. Thérèse van Amelsvoort

Prof van Amelsvoort is a professor of Transitional Psychiatry and a Psychiatrist at Maastricht UMC. She trained as a psychiatrist at The Maudsley Hospital / Institute of Psychiatry in London, UK (1994-2001). She has a longstanding interest in neurobiological mechanisms underlying psychosis and neurodevelopmental disorders, with a special interest in 22q11DS. Since 2012 she is working at The Department of Psychiatry & Psychology at Maastricht University Medical Centre which is headed by Professor Jim van Os. She has been heading the Dutch Adult 22q11DS clinic for more than 12 years. She obtained funding for, and supervised 15 PhD students. The total funding obtained as a Principal Investigator up until 2014 was more than 1.2M Euros, more than 26.0M euro’s including co-applications. She is a member of the Editorial Board of the Journal of Neurodevelopmental Disorders and the Dutch Journal of Psychiatry, Academic Editor of PLoSOne, and member of the International 22q11 Deletion Syndrome Consortium, International Association of Youth Mental Health, European College of Neuropsychopharmacology and the Society of Biological Psychiatry.

Dr. Rob Rouhl

Starting from his appointment in 2012 as a neurologist in the Maastricht University Medical Center+, Rob Rouhl focussed on epilepsy. His research interests are the new diagnostic and therapeutic possibilities for patients with epilepsy. He is involved in the deep brain stimulation for epilepsy and epilepsy surgery program of the Academic Center for Epileptology, a cooperation between MUMC+ and Kempenhaeghe, Center for Epileptology. His research in the diagnostic spectrum includes new techniques like whole exome sequencing and auto-antibody testing.
Dr. Pilar Martinez-Martinez

Dr Martinez is trained in molecular biology, biochemistry and neuroimmunology. She is an Associate Professor at the Department of Psychiatry and Psychology Division Neuroscience at the School for Mental Health and Neuroscience at Maastricht University. She received her PhD cum laude at the Faculty of Medicine at the University of Valencia. She leads her own research group Nervous System Neuroinflammation and Autoimmunity at Maastricht University and has received several awards like the predoctoral Marie Curie Fellowship and the Internationale Stichting Alzheimer Onderzoek ISAO award. She is the PI of several European and International grants examining neuroinflammation with special focus in neurodegenerative diseases and its relationship with the sphingolipid metabolism like the recently awarded Weston Brain Institute grant from Canada.
Amyloid imaging
Dr. Pieter Jelle Visser, Dr. Mario Losen

Amyloid aggregation in plaques is the pathological hallmark of Alzheimer’s disease (AD). Amyloid plaques can be visualised by PET imaging. Preclinical studies have shown that removal of plaques by monoclonal antibodies slow down disease progression. Antibodies can be labelled with immuno-PET probes. We tested whether immuno-PET tracers with amyloid antibodies can be used to in-vivo visualise amyloid in the brain of AD mice.

Dr. Pieter Jelle Visser

Pieter Jelle Visser, MD, PhD, is senior investigator at the Maastricht University Medical Centre and VU University Medical Center. He investigates the pathophysiology, diagnosis, prognosis and treatment of Alzheimer’s disease in large patient cohorts. He currently coordinates the IMI-funded European Medical Information Framework for Alzheimer’s disease (EMIF-AD).

Dr. Mario Losen

Mario Losen, PhD, is senior investigator at Maastricht University with a background in biology and immunology. His projects are aimed at developing (experimental) therapies and diagnostic methods for diseases of the nervous system, in particular myasthenia gravis and Alzheimer’s disease.
Translational Research: Genetics and Postoperative Pain

Nynke van den Hoogen, PhD student, Dr. Jo Vanoevelen

Chronic postsurgical pain (CPSP) is a common problem affecting between 10 and 60% of patients undergoing surgery. Both biological (e.g. genetic variations) and psychological (e.g. depressive symptoms) components play a role in chronic pain syndromes. Although demographic, clinical and psychological risk factors are well documented; little is known about genetic risk factors for CPSP. Research into the mechanisms behind the effects of the risk factors on the development of CPSP is necessary to understand the differential sensitivity to CPSP development.

A systematic literature search identified 14 articles which primarily analysed genetic variation in the development and severity of CPSP. In total, 239 SNPs were analysed divided over 54 genes. Five genes were selected as genes of interest (COMT, OPRM1, KCNS1, CAGNG2, and GCH1), in which 16 single nucleotide polymorphisms were assessed in a multi-centre cohort of hysterectomy patients (n=425). Next to the selected SNPs, a Genome Wide Association Study was performed. The analysis of the GWAS is still ongoing. However, analysis of psychological questionnaires has shown a large association of CPSP and depression scores in the current cohort. Interestingly, the COMT and GCH1 genes are important in dopaminergic transmission, involved in both biological and psychological processes. This could suggest a role for dopaminergic neurotransmission in the development and severity of CPSP and comorbid depression.

As the zebrafish genome contains functional counterparts of both genes, we intend to test this hypothesis using the zebrafish model. Both genes will be knocked down using an antisense strategy and their functional consequences studied both at the structural level (number of dopaminergic neurons in the brain) and the functional level (changes in responses in nociception assay). Moreover, the same assay will be used to explore the potential of compounds interfering with the functions of COMT and GCH1.

Nynke van den Hoogen is a PhD student at the department of Anaesthesiology and Pain Medicine, and division 3 Translational Neuroscience of MHeNS at Maastricht University. She received her Bachelor in Biomedical Sciences at Maastricht University in 2012, and joined the Research Master Programme in Cognitive and Clinical Neuroscience, specializing in Fundamental Neuroscience. Her major interest lies in unravelling the pathways that underlie individual differences in pain perception and susceptibility. Using a translational approach, topics like genetics and plasticity are studied. Recently, she joined the lab of Prof. Maria Fitzgerald at University College London for six months to be trained in in vivo spinal electrophysiology. Her PhD research, supervised by Prof. Joosten (Maastricht University) and Prof. Tibboel (Erasmus-MC Sophia) focusses on the influence of early life nociception (as a predictor), and treatment thereof, on adult postoperative pain behaviour.
Jo Vanoevelen is a junior PI at the Department of Clinical Genetics at the MUMC+.

After his studies in Biology at KULeuven (Belgium) he pursued his PhD research at the same university, studying the physiology of intracellular calcium-transport ATPases (2004). Funded by a grant from FWO (Flemish scientific research Fund), he moved to the Hubrecht Institute (Utrecht) for a 2-year postdoc focusing on the genetics of bone development in zebrafish in the group of Prof. Stefan Schulte-Merker. In 2012, he joined the Clinical Genetics department in Maastricht. Here, he is applying his experience in molecular cell biology and zebrafish genetics to generate disease models in zebrafish and became the driving force behind the introduction of the zebrafish model at Maastricht University. Zebrafish are an elegant model system for functional genetics due to their reproductive capacity, external fertilization and development, optical transparency and amenability to genetic modification. The aim of his research is to make use of genome-modifying technologies in zebrafish to:

- characterize disease-causing genetic variants
- understand pathophysiological mechanisms using disease models
- screen for novel therapeutic approaches

The current research focus is on, but not restricted to, the development of disease models for neuropathic pain (funded by a FP7-project). Additionally, models for heart disease (funded by a departmental RVE-11 grant) and metabolic disease (funded by Metakids) have been generated.
An experience sampling intervention in depression and dementia
Dr. Marjolein van de Vugt, Dr. Claudia Simons

Background: Experience sampling (ESM), a method in which individuals repeatedly assess their affective experiences and behavior in real-time, holds opportunities for the development of ecologically valid and person-tailored interventions. Real-life self-monitoring combined with personalized feedback on positive affect experience might help to increase insight into patterns of positive emotions and the context in which they are experienced. Positive emotions have been found to promote adaptive coping in stressful situations and play an important role in resilience against depression. Experience sampling interventions could be a promising tool to strengthen individuals with depression and caregivers of people with dementia who often experience high levels of stress and burden.

Depression
A randomized controlled trial was conducted in depressed patients

Methods: Participants were randomly assigned to the experimental group (six-week intervention consisting of ESM self-monitoring and personalized feedback), pseudo-experimental group (six-week pseudo-intervention consisting of ESM self-monitoring without feedback), or control group (usual care). Effects were evaluated from pre- to post-intervention (empowerment and ESM measures of affect and behaviour) and over 32 weeks follow-up (depression, costs and quality of life).

Results: ESM-intervention was associated with a clinically relevant decrease in depressive symptoms during the 32-week follow-up period—a decrease that was significantly larger compared to the other groups. An economic evaluation tentatively suggested that ESM-intervention is cost-effective. Although ESM-intervention showed positive changes at immediate post-intervention, changes in affect, behavior and empowerment were only significant different compared with the control but not the pseudo-intervention group.

Dementia care
Based on the study above, the experience sampling intervention ‘Partner in Sight’ was developed for dementia caregivers and evaluated in a similar design.

Methods: A randomized controlled trial with 76 spousal caregivers of community-dwelling people with dementia was performed. Participants were randomly assigned to the experimental group (six-week intervention ‘Partner in Sight’ consisting of ESM self-monitoring and personalized feedback), pseudo-experimental group (six-week pseudo-intervention consisting of ESM self-monitoring without feedback), or control group (usual care). Effects were evaluated pre- and post-intervention, and at two-months follow-up using retrospective measures of caregiver sense of competence, mastery, and psychological complaints (depression, anxiety, and perceived stress). Complementary, ESM measures of positive and negative affect were collected pre- and post-intervention.

Results: Both the experimental and pseudo-experimental group showed a significant increase in retrospectively measured sense of competence and a decrease in retrospectively measured perceived stress at two-months follow-up. Immediately after the intervention the experimental group showed a decrease in momentary negative affect compared to the pseudo-experimental and control group. No effects were found for retrospective mastery, depression, and anxiety, and for momentary positive affect.

Overall conclusion: Self-monitoring of daily life affect and context coupled with person-tailored feedback may be a promising clinical tool to enhance personalized treatment by
providing insight into daily activities that enhance wellbeing. ESM interventions could be an important asset to increase caregiver resources that could help to better adapt and manage difficult situations, and to protect caregivers against negative emotions.

Dr. Marjolein de Vugt

Marjolein de Vugt is a health care psychologist and associate professor at the research school Mental Health and Neurosciences at Maastricht University. She is head of the Alzheimer Center Limburg and has a research line into psychosocial aspects of dementia. Specific research topics are E-health interventions to support caregivers and Young Onset Dementia. Internationally, she is involved in several European studies on psychosocial aspects of dementia as project leader of the Actif care study, work package leader of the RHAPSODY study, both granted by the Joint Program of Neurodegenerative Diseases, a pan-European Erasmus project POSADEM, and a Marie-Curie international training network INDUCT.

She is board member of the European network on research into early detection and timely intervention in dementia (INTERDEM) and the Dutch society of Neuropsychology.

Dr. Claudia Simons

Claudia Simons is a senior researcher at the department of Research, Development and Innovation at GGz Eindhoven and De Kempen in collaboration with the School for Mental Health and Neurosciences at Maastricht University. Her research focusses on neuropsychological and affective factors that influence vulnerability for mental disorders, specifically psychotic and depressive symptoms, including gene-environment interactions. In addition, she focusses on mobile health interventions based on experience sampling methodology.

Claudia Simons obtained her master’s degree (cum laude) at Maastricht University, The Netherlands, in 2004. As a PhD candidate at the School for Mental Health and Neuroscience, she studied the association between aberrant information processing as risk factor for the development of psychotic disorders. She spent time abroad at the Institute of Psychiatry at King’s College London (prof. Shergill), were she studied the functional neuroanatomy of inner speech in schizophrenia. Claudia obtained her PhD in June 2010.
She is currently a senior researcher at the department Research, Development and Innovation of GGz Eindhoven and De Kempen in collaboration with the department of Psychiatry and Neuropsychology of Maastricht University. Here, she extended her prior research on neuropsychological and affective factors that influence vulnerability for and course of mental disorders and, additionally, investigates mobile health interventions that use self-monitoring of affect within the context of daily life as a clinical tool.
Neuroimaging and Genetics – Paradigms for Integration across Mental Health and Clinical Neurosciences

Prof. dr. David Linden

The past decade of discovery in psychiatric genetics has revealed a considerable overlap of risk factors for different mental disorders but also across psychiatric and neurological diseases. Several of the recently identified rare risk variants for psychosis, for example, also confer risk for intellectual disability, epilepsy, and neurodegeneration. This pleiotropy opens up an opportunity for the investigation of biological mechanisms that may be shared between these disorders. More broadly, it indicates that disease processes are not mapped onto traditional disciplinary boundaries and that their investigation will proceed most fruitfully through joint working across the whole clinical and research spectrum of psychiatry and neurosciences. I will give three examples of such an approach, two from genetic imaging and one from neuroimaging-based treatment development, which also derives considerable synergies from such an integrative approach. My genetic imaging examples are from the investigation of brain effects of common risk variants (and polygenic risk scores derived from them) for neurodegenerative disorders and psychosis and from the investigation of changes in brain connectivity in carriers of high-penetrance risk variants for neurodevelopmental disorders (copy number variants). My case study of neuroimaging-based treatment development refers to neurofeedback protocols for mental disorders and neurorehabilitation that we are evaluating together with collaborators in our European consortium. Training self-regulation of dysfunctional or compensatory brain circuits might have beneficial effects as an add-on to psychotherapy (for example in substance use disorders) or to physiotherapy (for example in stroke rehabilitation), and the neurofeedback approach can thus become paradigmatic for an approach to brain disorders that integrates disciplines and professions.

David Linden read medicine, classics and philosophy in Germany. He obtained a DPhil from the University of Oxford for his work on medical ethics in antiquity in 2000 and a Dr. med. in neuroscience at the Max Planck Institute for Brain Research in 1999. He trained in psychiatry at Frankfurt University and has a special interest in clinical neuropsychiatry and neurodevelopmental genetic syndromes. Since 2011 he has been Professor of Translational Neuroscience at Cardiff University and Head of the Neuroimaging theme group of the MRC Centre for Neuropsychiatric Genetics and Genomics. He is also the director for clinical research at the Cardiff University Brain Research Imaging Centre. In his research he applies structural and functional magnetic resonance imaging (MRI), neurophysiological techniques and genetics in order to understand the function of the brain in health and disease. Current research interests include functional imaging of psychopathology, neural substrates of social cognition and decision making, genetic imaging, treatment and training effects on the brain, and neurofeedback. David is the author of “The Biology of Psychological Disorders” (2012),
“Brain Control” (2014) and “Neuroimaging and Neurophysiology in Psychiatry” (2016) and over 180 scientific papers in the fields of biological psychiatry, functional brain imaging, visual and social cognitive neuroscience, and neurofeedback. He has coordinated trials of functional MRI-based neurofeedback in depression and Parkinson’s disease. He is also the coordinator of the European Consortium “BRAINTRAIN” (www.braintrainproject.eu), funded by the European Commission under the 7th Framework Programme, which develops and evaluates imaging-based neurofeedback methods for a range of mental disorders.
ABSTRACTS
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Fornix DBS enhances long-term spatial memory independent of hippocampal neuroplasticity

Majed Aldehri¹, Yasin Temel¹², Ali Jahanshahi¹, Sarah Hescham¹

Departments of ¹Neuroscience and ²Neurosurgery, Maastricht University, Maastricht, The Netherlands

Introduction: Deep brain stimulation (DBS) of the fornix can restore memory functions in animals with experimental dementia. We have shown that one potential underlying mechanism is the enhanced release of acetylcholine in the hippocampus. Another suggested mechanism of action is neuronal plasticity.

Objective: Here, we have tested the hypothesis that acute fornix DBS can have long-term beneficial effects on memory by enhancing histological parameters of neuronal and synaptic plasticity.

Materials and Methods: Rats were implanted with bilateral electrodes at the site of the fornix and received DBS at 100 Hz, 100 μA and 100 μs pulse width for 4 h. Three days after stimulation, rats received BrdU injections twice daily for a period of 3 days. After 5 weeks, fornix DBS and sham rats were tested in the water maze task. Probe trials were given after 1 h and 48 h. About 6.5 weeks after DBS, rats were sacrificed and their brains processed for BrdU/NeuN, p-CREB or synaptophysin immunohistochemistry.

Results: Fornix DBS rats visited the target annulus more frequently than sham rats in the probe trial with 1 h delay. We did not find any differences for the number of double-labelled BrdU/NeuN or p-CREB cells for fornix DBS rats when compared to sham. Synaptophysin-immunoreactive presynaptic boutons, however, were significantly decreased in the CA1 and CA3 subfield of the hippocampus for fornix DBS rats when compared to sham.

Conclusion: Fornix DBS enhances long-term spatial memory independent of the neuroplasticity markers, which were used in the present study. An interesting finding is the decrease in the synaptic-neuroplasticity marker, which might suggest a long-term depression related mechanism.

Keywords: Fornix, DBS and memory.

References:
Role of PDE inhibitors on AMPA receptor trafficking and downstream cyclic nucleotide signaling

Elentina K. Argyrousi¹, Susana R. Neves-Zaph², Jos Prickaerts¹

¹Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands.
²Departments of Pharmacology and Systems Therapeutics, Friedman Brain Institute, and System Biology Center New York, Icahn School of Medicine at Mount Sinai, New York, New York 10029.

Previous studies have shown that the cGMP-selective PDE5 inhibitor, vardenafil, and the cAMP-selective PDE4 inhibitor, rolipram, could improve synaptic plasticity when they are applied in specific time windows. Subsequently it is proposed that the distinction of long term potentiation (LTP) into early and late phase relies on distinguish molecular cascades activating the cGMP/protein kinase G (PKG) and cAMP/protein kinase A (PKA), respectively. In the present study we aim to shed light into the mechanism that underlies the role of the above cascades in synaptic enhancement. A major player of mediating the effects of nucleotide signaling on synaptic plasticity is the glutamatergic AMPA receptor (AMPAR). Interestingly, AMPAR insertion into the membrane might be involved in early LTP, while increased synthesis could participate in synaptic strengthening that characterizes the late phase of LTP. In order to examine the above hypothesis we perfuse mouse hippocampal slices either with vardenafil 10 min before induction of chemical LTP or with rolipram 60 min after the chemical LTP. Subsequently, membrane and total fractions of the GluR1 subunit of the AMPAR were assessed via separation of surface biotin-labeled proteins from the cytosolic unlabeled proteins using streptavidin. Our findings show that perfusion of vardenafil before chemical LTP increases the number of AMPAR in the membrane. Considering that this upregulation is accompanied with increased AMPA phosphorylation, a pre-requisite of its insertion in the membrane, we confirm that perfusion with the PDE5 inhibitor before chemical LTP promotes the trafficking of the already existing pool of AMPAR without affecting the total number of the receptors. Accordingly, PDE4 inhibition at the late phase of LTP increases the synthesis of new AMPAR rather than increasing their trafficking into the membrane. Importantly the effect of the PDE4 inhibitor is mediated by upregulation of CREB phosphorylation, which is known that promotes genes expression including synthesis of new AMPAR.

Keywords: AMPA receptors, long term potentiation, PDE inhibitors.
Biomarkers of Alzheimer’s disease and affective neuropsychiatric symptomatology

Leonie Banning¹, Inez Ramakers¹, Frans Verhey¹, Pauline Aalten¹,

¹Alzheimer Center Limburg, School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Center, Maastricht, The Netherlands. Contact e-mail: leonie.banning@maastrichtuniversity.nl

Background: Depression, anxiety and apathy are common neuropsychiatric symptoms (NPS) in persons with mild cognitive impairment (MCI) and Alzheimer’s disease (AD) and have been associated with an increased risk for progression from MCI to AD. We examined the association between abnormal values of AD biomarkers and the presence of NPS, among the whole spectrum of cognitive decline. Methods: We included memory clinic patients from the Maastricht University Medical Centre with subjective cognitive decline (SCD) (N = 41), MCI (N = 88) and dementia (N =31). Cerebrospinal fluid (CSF) levels of amyloid-beta (Aβ42), total tau (t-tau) and phosphorylated tau (p-tau), medial temporal lobe atrophy (MTA), white matter lesions (WML) markers, and apolipoprotein ε4 (APOE ε4) carriership were used as AD biomarkers. Depression, anxiety and apathy were measured with the Neuropsychiatric Inventory (NPI), Geriatric Depression Scale (GDS) and Apathy Evaluation Scale (AES). Using binary logistic regression analyses, abnormal values of AD biomarkers were associated with the presence of NPS. Results: Depressive symptoms were reported by 54.4%, anxiety by 30% and apathy by 33.1% of the subjects. No association between abnormal biomarker values and presence of NPS was found. Carriers of the APOE ε4 allele were found to have less often symptoms of apathy compared to non-carriers. Conclusions: Symptoms of depression, anxiety and apathy were not associated with AD pathology. However, stratifications based on diagnosis were not possible due to small sample size. In addition, in our sample there was a lower prevalence of MCI subjects with AD pathology as compared to similar cohorts, which might have influenced our results. Therefore, this preliminary study will be replicated in a multi-center database with longitudinal data.

Keywords: Neuropsychiatric symptoms – biomarkers – Alzheimer’s disease.
Operant behavioral testing in experimental painful diabetic polyneuropathy; from reflexes to decisions?

M. van Beek\(^1, 2\), E.A. Joosten\(^1, 2\)

\(^1\)Department of Translational Neuroscience, School of Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands.
\(^2\)Department of Anesthesiology and Pain Management, MUMC+, Maastricht, the Netherlands.

**Introduction:** The field of experimental pain research has relied on reflex (sensory aspects of pain) based testing for decades. However, pain is a multidimensional condition with sensory, cognitive, and motivational components. It is therefore that operant tests have been developed to analyze and quantify avoidance behavior or place preference associated with pain relief, thereby taking into account more than just the sensory domain of pain. Diabetes Mellitus and development of diabetic polyneuropathy is among the major indications for development of chronic neuropathic pain. Therefore, we aimed to assess and validate mechanical conflict avoidance behavior with the use of the Mechanical Conflict Avoidance System (MCS) in experimental PDPN and compared escape – and crossing latency with classical reflex based measurements to gain insight in motivational and cognitive processes associated with mechanical hypersensitivity in experimental PDPN.

**Methods:** Streptozotocin induced diabetic rats (n=20) and control rats (n=5) underwent training to escape a bright light compartment to a dark compartment of the set up. Two days of five min apparatus familiarization was followed by three days of crossing training without spikes (0mm). During data collection, a spike bed with incrementing spike heights (.5-5mm) was introduced between the light and dark compartment. Escape latency and crossing latency were quantified. In addition, Von Frey (withdrawal to filaments) and Hargreaves (infrared heat source) testing were performed to quantify mechanical and thermal sensitivity respectively.

**Results:** Diabetic rats, compared with non-diabetic rats, showed longer average crossing latencies on 0mm (4.61 s V.S. 2.66 s, \(p=0.011\)), 2mm (10.38 s V.S. 7.06 s, \(p=0.043\)), 3mm (14.38 s V.S. 9.46 s, \(p=0.058\)), 4mm (14.17 s V.S. 7.2 s, \(p<0.01\)), and 5 mm probe height (15.22 s V.S. 8.4 s, \(p<0.01\)). Both control and diabetic rats showed lower average withdrawal thresholds to mechanical stimulation with Von Frey filaments. Diabetic rats show lower average withdrawal latency to an infrared heat source, whereas control rats did not.

**Conclusion:** MCS allows the detection of differences in pain related operant behavior between diabetic and non-diabetic animals which did not differ in response to Von Frey withdrawal reflex assessment. This underlines the importance of taking into account supraspinal pain processing in experimental pain research in addition to classical reflex based pain measurements.
Mindfulness training for people with dementia and their caregivers: rationale, current research, and future directions

Lotte Berk¹, Martin van Boxtel¹, Franca Warmenhoven¹,², & Jim van Os¹

¹Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, The Netherlands
²Department of Educational Development and Research, Faculty of Health Medicine and Life Sciences, Maastricht University, The Netherlands

The world population is aging and the prevalence of dementia is increasing. In the Netherlands, those aged 65 years and older are expected to almost double to 2040, making up a quarter of the population. There is no cure for dementia and the progression of symptoms with no hope of improvement is difficult to cope with, both for patients and their caregivers. New strategies are needed to support the well-being of both caregiver and patient. Mindfulness training is an intervention that has shown to improve psychological well-being in a variety of mental health conditions. Mindfulness, a nonjudgmental attention to one’s experience in the present moment, is a skill that can be developed with a standard 8-week training. Research has showed promising preliminary support for mindfulness-based interventions to benefit people with dementia and caregivers. However, studies suggest that the standard 8-week mindfulness training could be adjusted to better suit the needs of this population. The aim of this review is to (a) provide a rationale for the application of mindfulness training to individuals recently diagnosed with dementia and their caregivers, (b) describe the current state of research for mindfulness training in older people, people with dementia and caregivers, (c) summarize suggestions for adjustments in the training and (e) discuss future directions of protocol development specific to people with dementia and their caregivers.

Keywords: Mindfulness, MBSR, aging, cognitive decline.
Non-invasive detection of ketorolac tromethamine in eyes analyzed with Raman spectroscopy and quantified by HPLC

C.J.F. Bertens B.A.Sc., M.Sc.\textsuperscript{1,2,3}, S. Zhang M.Sc.\textsuperscript{2,3}, M. Gijs Ph.D.\textsuperscript{1,2,3}, F.J.H.M. van den Biggelaar Ph.D.\textsuperscript{1,2}, T.T.J.M. Berendschot Ph.D.\textsuperscript{2,3}, R.M.M.A. Nuijts M.D., Ph.D.\textsuperscript{1,2}

\textsuperscript{1}Chemelot Institute for Science and Technology (InSciTe), Geleen, the Netherlands
\textsuperscript{2}University Eye Clinic Maastricht, Maastricht University Medical Centre + (MUMC+), Maastricht, the Netherlands
\textsuperscript{3}School for Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands

Introduction: Treatment of ocular diseases is mostly done with eye drops. Eye drops are easy to administer and well accepted by patients, but contain low drug concentrations. This results in higher administration frequencies (thus, lower patient compliance) and additives to enhance penetration (increases the risks on side effects). Moreover, eye drops have a low drug bioavailability (<5%). As a result, many researchers focus on developing ways to enhance the level of drug absorption into the eye.

The level of drugs in the eye can only be detected by analyzing an aqueous humor sample by, for example, HPLC. Raman spectroscopy bears the possibility to quantify drug concentrations in vivo in the anterior chamber of the eye. Raman spectroscopy is based on the detection of Raman’s scatter by light-matter interaction. In this project, we would like to explore whether Raman spectroscopy can be a valuable and non-invasive alternative to HPLC for the quantification of ocular drug levels.

Method: In vitro Raman spectroscopy and HPLC were analyzed in terms of sensitivity of detection. Enucleated rabbit eyes were treated with different concentrations of Ketorolac Tromethamine (KT). Hereafter, the eyes were analyzed ex vivo by Raman spectroscopy. Finally, the eyes were dissected and KT was extracted from the eyes according to different methods. The extraction products were analyzed by in vitro Raman spectroscopy and HPLC using the US pharmacopoeia method. Mass spectrometry was used to confirm the identity of KT.

Results: The sensitivity of detection of HPLC was superior to in vitro Raman spectroscopy. Raman spectroscopy was able to detect KT in ex vivo treated eyes. After dissection and KT extraction, KT could be detected and quantified by HPLC but not by in vitro Raman spectroscopy due to the presence of interfering signals.

Discussion: The detection limit of in vitro Raman spectroscopy is significantly lower compared to HPLC, which makes latter technique more suitable for quantitative measurements. The detection of KT by ex vivo Raman spectroscopy seems promising, although low concentrations are difficult to detect. So far, Raman spectroscopy has shown potential in vitro and ex vivo, but needs further optimization for in vivo applications.

Keywords: Raman spectroscopy, non-invasive drug detection, high performance liquid chromatography.
Can environmental exposure to agents like pesticides induce Parkinson’s disease in human dopaminergic neurons?

Sacha Bohler¹, Jos Kleinjans¹

¹Maastricht University, Department of Toxicogenomics, Maastricht, The Netherlands

Parkinson’s disease (PD) is one of the most common neurodegenerative diseases, accompanied by symptoms like tremors, dyskinesia, and mood changes. Even though several mutations have been identified as possible causes for PD, only 10% of PD cases can be attributed to these familial mutations. The remaining 90% is suspected to be related to exogenous environmental factors.

To evaluate the effects of exogenous factors on the development of PD, the human neuroblastoma cell line SH-SY5Y was used. This cell line was differentiated into dopaminergic neurons, the same type of neurons that is involved in PD in the brain. After differentiation, the cells were exposed to various environmental compounds suspected to facilitate the development of PD, and compared to MPP+, a known inducer of PD.

First focus is on Paraquat and Rotenone, two pesticides suspected to facilitate the development of the disease. Dopaminergic neuronal cells were exposed to different concentrations and for different time points, of the chosen molecules, in order to obtain an advanced mechanistic insight into of the molecular aspects.

Initially, PD-like response of the cells was tested by qPCR of genes involved in familial PD, namely SNCA, PINK1, LRRK4 and PARK7. Additionally, also measurement of phenotypical events involved in PD, like ROS, will be evaluated in order to unravel the involvement of oxidative stress in disease progression of PD by environmental agents.

Keywords: Parkinson’s disease, SH-SY5Y, Environmental factors.
The relationship between cerebrovascular disease, Alzheimer’s disease and cognitive decline in individuals with SCI or MCI

Isabelle Bos¹, Stephanie J.B. Vos¹, Vivian Hendrickx¹, Inez Ramakers¹, Pauline Aalten¹, Frans Verhey¹, Pieter Jelle Visser¹,² on behalf of the DESCRIPA and LeARN consortia

¹Alzheimer Center Limburg, Department of Psychiatry and Neuropsychology, School for Mental Health & Neuroscience, Maastricht University, Maastricht, the Netherlands
²Alzheimer Center & Department of Neurology, VU University Medical Center, Amsterdam, the Netherlands

Background: Cerebrovascular disease (CVD) and Alzheimer’s disease (AD) are both associated with cognitive decline and commonly coexist in elderly individuals. To date the relationship between these two pathologies in pre-dementia stages of AD is still unclear. We investigated the association between CVD and AD pathologies and the relation with neurodegeneration and cognitive decline in non-demented patients.

Methods: We included 269 individuals from the Maastricht BBACL, DESCRIPA and LeARN studies with a baseline diagnosis of subjective cognitive impairment (SCI) or mild cognitive impairment (MCI). Subjects were classified as AD positive when CSF amyloid beta (Aβ) 1-42 and tau levels were abnormal. White matter hyperintensities (WMH) were used as a marker of CVD, defined as Fazekas score >2. Four groups were created based on AD status (+/-) and WMH status (+/-). We compared AD/WMH groups on baseline and follow-up characteristics using ANOVA and Chi-Square tests. Associations between AD/WMH groups and change on cognitive measures (global cognition, memory, processing speed and executive functioning) were assessed by slope analyses with linear mixed models. Survival analyses were performed to test the differences between the groups in progression rate to dementia.

Results: We found that both the AD+ groups (AD+ WMH-, AD+ WMH+) as well as the group with only WMH had lower levels of Aβ 1-42, increased medial temporal lobe atrophy (MTA) and higher levels of total tau, compared to the group without any pathology. Abnormality of amyloid and total tau levels was more pronounced in the AD+ groups. Phosphorylated tau was elevated only in the AD+ groups. Concerning cognitive decline, we found that the group with mixed pathology (AD+WMH+) showed more rapid decline in global cognition and memory compared to the group without pathology. The groups with AD pathology had the greatest risk of progression to dementia.

Conclusion: We showed that decreased Aβ 1-42, elevated total tau and MTA are associated with both AD and CVD, however more pronounced in AD. We found phosphorylated tau to be specific for AD. CVD had an influence on cognitive decline and progression to dementia, but was overshadowed by the influence of AD pathology.

Keywords: Cerebrovascular disease, Alzheimer’s disease, biomarkers.
Synthesis, radiosynthesis and preliminary in vitro and in vivo evaluation of fluorinated ceramide trafficking inhibitor (HPA-12) for brain applications

Simone M. Crivelli1, Andreas Paulus2, Jozef Markus3, Matthias Bauwens2, Dusan Berkes3, Mario Losen1, Pilar Martinez-Martinez1

1Maastricht University, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht, the Netherlands
2Department of Nuclear Medicine, MUMC+, Maastricht, the Netherlands
3Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, 81237, Bratislava, Slovak Republic

Ceramides are ubiquitous structural lipids in cellular membranes and also potent regulators of critical biological processes. In the brain, ceramides are abundantly present in different cell types, including neurons and glial, and in the vascular compartment. To guarantee optimal neuronal function, these lipids are tightly regulated. In contrast, ceramide levels are increased in blood and brain tissue of Alzheimer’s disease (AD) patients and proteins controlling ceramide metabolism are abnormally concentrated in AD brains. Since the ceramide transporter protein (CERT) is the only known protein able to transfer ceramide between organelle membranes, the modulation of its function may impact on ceramide accumulation. The ability of CERT to transport ceramide between organelles is conferred by the (StAR)-related lipid transfer (START) domain. CERT inhibitors like (1R,3S)-N-(3-Hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12) are able to bind to the hydrophobic START domain and interfere with ceramide trafficking and may help us to understand the role of ceramide/CERT in AD pathology. Here we first report the synthesis and in vitro properties of HPA-12 radiolabeled with fluorine-18 ([18F]HPA-12) and we present the preliminary in vitro and in vivo positron emission tomography (PET) imaging and biodistribution data. In vitro results demonstrated that the radiosynthesis did not alter the biological properties of HPA-12 since the unlabeled version, [19F]HPA-12, interferes with 5-DMB-ceramide distribution in HEK293 cells and binds to the START domain. [18F]HPA-12, was obtained with a radiochemical yield above 90% and a specific activity of 73 MBq/µmol. The compound was formulated in a PEG400/saline mixture (1:1) after synthesis and showed to have shelf life of 4 hours and to be stable in human blood for 1 hour. PET imaging on gas anesthetized C57Bl6/J wild type mice showed a fast hepatobiliary clearance and a brain uptake on the order of 0.5 standard uptake values (SUV) one hour post injection. Furthermore, biodistribution data showed that after intracardial perfusion radioactivity was still measurable in the brain demonstrating that the [18F]HPA-12 crosses the blood brain barrier and is retained in the brain.
Development and feasibility of Inlife: an online social support platform for dementia caregivers

Alieske E.H. Dam¹, Martin P.J. van Boxtel¹, Frans R.J. Verhey¹ and Marjolein E. de Vugt¹

¹Department of Psychiatry and Neuropsychology/Alzheimer Centre Limburg, School for Mental Health and Neuroscience

Background: Informal caregivers are increasingly involved in dementia care. Online social media interventions might offer a new opportunity to heighten access to social support and enhance positive interaction and openness in dementia care networks.

Objective: This explorative pilot study describes (1) the development of an online social support intervention, and (2) aimed to evaluate the feasibility and required data to assess effectiveness.

Methods: The Medical Research Council (MRC) framework guided the development of the online social support intervention. This is a stepwise approach that integrates potential user views with development and validation of the program content. The program was developed by combining (1) individual caregiver interviews (n=10) (2) focus group sessions with experts and web-designers (n=6), and (3) individual think-aloud test (n=2). Subsequently, a pilot study was conducted (n=23) to examine feasibility and preliminary effectiveness. Online self-report measures were completed at baseline and four follow-up time points.

Results: Following the different steps of the MRC framework resulted in a newly developed social support platform – Inlife. In total, 23 participants completed the Inlife intervention. Although the high amount of low-active Inlife users (17/23, 73%), we demonstrated a good feasibility score of 7.1 (range 1-10). The calendar end timeline were used most frequently and contributed to better care coordination and positive interaction between network members.

Conclusions: The Inlife platform was adapted to limit the amount of low-active users and improve user-friendliness. Recommendations for further treatment adherence are provided. The development according to the MRC-framework and the confirmation of feasibility formed the basis for a future effectiveness study.

Keywords: dementia, informal carers, Internet, social support, psychosocial interventions.
Targeting plasma cells with proteasome inhibitors for treatment of myasthenia gravis

Marina Mané-Damas¹ - Abi Saxena¹ - Gisela Nogales¹ - Maarten Beek¹ - Nienke Van Den Hoogen¹ - Peter Molenaar¹ - Bert Joosten¹ - Nick Willcox² - Pilar Martinez-Martinez¹ - Mario Losen¹

¹Psychiatry and Neurospychology department, Maastricht University, Maastricht, The Netherlands
²Nuffield department of Clinical Neurosciences, Weatherall Institute for Molecular Medicine, University of Oxford, Oxford, United Kingdom

Autoantibodies against the muscle AChR are mainly produced by both short- and long-lived plasma cells, which are resistant to standard immunosuppressive drugs (e.g. glucocorticoids). A novel therapy to eliminate plasma cells is the proteasome inhibitor bortezomib, which is used to treat patients with multiple myeloma (MM, a plasma cell malignancy). Previously, we demonstrated that bortezomib also reduced autoantibody titers in an animal model of MG (Gomez, A. M. J. Immunol. 2011).

The thymus of MG patients is frequently enriched in germinal centers and contains plasma cells that produce autoantibodies in vitro, even after irradiation (which depletes B and T lymphocytes). We studied the in vitro effects of bortezomib in cultured thymus cells from MG patients undergoing therapeutic thymectomy. Treatment with a single dose of bortezomib eliminated plasma cells and thereby blocked the production of IgG, including pathogenic autoantibodies. Ultrastructural signs of apoptosis were detected in plasma cells as early as 8 h after addition of bortezomib; at 24 h, no plasma cells could be detected (Gomez, A. M. J. Immunol. 2014). Finally, we are currently testing in vitro and in vivo second-generation proteasome inhibitors efficient in eliminating autoreactive plasma cells with special focus in investigating their side effects such as peripheral neuropathy.

Keywords: Myasthenia gravis, plasma cells, therapy.
Anti-TPO encephalitis case report: presence of IgG autoantibodies against hippocampal proteins in a case tested negative by antigen-specific assays

Marina Mané-Damas¹ - Carolin Hoffmann¹ - Shenghua Zong¹ - Mario Losen¹ - Jan Damoiseaux² - Suzanne Koudijs³ - Rob Roull³ - Pilar Martinez-Martinez¹

¹Psychiatry and Neuropsychology department, Maastricht University, Maastricht, The Netherlands
²Central Diagnostic Laboratory, Maastricht UMC+, Maastricht, The Netherlands
³Neurology department, Maastricht UMC+, Maastricht, The Netherlands

Anti-TPO encephalitis is characterized by neurological and cognitive impairment. Like other types of encephalitis recently described, the origin of the pathology is based on the presence of autoantibodies, in this case, against thyroid peroxidase (TPO). Recently, antibodies to GABA<sub>A</sub> receptor have been identified as pathogenic antibodies, co-occurring in some cases with GAD65 or TPO antibodies. The presence of both antibodies at the same time may result in misdiagnosis of the patient.

The present case report describes a 12-year old boy, diagnosed with an anti-TPO encephalopathy, with a clinical symptomatology of chronic headache, fatigue and concentration problems. He had circulating anti-TPO antibodies (57-69 IU/mL) and he was also tested negative in a commercial cell-based assay (CBA; Autoimmune Encephalitis Mosaic 6, Euroimmun) for autoimmune reactivity against a spectrum of neuronal surface antigens (NMDAr, AMPA, GABA<sub>B</sub>r, GABA<sub>A</sub>r, Caspr2, LGI1) in serum and cerebrospinal fluid (CSF). Also antibodies to GAD65 were undetectable by ELISA. However, by using an immunohistochemistry assay using 3,3'-diaminobenzidine (DAB) on rat brain, the serum of the patient showed a clear, IgG specific staining pattern in the hippocampus. To unravel the antigen-specificity, we performed fix CBA for the antibodies already examined in the commercial assays, and in addition for GAD67; none of the antigens tested showed reactivity. Since antibody-antigen recognition may be sensitive to conformation, live CBA using non-fixed cells will be performed to test the reactivity. We will also incubate hippocampal and cerebellar cortex neuron primary cell cultures with the serum and the CSF of the patient to confirm the reactivity. Finally, in case all these tests are negative, we will perform an immunoprecipitation assay to identify the potentially novel antigen.

Keywords: encephalitis, autoimmunity, case report.
Autoimmune encephalitis, are we using the right techniques?

Marina Mané-Damas¹ - Carolin Hoffmann¹ - Shenghua Zong¹ - Peter Molenaar¹ – Rob Rouhl² - Jan Damoiseaux³ - Mario Losen¹ - Pilar Martinez-Martinez¹

¹Psychiatry and Neuropsychology department, Maastricht University, Maastricht, The Netherlands
²Neurology department, Maastricht UMC+, Maastricht, The Netherlands
³Central Diagnostic Laboratory, Maastricht UMC+, Maastricht, The Netherlands

Autoimmune encephalitis is a disease with a wide range of symptoms, where patients can suffer from catatonia to pure psychosis. It is well known that infections and autoimmunity are the most prevalent origins of the disorder. Autoantibodies targeting neuronal surface antigens, such as NMDAr, AMPAr, GABAβr, GABAαr, and some proteins associated with voltage gated potassium channel, like Caspr2 and LGI1, have been identified. Diagnosis of these patients is performed routinely in the clinic using commercial assays based on cell based assay (CBA). We have developed in house assays, using rat brain immunohistochemistry (IHC) and CBA, and studied the reactivity of sera from patients suspected of encephalitis (n=63); all sera tested negative by the Euroimmune CBA kit. Here we report some preliminary data where 14.3% (9/63) of the patients showed a reactive pattern in the hippocampus and 2/63 patients, negative for IHC, reacted against GAD67 by CBA. These results warrant further investigation in order to understand which antigen the autoantibodies are recognizing in the patient.

Keywords: autoimmunity, technique, validation.
Angina pectoris, myocardial infarction and risk for cognitive impairment or dementia: a systematic review and meta-analysis

Kay Deckers¹, Syenna HJ Schievink¹, Maria MFRodriuez², Robert J van Oostenbrugge³, Martin PJ van Boxtel¹, Frans RJ Verhey¹, Sebastian Köhler¹

¹ Maastricht University, School for Mental Health and Neuroscience, Alzheimer Centrum Limburg, Maastricht, the Netherlands
² Complexo Universitario de Vigo, Hospital Alvaro Cunqueiro, Departamento de Psiquiatria, Vigo, Spain
³ Maastricht University Medical Center, Department of Neurology, Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands.

Background: Accumulating evidence suggests an association between coronary heart disease and risk for cognitive impairment or dementia, but no study has systematically reviewed this association. Therefore, we summarized the available evidence on the association between coronary heart disease (myocardial infarction, angina pectoris) and risk for cognitive impairment or dementia in a systematic review and meta-analysis.

Methods and Findings: We searched Medline, Embase, PsycINFO, and CINAHL for all publications until 8th January 2016. Articles were included if the fulfilled the inclusion criteria: (1) myocardial infarction, angina pectoris or a combination of both as predictor variable; (2) cognition, cognitive impairment or dementia as outcome; (3) population-based study; (4) prospective (≥1 year follow-up), cross-sectional or case-control study design; (5) ≥100 participants; and (6) aged ≥45 years. Reference lists of publications and secondary literature were hand-searched for possible missing articles. Two reviewers independently screened all abstracts and extracted information from potential relevant full-text articles using a standardized data collection form. Study quality was assessed with the Newcastle-Ottawa Scale. We pooled estimates from the most fully adjusted model using random-effects meta-analysis.

We identified 6,132 abstracts, of which 24 studies were included. Coronary heart disease was associated with increased risk of cognitive impairment or dementia (OR = 1.47, 95%CI 1.26-1.71). Similar significant associations were found in separate meta-analyses of prospective studies for all three individual predictors (myocardial infarction, angina pectoris, and combination of both). In contrast, meta-analyses of cross-sectional and case-control studies were inconclusive. Key limitations include the substantial heterogeneity observed in both cross-sectional and case-control studies, probably related to the number of included studies and differences in methodology across studies.

Conclusions: This meta-analysis supports the evidence from prospective population-based studies that coronary heart disease is associated with increased odds of developing cognitive impairment or dementia. Given the projected worldwide increase in the number of people affected by coronary heart disease and dementia, future studies should focus on understanding underlying causal mechanisms or common pathways, and to implement these findings in future prevention trials.

Keywords: angina pectoris, myocardial infarction, dementia.
Differences in cognitive profile between post-stroke depression and apathy: The CASPER study

Elles Douven¹, Pauline Aalten¹, Julie Staals², Frans RJ Verhey¹, Syenna Schievink¹, Robert J van Oostenbrugge¹,², Sebastian Köhler¹

¹ Department of Psychiatry & Neuropsychology, School for Mental Health and Neuroscience MHeNs, Maastricht University, Alzheimer Center Limburg, Maastricht, The Netherlands.
² Department of Neurology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands

Objective: Apathy and depression are frequent neuropsychiatric symptoms after stroke and are negatively associated with quality of life, long-term prognosis, and cognitive impairment. In the present study, differences in the course of cognitive performance between patients with and without post-stroke depression (PSD) and with and without post-stroke apathy (PSA) were studied.

Methods: The Cognition and Affect After Stroke: A Prospective Evaluation of Risks (CASPER) study included 250 stroke patients, who underwent a neuropsychological and neuropsychiatric assessment three months after stroke (baseline), with follow-up at six and twelve months. A 3T MRI brain scan was conducted at baseline in 186 participants. Linear mixed models with random effects for intercept and slope (time), adjusted for age, gender, and highest level of education were performed.

Results: Of 248 patients assessed at baseline, 97 (39.1%) patients were depressed, whereas only 42 (16.9%) were apathetic. Patients with baseline PSD were more often female than patients without PSD, and patients with baseline PSA had a significantly higher age compared to patients without PSA. On verbal memory, patients with PSD had a slower improvement on immediate recall over time compared to patients without PSD. Patients without PSD had worse recognition compared with patients without PSD at all time points. Information processing speed improved over time in the PSD group, while the no PSD group had a better performance on baseline and remained stable over time. Performance on executive functioning was worse in the no PSD group at baseline and improved over time, whereas patients with PSD showed the opposite pattern. Patients with PSA performed worse compared with patients without PSA on information processing speed and psychomotor speed at all time points.

Conclusions: The present results show a difference in cognitive profile between patients with PSD and PSA. While PSD is associated with a more widespread pattern of cognitive impairment, including verbal memory, executive functioning, psychomotor speed, and information processing speed, PSA seems to be more limited to slowed information processing speed and psychomotor speed.

Keywords: stroke, depression, apathy.
Dairy phantom as a validation for myelin imaging.

Gerhard Drenthen¹, Walter Backes², Jacobus Jansen³.

¹, ², ³ Maastricht University Medical Center, School for Mental Health and Neuroscience, Department of Radiology

Myelin is an electrical insulating substance that surrounds the axons in the brain. It plays a vital part in the correct functioning of the nervous system. Quantifying myelin loss in the brain can provide insight in several neurological diseases, neurodegeneration and brain maturation. In an upcoming longitudinal study, with epileptic children we will determine the myelin content to assess if aberrant maturational development exists in epilepsy. Previous MRI studies have shown that myelin can be indirectly imaged by utilizing the distinct short T2 relaxation time of water bound by myelin sheets (approximately 50ms). Intra-extracellular water has a longer T2 time (approximately 200ms)[¹]. The fraction of myelin water content and total water content represents the myelin content. To find these two components, the non-negative least squares (NNLS) method has widely been applied. However, the result can differ a lot depending on the set of basis functions used in the NNLS. Therefore, we want to validate this method on a multi-exponential phantom. Previously, Jones et al.[²] found that dairy cream is a convenient multi-exponential phantom with a short T2 component that is highly correlated to the fat percentage. Therefore, in this study we will use dairy cream to validate the multi-exponential analysis. A two compartment phantom was prepared consisting of fat-free (0% fat) milk and dairy cream (26% fat). T2 decay curves with 32 echoes where acquired by scanning the phantom on a 3.0T Philips MRI using a multi echo GRASE sequence. Thereafter, the T2 decay curves of both compartments were analyzed using the NNLS with a varying set of 40, 120, 400 and 1000 basis functions each with a different T2 time (logarithmically spaced between 20-1000ms).

It was observed that the fat percentage is highly influenced by the number of basis functions used. Using the set of 400 basis functions provides the best estimation, as the fat percentage in the milk is estimated to be ~1%, and in the dairy cream ~16%. Currently, we work on the optimization of the data acquisition and analysis process.

Keywords: Myelin, non-negative least squares, multi-exponential decay.

References:


Reward Learning and dopamine release in adults with 22q11DS

Esther van Duin¹, Zuzana Kasanova², Jenny Ceccarini², Dennis Hernaus¹, Alexander Heinzel⁴, Felix Mottaghy⁴, Jan Booij³, Inez Myin-Germeyns², Therese van Amelsvoort¹

¹Department of Psychiatry & Psychology, Maastricht University, Maastricht, The Netherlands
²Department of Psychiatry, University Hospital Leuven, Belgium
³Department of Nuclear Medicine, Academic Medical Centre Amsterdam, The Netherlands
⁴Department of Nuclear Medicine, University Hospital RWTH Aachen University, Germany

Background: 22q11.2 deletion syndrome (22q11DS) is a genetic disorder caused by a microdeletion on chromosome 22q11.2 and associated with an increased risk for psychosis. A dysfunctional motivational reward system is thought to be one of the salient features in psychosis caused by abnormal dopamine functioning. It is unknown whether patients with 22q11DS have a dysfunctional reward system.

Methods: This study aims to examine the role of striatal DAergic neuromodulation in reward learning in 22q11DS. The study included 12 adults with 22q11DS (age: 34.6 years, 67% females) and 16 healthy controls (HC, age: 38.1 years, 75% females). A single infusion DA D₂/₃ receptor [¹⁸F]fallypride positron emission tomography (PET) scan was acquired to investigate the DAergic activity in the striatal (putamen, caudate nucleus [CN], ventral striatum [VST]). During the PET scan all subjects performed a version of the learning phase of the Probabilistic Stimulus Selection Task (PSST) for reward learning (RL), modified to deliver social feedback.

Results: IQ-scores were significantly lower in the 22q11DS group (p<.001) compared to HC. The 22q11DS group earned significantly less money (p <.05) and performed worse during the RL-task (p<.05) than HC. However, the learning curve for the RL-task was the same for both groups. IQ-scores were a significant positive predictor for earnings (p<.05) and performance (p <.05), but not for the learning curve. Preliminary PET analyses show that the percentage of active voxels during reward learning is significantly higher in 22q11DS compared to HC in the right caudate nucleus (p <.05).

Conclusions: These preliminary results indicate that people with 22q11DS are capable of reward learning at the same speed as HC, however they are less susceptible for reward than HC because their overall performance during RL is worse than HC. In addition, people with 22q11DS showed different special extent of reward-induced DA release in striatal regions compared to HC. The lower reward sensitivity could be a result of haplo-insufficiency of COMT in 22q11DS and consequently abnormal dopamine functioning.

Keywords: 22q11 Deletion Syndrome, Reward Learning, PET.
A zebrafish model for small-fiber neuropathy

Eijkenboom I1, Gerrits MM1, Almomani R1, Hoeijmakers JG2, Lauria G3, Waxman SG4, Smeets HJM1, Merkies IS5, Faber CG2, Vanoevelen JM1

1Department of Clinical Genetics, Maastricht University Medical Centre, Maastricht, The Netherlands; 2Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands; 3Neurological Institute Carlo Besta, Operative Unit of Neurology, Milan, Italy; 4Department of Neurology, Yale University School of Medicine, New Haven, CT, USA; 5Department of Neurology, Spaarne hospital, Hoofddorp, The Netherlands.

Small-fiber neuropathy (SFN) patients experience a spectrum of painful sensations. Gain-of-function mutations in the voltage-gated sodium channels SCN9A and SCN10A, altering the sensitivity of sensory neurons, have been identified as an underlying genetic cause. To further unravel the genetic aspects of SFN, members of our Consortium (Propane) apply unbiased sequencing approaches to identify genetic variants in a large patient population with SFN. Since the numbers of possible pathogenic mutations detected are expected to be high, a need for medium throughput screening models exists. Therefore our aim is to develop a zebrafish model of SFN which allows us to test the pathogenicity of identified variants; in order to do this we set up and validated a panel of read-out parameters reflecting SFN in zebrafish. Our read-out panel is based on clinical-diagnostic tests and exists of behavioral tests and morphological characteristics. For this we have developed a customized ZebraBox system which allows us to assess and quantify touch-evoked responses and reaction to temperature changes in zebrafish embryos. Validation of this system has been performed using various methods (morpholino-mediated knockdown and a knockout line) to inactivate a homologous voltage-gated sodium channel in the zebrafish, Scn8aa. Importantly, we showed that downregulating scn8aa (knockdown/knock-out) results in a reduced touch response and in a significantly diminished behavioral response to increasing temperatures. Moreover, expressing the pathogenic mutation I228M in the human sodium channel (SCN9A) in zebrafish embryos causes these fish to have aberrant temperature sensitivity. Furthermore, these zebrafish have a decreased density of the small nerve fibers. The next step is to express unknown variants in SCN9A. The combination of these parameters makes the zebrafish a valuable complementary model for SFN. To conclude, we have set up and validated a read-out panel reflecting SFN in the zebrafish. This panel allows us to screen the pathogenicity of variants identified with unbiased sequencing approaches.
A prognostic marker candidate for multiple sclerosis: Switch associated protein 70 antibodies

Ece Erdag¹, Erdem Tuzun², Cem Ismail Kucukali²

¹Maastricht University, Faculty of Health, Medicine and Life Sciences, Department of Neuroscience
²Istanbul University, Faculty of Medicine, Department of Neuroscience

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disease of the central nervous system characterized by white matter inflammation, demyelination, and axonal damage. MS has not any specific prognostic marker yet. Recently, we identified the switch-associated protein 70 (SWAP-70) antibody in the sera of relapsing-remitting MS (RRMS) patients [¹]. This antibody was mostly detected during or shortly after relapse, and its serum levels were inversely correlated with the expanded disability status scale (EDSS) scores of the patients. This study was conducted to identify a biomarker for MS that can be used as a predictor of relapse and disability.

Sera of 26 consecutive RRMS patients were screened for SWAP-70 antibody, which was previously identified by protein macroarray. The serum levels of several cytokines, chemokines and soluble adhesion molecules related to MS attacks were measured by enzyme-linked immunosorbent assay (ELISA). A possible correlation was sought among levels of SWAP-70 antibody, measured humoral factors and disability score.

ELISA studies showed high-titre SWAP-70 antibodies in 16 (61.5%) RRMS sera obtained during the attack period and 9 (34.6%) sera obtained during remission. There was a significant inverse correlation between SWAP-70 antibody levels and EDSSs, CXCL10, soluble VCAM-1, CXCL13 and soluble VLA-4 levels.

Our results confirm that SWAP-70 antibody levels are elevated during MS attacks. Moreover, the inverse correlations between SWAP-70 antibody levels and EDSS scores and cytokine/chemokine levels suggest that SWAP-70 is involved in the MS attack pathogenesis. Overall, our findings suggest that SWAP-70 antibodies can potentially be utilized as relapse and prognosis biomarkers in MS [²,³].

Keywords: SWAP70, multiple sclerosis, prognosis

References:


Spinal cord stimulation of the L5 dorsal root ganglion for the treatment of experimental painful diabetic polyneuropathy

Glenn Franken1,2, Eva Koetsier3, Jacques Debets4, Wiel Honig2, Bert Joosten1, Paolo Maino3

1Department of Anesthesiology and Pain Management, University Pain Clinic Maastricht (UPCM), Maastricht, The Netherlands
2Department of Translational Neuroscience, School for Mental Health and Neuroscience (MHeNS), Maastricht, The Netherlands
3Ospedale Regionale di Lugano, Centro per la terapia del dolore, Via Capelli, 6962, Viganello
4Muroidean Facility, School for Cardiovascular Diseases (CARIM), Maastricht, The Netherlands

Diabetes is a worldwide epidemic which affects approximately 300 million people worldwide. With a prevalence of 10-26% of all patients, painful diabetic polyneuropathy (PDP) is one of the most common long-term complications of diabetes. PDP is a disorder of the peripheral nervous system which affects thinly myelinated Aδ, and unmyelinated, nociceptive C-nerve fibers, and manifests as burning, sharp or shooting pain in the lower limbs. The fact that PDP can be debilitating, in combination with the fact that effectiveness of conventional pharmacological drugs are limited, creates an urgent need for novel interventions. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) has recently emerged as a new neuromodulation modality in the treatment of pain. DRG-SCS was developed to improve upon the effectiveness of SCS of the dorsal column. The latter is limited due to some patients having inadequate pain relief, or due to inexact anatomic specificity in terms of pain-paraesthesia overlap in axial locations such as the lower back, and extremities such as the feet. In this regard, DRG-SCS is hypothesized to achieve better pain-paraesthesia overlap of difficult-to-reach areas because of selective stimulation of specific dermatomes, making DRG-SCS a promising intervention for PDP. The goal of this study was to develop the technique of experimental DRG-SCS and gain first insight in the effect of L5 DRG-SCS in female PDP Sprague-Dawley rats. Diabetes was induced by intraperitoneal injection of Streptozotocine. Animals were then tested for mechanical hypersensitivity using Von Frey hindlimb withdrawal testing at baseline, and once a week for 4 weeks following Streptozotocine injection, for the purpose of selecting animals that developed PDP. Subsequently, animals were implanted with a monopolar DRG-SCS electrode at L5 and stimulated for 30 minutes at 2 and 3 days following implantation. Immediately before stimulation, 15 and 30 minutes during stimulation, and 15 and 30 minutes after stimulation, animals were tested for mechanical hypersensitivity. As the technique is now operational, first data indicate successful implantation and successful reduction in mechanical hypersensitivity upon DRG-SCS in PDP rats. Further analysis in more animals is needed to substantiate the pain relieving effect of DRG-SCS in experimental PDP.

Keywords: Dorsal root ganglion spinal cord stimulation, painful diabetic polyneuropathy, neuromodulation
Blood-brain barrier disruption in the aetiology of intracerebral haemorrhage – a systematic literature review

Freeze WM¹², Jacobs HI¹, van Oostenbrugge R³, Backes WH², Verhey FR¹, and Klijn CJM⁴.

¹Department of Psychiatry and Neuropsychology, Maastricht University, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht, the Netherlands.
²Department of Radiology & Nuclear Medicine, Maastricht University, School for Mental Health and Neuroscience, Maastricht, the Netherlands.
³Department of Neurology, Maastricht University Medical Center, School for Mental Health and Neuroscience, Maastricht, the Netherlands.
⁴Department of Neurology, Donders Institute for Brain Cognition and Behaviour, Center for Neuroscience, Radboud University Medical Center, Nijmegen, the Netherlands.

Objective: The pathophysiological processes underlying spontaneous intracerebral haemorrhage (ICH) and cerebral microbleeds (CMBs) are not completely understood. Cerebral amyloid angiopathy (CAA) and hypertensive vasculopathy (HV) are distinct types of cerebral small vessel disease (cSVD) thought to be responsible for lobar and deep ICH/CMBs respectively. Blood-brain barrier (BBB) disruption may be a common mechanism involved in both types of cSVD. We systematically reviewed the literature for studies reporting on BBB disruption in the aetiology of cSVD-based ICH.

Methods: We searched Medline 1946-2016 and Embase 1974-2016 for studies reporting on BBB disruption associated with ICH or MBs, distal from the ICH or preceding the ICH in time.

Results: We identified 2460 unique papers of which 27 were eligible for inclusion. Fifteen studies were carried out in human samples and twelve studies examined animals. Eleven studies assessed BBB abnormalities in relation to ICH. Two out of three studies that examined ICH with HV as underlying cSVD found evidence of BBB disruption, and three out of four studies examining ICH with CAA found evidence of BBB disruption. Four studies did not differentiate between hypertension- and CAA-related cSVD; in all four, the authors found evidence of BBB disruption in ICH. The remaining sixteen studies addressed the relationship between CMBs and BBB disruption. All four studies on HV-related CMBs found evidence of BBB disruption. Among ten studies that assessed CAA-related CMBs, seven studies found evidence of BBB disruption. Two studies did not specify the type of cSVD and found evidence of BBB disruption related to CMBs.

Conclusions: ICH-related BBB disruption was apparent in the majority (22 out of 27) of the included studies, and evident in both CAA- and HV-related ICH. Studies were heterogeneous in nature. Whether supporting BBB integrity may be a potential target in developing prevention strategies for cSVD-based spontaneous ICH, deserves further investigation.

Keywords: Intracerebral haemorrhage, blood-brain barrier, cerebral small vessel disease.
Intravenous immunoglobulin therapy for small fiber neuropathy

Bianca T.A. de Greef¹, M. Geerts¹, Janneke G.J. Hoeijmakers¹, Catharina G. Faber¹, Ingemar S.J. Merkies¹,².

¹Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands.
²Department of Neurology, St. Elisabeth Hospital, Willemstad, Curaçao.

Small fiber neuropathy (SFN) is a condition that predominantly affects the thinly myelinated Aδ-fibers and unmyelinated C-fibers, and often leads to severe neuropathic pain. The currently available neuropathic pain medication does not relieve pain substantially. Several conditions are associated with SFN, but in a large proportion of patients no underlying cause is found. Immunological mechanisms may play a causal role. Some case studies show a beneficial effect of intravenous immunoglobulin (IVIg) on neuropathic pain in patients with SFN and an immunological disease. To date no randomized controlled study with IVIg in patients with SFN has been performed. This study is a randomized, placebo-controlled, double-blind study in a cohort of patients with a skin-biopsy proven idiopathic SFN. Sixty patients will be included in the study and randomized to receive either IVIg or placebo (saline 0.9%). The first treatment will start with a loading dose of 2 g/kg body weight in 2 consecutive days, followed by a maintenance dose of 1 g/kg body weight given 3 times at 3 weeks interval. The primary objective is to evaluate the efficacy of IVIg treatment compared to placebo on pain alleviation. A responder is defined as ≥ 1-point Pain Intensity Numerical Rating Scale (PI-NRS) improvement on the mean weekly peak pain relative to baseline. The secondary outcomes are pain intensity, pain qualities, other SFN-related complaints, daily functioning, and quality of life. Furthermore safety assessments will be performed like adverse events, vital signs and laboratory findings. Responders during the 12 weeks treatment period will be followed during a 3-month extension phase. The study has been approved by the Maastricht University Medical Center medical ethics committee, started in August 2016 and is supported by the Grifols Investigator-Sponsored Research Program. Its design will be presented.

Keywords: small fiber neuropathy, intravenous immunoglobulin, therapy.

Angélique AA Gruters¹, Inez HGB Ramakers¹, Roy PC Kessels² Marjolein E de Vugt¹, Frans RJ Verhey¹

¹Department of Psychiatry & Neuropsychology, Alzheimer Centre Limburg, School of Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, the Netherlands
²Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands.

Background: Memory clinics (MCs) are characterized by multidisciplinary teams and have become globally accepted as useful settings for early diagnosis and treatment of memory disorders, including dementia. To gain more insight in the development and efficacy of these clinics, a national survey was conducted in 1998, 2004 and 2009 in the Netherlands. The results showed an increase in number and capacity of MCs from 12 in 1998 to 63 in 2009. Furthermore, when compared to the situation in 1998 MCs had less attention for university-based research, more collaborations with regional institutions and conducted more neuropsychological assessments. It was noteworthy that although dementia was still the most common syndromal diagnosis, more patients were diagnosed with mild memory disorders. The present situation however has been subject to change. Since 2009 new MCs have started and more emphasis was placed on collaborations with regional and integrated care. The guideline “Diagnostics and Treatment in Dementia” was revised in 2014. In this guideline the diagnostic value of neuropsychological assessment was highlighted. In general, the contribution of this assessment method to clinical practice has been acknowledged. As a result of these changes it is important that the survey is updated to have a better understanding of the current situation in MCs.

Aim: The aim of this study is to determine the number, characteristics and working methods of MCs in the Netherlands in 2015. The results will be compared to the surveys conducted in 1998, 2004 and 2009 to investigate changes. Furthermore, we will focus on collaborations, neuropsychological assessments and procedures in MCs.

Methods: The survey from 2009 was revised by an expert group, hence making it representative and relevant for the current situation. It concerns questions about organisation, collaboration, patient characteristics, referrals, diagnostics and additional assessments. The survey will be sent out to all operational MCs in the Netherlands at the end of October. A second survey, about neuropsychological assessment, will be sent to neuropsychologists involved in all operational MCs. First results are expected around January 2017.

Keywords: memory clinics; neuropsychological assessments; early diagnosis of dementia.
Electrophysiological effects of the PDE4 inhibitor roflumilast on the tri-phasic response of the substantia nigra pars reticulata

Pim Heckman¹,², Arjan Blokland², Judith Schweimer³, Trevor Sharp³, Peter Magill⁴, Jos Prickaerts¹

¹Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, 6200 MD Maastricht, the Netherlands  
²Department of Neuropsychology and Psychopharmacology, Maastricht University, 6200 MD Maastricht, the Netherlands  
³Department of Pharmacology, University of Oxford, Mansfield Road, Oxford OX1 3QT, United Kingdom  
⁴Medical Research Council Brain Network Dynamics Unit, Department of Pharmacology, University of Oxford, Oxford OX1 3QT, United Kingdom

The fronto-striatal circuits constitute the neurobiological basis for several neuropsychiatric disorders, including Parkinson’s disease, Huntington’s disease, schizophrenia, attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). Glutamatergic and GABAergic signaling within the fronto-striatal circuits as well as their dopaminergic modulation are mediated by cyclic nucleotides and therefore controlled by phosphodiesterases (PDEs). Multiple PDEs with different substrate specificities and subcellular localization are expressed in the fronto-striatal circuits, including the PDE4 subfamily. The functional roles of PDE4 are extensively studied in relation to fronto-striatal circuitry expression. However, the main site of action of PDE4 inhibition is inferred from biochemical analyses of striatal cAMP/PKA effectors, behavioral phenotypes of PDE4 knockout mice and the observation of effects of PDE4 inhibitors (PDE4-I) on dopamine-related behavior. Therefore, in the current study we tried to more precisely determine the main site of action within the basal ganglia hyperdirect, direct and indirect pathways through in vivo electrophysiological recordings by means of the tri-phasic response in the substantia nigra pars reticulata (SNr). We show results of acute administration of the PDE4-I roflumilast on the tri-phasic response of the SNr.

Keywords: roflumilast, tri-phasic response, in vivo basal ganglia electrophysiology.
Analyzing neuronal auto-antibodies in psychotic disorders

Carolin Hoffmann1, Shenghua Zong1, Marina Damas1, Mario Losen1, Maarten J Titulaer2, Cem İsmail Küçükali3, Erdem Tüzün3, Nazlı Yalçınkaya3, Andrei Szoke4,5, Marion Leboyer4,5, Marc De Hert6, Nico J M van Beerven7, Emiliano González-Vioque8, Celso Arango8, Bart P Rutten1, Jim van Os1, Pilar Martinez-Martinez1

1Department of Psychiatry and Psychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands; 2Department of Neurology, Erasmus Medical Center, Rotterdam, the Netherlands; 3Department of Neuroscience, Institute for Experimental Medical Research (DETAE), Istanbul University, Istanbul, Turkey; 4Pôle de psychiatrie, Hôpital Henri Mondor – Albert Chenevier – Assistance publique – Hôpitaux de Paris, Université Paris-Est Créteil, Créteil, France; 5INSERM U955, Equipe 15 Psychiatrie Génétique, Créteil, France; 6University Psychiatric Centre Catholic University Leuven, Campus Kortenberg, Kortenberg, Belgium; 7Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands; 8Child and Adolescent Psychiatry Department, Hospital General Universitario, School of Medicine, Gregorio Marañón Universidad Complutense, IISGM, CIBERSAM. Madrid, Spain.

Auto-antibodies against a variety of neuronal antigens (such as N-methyl-D-aspartate receptor, Leucine-Rich, Glioma Inactivated 1, contactin-associated protein-like 2, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and more) are present in various central nervous system (CNS) excitability disorders. In recent years an increasing number of studies address the question whether these type of antibodies are also seen in a subgroup of patients with psychotic disorders. We aimed to identify the presence of neuronal auto-antibodies in sera of patients with psychotic disorders and controls. We analyzed 631 sera from psychotic diseases and 238 healthy controls on rat brain immunohistochemistry. To verify the results, we also screened 230 psychotic disorder patients and 293 controls using a cell based assay (CBA) for NDMAr and 120 schizophrenia patient sera were additionally screened for the presence of VGKC complex autoantibodies using radio immuno assay (RIA) from DLD Diagnostika GmbH. Sera tested positive by RIA were retested with rat brain immunohistochemistry (IHC) and CBA of transfected HEK293 cells for the VGKC complex proteins leucine-rich glioma inactivated-1 (LGI-1) and contactin-associated protein-like 2 (CASPR2). In our preliminary results 78 out of 631 (12.4 %) of psychotic patients and 19 out of 238 (8 %) controls showed a positive result (hippocampal staining). The specific antigens of these positive IHC results remain to be confirmed. Because neuronal autoantibodies are also prevalent in the cohort of healthy controls it is important to determine whether the specific antigens in the cohorts differ. In the VGKC complex RIA, 2 patients were positive and 5 inconclusive for VGKC complex autoantibodies when tested by RIA but none could be confirmed as positive on CBA or rat brain IHC. Our results add on to growing evidence indicating an increased prevalence of neuronal auto-antibodies in psychotic disorders and are urging for studies to investigate the pathological role of auto-antibodies in these conditions.

Keywords: psychotic disorder, autoantibodies, immunohistochemistry.
The Vitamin D analogue Bxl-628 alters excitation contraction coupling in the isolated bladder in aged wildtype mice differently compared to bladders from age-matched transgenic Alzheimer’s disease mice

Hohnen R¹, Stouthandel MEJ¹, den Hartog GJM², Meriaux C¹, van Koeveringe GA¹,³

¹Department of Neuroscience, Maastricht University,
²Department of Pharmacology and Toxicology, Maastricht University,
³Department of Urology, Maastricht University Medical Center

Hypothesis / aims of study: This is the first study to provide insights into the mechanisms involved in dysregulation of the urinary bladder in a transgenic model of Alzheimer’s disease (AD). One of the most debilitating autonomic dysfunctions related to AD is urinary incontinence. Transgenic AD mice show behavioural characteristics of Alzheimer’s disease, altered micturition behaviour, morphological changes within the bladder (1), as well as altered contractile responses to KCl and muscarinic stimulation in an ex vivo setting (2). Vitamin D could improve bladder function by influence of different signalling systems. We therefore hypothesize that incubation with a Vitamin D3 analogue counteracts a potential misbalance of signalling systems within the dysfunctional AD.

Study design, materials and methods: Bladders and the proximal urethra from ten mice of the transgenic Alzheimer’s disease model APPswe/PS1ΔE9 and 10 wildtype (WT), aged 91-93 weeks, were dissected, transurethrally catheterised and transferred to a heated organ bath (20 mL, 37 °C) containing continuously aerated Krebs’ solution. Subsequently, the bladder was filled to 90 μl with a filling rate of 0.2 ml/hour. After a resting period, washing steps were performed, followed by a sequence of electrical and pharmacological stimulations. After a first sequence of stimulations, bladders were incubated for 10 minutes with the vitamin D3 analogue Bxl-628. During incubation with Bxl-628 a second sequence of stimulations was given.

Results: In bladders originating from WT mice, incubation with the Vitamin D analogue significantly improved contraction development after both, pharmacological and electrical stimulation (p-values). This improvement was, except for one stimulation parameter, not seen in bladder originating from transgenic AD mice. Changes of the amplitude were only detected after one type of pharmacological stimulation.
Conclusion: We identified a couple of signalling systems which might be of importance in bladder excitation contraction coupling associated with AD, as these systems act downstream of the vitamin D receptor, such as the Rho A/Rho kinase system and calcium signalling in general. Future research should focus on identifying the role of potential amyloid-beta aggregation within the bladder wall to elucidate which interaction with specific proteins or ion-channels takes place, thereby influencing bladder function.
Painful procedures during neonatal development: long-term consequences on spinal nociceptive processing

N.J. van den Hoogen\textsuperscript{1,2}, C.H.T. Kwok\textsuperscript{3}, M. Fitzgerald\textsuperscript{3}, J. Patijn\textsuperscript{1}, D. Tibboel\textsuperscript{4}, E.A. Joosten\textsuperscript{1,2}

\textsuperscript{1}Department of Anaesthesiology, Pain Management and Research Centre, Maastricht University Medical Centre
\textsuperscript{2}Department of Translational Neuroscience, School of Mental Health and Neuroscience, Maastricht University
\textsuperscript{3}Department of Neuroscience, Physiology and Pharmacology, University College London, London
\textsuperscript{4}Intensive Care and Department of Paediatric Surgery, Erasmus MC-Sophia, Rotterdam

Introduction: In the Neonatal intensive care unit (NICU), new-born babies routinely undergo painful procedures, approximately 10-14 times per day. Clinical and experimental data suggests that noxious stimulation at critical stages of development has long-term consequences on nociceptive processing in later life. Here, we use an experimental model of repeated procedural pain closely mimicking the clinical situation in the NICU. The aim of this study is to elucidate the long-term consequences of repetitive needle pricking in neonatal rats upon the activity of nociceptive circuits in central nervous system.

Methods: Neonatal rats received four needle pricks per day in the left hind-paw from postnatal day 0 to 7 as a model of procedural pain in infancy (n=13). Control pups were handled in the same way but did not receive pricks (n=11), or were left undisturbed (n=17). At the age of 8 weeks, animals received an ipsilateral hind-paw incision as a model for post-operative pain in adulthood. The effect of neonatal injury on adult pain sensitivity was quantified by in vivo measurements of excitability of spinal cord dorsal horn neurons in extracellular single unit recordings. Under isoflurane anaesthesia, wide dynamic range neurons (n=206) were located and recorded in the lumbar dorsal horn, with a receptive field in the plantar surface of the ipsilateral hind paw. Potentials were evoked using different stimuli; touch, pinch and Von Frey filaments.

Results: In adulthood, spinal cord dorsal horn neurons of neonatal needle prick animals showed increased responses to touch and noxious stimuli, as well as enlargement of receptive field sizes. Following paw incision in adulthood, enhanced responses were observed up to 5 days.

Conclusion: Repeated procedural pain during early life primes spinal nociceptive circuits and results in enhanced activity in spinal cord dorsal horn neurons to different stimuli.

Keywords: Neonatal pain, single unit electrophysiology, postoperative pain.
Cellular localization of the expression of glaucoma risk genes

Wouter Hubens\textsuperscript{1,2}, Carrol Webers\textsuperscript{1}, Theo Gorgels\textsuperscript{1}

\textsuperscript{1}University Eye Clinic Maastricht, Maastricht University Medical Centre+, Maastricht, The Netherlands
\textsuperscript{2}School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands

Introduction: Glaucoma, a neurodegenerative disease of the optic nerve, is one of the most prevalent causes of blindness worldwide. The most important and modifiable risk factor for developing glaucoma is a high intraocular pressure (IOP). IOP is determined by a balance between production and drainage of aqueous humor (AH). As with other neurodegenerative diseases there is a strong genetic involvement. Up to date over 150 genes have been associated with an increased risk of developing glaucoma. For most of these genes their cellular localization and expression within the eye have not been established. In order to increase our knowledge of glaucoma pathophysiology we aim to set up in situ hybridization in order to localize the expression of glaucoma risk genes.

Methods: C57BL/6 mice of 2 months old were anesthetized with CO\textsubscript{2} and sacrificed by cervical dislocation. Eyes were dissected out and fixed in 4\% PFA for 16 hours prior to paraffin embedding. A commercially available method of in-situ hybridization was utilized. We used three probes, a positive control probe for RNA polymerase II, a negative control probe for bacterial DapB and one target probe for the glaucoma risk gene transforming growth factor beta receptor 3 (Tgfbr3).

Results: Reaction conditions were optimized using the positive and negative control probes. Signal was highly specific. Staining for Tgfbr3 was distributed widely in the eye. Staining occurred in all three layers of the cornea (epithelium, stroma and endothelium), lens anterior epithelium, trabecular meshwork, ciliary processes, retinal ganglion cells and the inner nuclear layer. No Tgfbr3 signal was seen in the lens fiber nuclei, outer nuclear layer and photoreceptors.

Discussion: Positive signal for Tgfbr3 was observed in three important glaucoma associated tissues: trabecular meshwork, ciliary process and retinal ganglion cells. This may indicate that this gene is involved in glaucoma pathology in these cell types. The employed in-situ hybridization method is promising however further optimization may be required for localization of gene expression in human post mortem tissue. Once we established this, we will focus on the cellular localization of gene expression of glaucoma associated risk genes suspected to be involved in AH metabolism.

Keywords: Glaucoma, in-situ hybridization, cellular localization.
Untimely access to care in community dwelling people with dementia: does it affect costs and quality of life?

Niels Janssena, Ron Handelsab, Anders Skoldunerb, Frans Verheyaa & Anders Wimoab, & Actifcare consortium

aMaastricht University, Maastricht, Netherlands
bKarolinska Institutet, Stockholm, Sweden

BACKGROUND: Timing of formal home and daycare services is important as this could reduce nursing home placement and improve quality of life. No studies have examined the consequences in terms of costs and quality of life of untimely access to formal care in community dwelling people with dementia.

OBJECTIVE: To examine consequences of untimely access to care in terms of costs and quality of life in community dwelling people with dementia.

METHODS: This explorative study is part of the ACTIFCARE study, a longitudinal cohort study in which 453 community dwelling people with dementia in 8 EU countries were followed for one year. Untimely access to care was operationalized as having an unmet need for care (e.g. self-care) using the Camberwell Assessment of Needs for Elderly instrument (CANE); an instrument designed to assess needs of older people with mental disorders, comprising 24 items. A backward mixed model was used to identify significant needs related with total mean costs and quality of life, while controlling for demographic and clinical confounders. Costs were log transformed using \( \ln(\text{costs} + 10) \).

PRELIMINARY RESULTS: Having an unmet need on memory was significantly related with lower total costs (€4.307) compared to having a met need. Having an unmet need on mobility/falls, drugs or abuse/neglect was associated with significantly lower quality of life, compared to having a met need.

CONCLUSION: Preliminary evidence suggest services and interventions could focus on preventing unmet needs on mobility, drugs and abuse to improve quality of life.

Keywords: access to care, health economics, dementia.
Fecal incontinence treated by sacral neuromodulation: world’s largest single center study

P.T. Janssen¹, S.Z. Kuiper¹, L.P. Stassen¹, Y. Temel², N.D. Bouvy¹, S.O. Breukink¹, J. Melenhorst¹

¹Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands
²Department of Neurosurgery and translational Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands

Aim: Long-term results of large patient cohorts with fecal incontinence (FI) treated by sacral neuromodulation (SNM) are limited. This study shows the long-term results of SNM for FI of the world’s largest single high-volume center.

Methods: All patients treated with SNM for FI were evaluated. Primary outcome was a reduction in episodes of FI. Decrease was objectified by a 3-week bowel-habit-diary. Quality-of-life was assessed using the Short-Form 36, Fecal Incontinence Quality of Life Score and the Vaizey-score. Results were analyzed according to intention-to-treat and per-protocol analysis.

Results: 374 patients were included for SNM-screening and 325 patients (ITT, 86.9%) received permanent SNM. Mean age was 56.5 (17-82) years. SNM remained beneficial in 197 patients (ITT, 52.7%) after a mean follow-up of 7 years (3.0-183.4 months). Episodes of fecal loss per 3 weeks decreased from 16.1(3.0-107.0) to 3.0 (0.0-24.0) after SNM (p<0.001). This decrease was maintained up to 15 years of follow-up (p<0.001). Quality-of-life did not differ from the Dutch population however, 103 patients had a Vaizey score >6, indicating major incontinence (PP, 31.7%; ITT 27.5%).

Conclusion: In 52.7% (ITT) of the patients with fecal incontinence long term efficacy was achieved. Quality-of-life of patients with SNM for FI was nog significantly different from the Dutch population.
Factors associated with the utilization and non-utilization of formal care services in Europe

Liselot, Kerpershoek1,2, Marjolein de Vugt2, Claire Wolfs2, Hannah Jelley3, Martin Orrel4, Bob Woods3, Astrid Stephan5, Anja Bieber5, Gabriele Meyer5, Knut Engedal6, Geir Selbaek6, Ron Handels1,7, Anders Wimo7, Louise Hopper8, Kate Irving8, Maria Marques9, Manuel Gonçalves-Pereira9, Elisa Portolani10, Orazio Zanetti10, Frans Verhey2 and the Actifcare Consortium

2Maastricht University, Maastricht, Netherlands. 3Bangor University, Bangor, UK. 4UCL, London, UK. 5Martin-Luther University Halle-Wittenberg, Halle, Germany. 6Oslo University Hospital, Oslo, Norway. 7Karolinska Institutet, Solna, Sweden. 8Dublin City University, Dublin, Ireland. 9CEDOC, Nova Medical School | Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal. 10Alzheimer’s Research Unit-Memory Clinic, IRCCS “Centro S.Giovanni di Dio, Brescia, Italy.

Introduction: Previous studies have shown that one in three carers of people with dementia are not using formal care services. The decision to initiate formal care is complex and is influenced by many factors, such as characteristics of the person with dementia and carer, available resources, national policies, and care standards. There are several studies into the factors that influence access to formal care. The Anderson Behavioral Model of Use of Health Service describes predisposing and enabling variables in relation to needs and service use, which might explain the potential inequity of access to and utilization of services. In the Actifcare study (Access to Timely Formal Care) we investigate which predisposing, enabling and need variables are associated with formal care use.

Methods: In a longitudinal cohort study conducted in eight European countries 453 people with dementia and informal carers are assessed three times in 1 year (baseline, 6 and 12 months). In this year we closely monitor the process of finding access to formal care. Data on service use, quality of life and needs is collected. We will investigate the association between several predictors (disease severity, demographics, personality traits, informal care situation, (un)met needs) and service use.

Results: We are currently conducting the analyses. Results will be available soon and presented at the research day.

Keywords: Dementia, Formal Care, Service use.
Investigating the use of experience sampling method and mood networks in a n=1 study of a bipolar patient

Elles Revenich¹, Christian Jacobs¹, Aimée Voigt¹, Narcis Serafras¹, Manon Wiersma¹, Daniël Kreiter¹, Marjan Drukker², Maarten Bak²

¹Honours student FHML
²Afdeling Psychiatrie en Neuropsychologie, School for Mental Health and Neuroscience MHeNS, Maastricht University Medical Centre.

Background: Bipolar Disorder (BD) is characterized by manic and depressive episodes. Using longitudinal data of a single person (Mrs Madison) can provide insight into the characteristics of those episodes and this insight can be used for treatment of a broader group of patients with this disorder.

Aim: Firstly, we aim to identify if the a priori selected mental states co-occur and co-vary. Secondly, to study whether the strength of connections between mental states depend on emotional highs and lows in BD. Thirdly, to detect differences between the objective observations and the subjective experiences of the mental states.

Method: Single-person research (n=1) was conducted using Experience Sampling Method (ESM). Mrs Madison received questionnaires at 10 random moments a day to report on the nature and quality of experiences and mood. This was done 7 days a week over a period of 3 months. Linear regression analyses were performed using data stratified by hypomanic and depressive episode. Dependent variables were an a priori selected set of variables consisting of: anxiety, down, cheerful, satisfied, tiredness and lonely. Independent variables were these same symptoms at one random moment earlier at the same day (lag). Regression coefficients were presented in network graphs containing nodes which each represent a variable.

Results: There was a clear distinction between the hypomonic and depressive period and mood fluctuated strongly over time. However, patterns of associations both differ and resemble one another regarding the hypomanic and depressive phases. Whereas the variable down was central in both networks, satisfied was of a stronger presence in the hypomonic network.

Conclusion: There were some differences in networks between the hypomonic and depressive phases. A psychiatrist should be aware that a patient can experience depressive symptoms during a hypomonic or even a manic episode, at first sight masked by feelings of satisfaction or other symptoms pertaining to mania. In the case of Ms Madison, satisfied showed to be the variable most causing a difference between the depressive and hypomonic phases. This plights for the notion that depression is not due to increase in negative affect but rather a decrease in positive affect.
Behavioral pattern separation and its link to the neural mechanisms of fear generalization

Iris Lange\textsuperscript{1a}, Liesbet Goossens\textsuperscript{a}, Stijn Michielse\textsuperscript{a}, Jindra Bakker\textsuperscript{a}, Jim van Os\textsuperscript{a,b}, Therese van Amelsvoort\textsuperscript{a}, Koen Schruers\textsuperscript{a,c}

\textsuperscript{a}Department of Psychiatry and Psychology, School of Mental Health and Neuroscience, EURON, Maastricht University Medical Centre, Maastricht, the Netherlands
\textsuperscript{b}King’s College London, King’s Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, England
\textsuperscript{c}Faculty of Psychology, Center for Experimental and Learning Psychology, University of Leuven, Leuven, Belgium

Background: Fear overgeneralization is a prominent feature of anxiety disorders and post-traumatic stress disorder. These disorders are characterized by reduced threat-safety discrimination, resulting in exaggerated fear responses to harmless stimuli that bear perceptual resemblance to disorder-relevant threat stimuli. Pattern separation, a hippocampal-dependent process, is critical for stimulus discrimination; it transforms similar experiences or events into non-overlapping representations. The current study is the first in humans to investigate the extent to which fear generalization relies on behavioral pattern separation abilities.

Methods: Forty-six healthy volunteers aged 16-25 completed a behavioral task taxing pattern separation, and a neuroimaging fear conditioning and generalization paradigm including 7 rings/rectangles increasing in size. The smallest or largest rings/rectangles served as the conditioned threat (CS\textsuperscript{+}) or safety stimuli (CS\textsuperscript{-}), and the intermediate circles/rectangles as generalization stimuli (GS). Fear scores, shock expectancy, and blood-oxygen-level-dependent (BOLD) responses were measured, and generalization gradients of these measures were obtained.

Results: Analyses revealed an association between lower behavioral pattern separation performance and increased generalization in shock expectancy scores. Furthermore, lower behavioral pattern separation was associated with diminished recruitment of the subcallosal cortex during GS presentation. This region showed functional connectivity with the orbitofrontal cortex and ventromedial prefrontal cortex.

Conclusions: Together, the data provide novel experimental evidence that pattern separation may serve as an underlying mechanism for fear generalization. Furthermore, the results imply that pattern separation drives fear inhibition processes in frontal regions. Deficient pattern separation may be critical in overgeneralization and therefore contribute to the pathophysiology of anxiety disorders and post-traumatic stress disorder.

Keywords: Behavioral pattern separation, fear generalization, fMRI.
The Mechanical Conflict-Avoidance Test in a rat model of neuropathic pain: assessment of cognitive and motivational aspects

Koen Meuwissen1,2, Wiel Honig2, Denise Hermes2, Dr. Sander MJ van Kuijk1, Prof. Dr. Bert Joosten1

1Department of Anesthesiology, Pain Management and Research Centre, Maastricht University Medical Centre
2Department of Translational Neuroscience, School of Mental Health and Neuroscience, Maastricht University

The Mechanical Conflict-Avoidance System (MCAS) addresses cognitive and motivational aspects of pain, elements often underscored by reflex-based preclinical pain tests. The animal is placed in a brightly lit compartment, and needs to cross an array of nociceptive probes in order to get to a, innately preferred, dark area. The latency to escape the light reflects the animal’s cognitive decision to either endure the bright light, or cross the probes. The motivational aspect is reflected by the crossing latency, which shows the attitude towards the noxious stimuli. The present study was performed to examine whether the MCAS is a valid method for the evaluation of neuropathic pain in rats. Naïve rats (n=26) were trained and tested on the MCAS, after which they received either a partial ligation of the sciatic nerve (PSNL) for the induction of neuropathic pain (n=18), or a sham-PSNL operation (n=8). Rats with tactile hypersensitivity to von Frey monofilaments (n = 17), and sham-PSNL animals underwent a second testing period on the MCAS to assess the effect of PSNL on MCAS measurements. Latency to escape the light compartment and time spent on the probes was evaluated at varying probe heights (0, 0.5, 1, 2, 3, 4, and 5 mm). Escape Latency increased as a function of probe height in Pre-PSNL, Sham and PSNL rats (p<0.001). At 4mm probe height PSNL rats showed significantly higher escape latencies, compared to Sham-PSNL rats (p=0.005). The Crossing Latency increased as a function of probe height in all three groups (p<0.001). The groups did not differ significantly at any of the probe heights, likely due to a large standard deviation observed in the PSNL-group at 3, 4, and 5 mm probe height. Based on video-recorded and observed behavior during testing, we were able to sub divide the PSNL-group into a Fast (p=0.025 vs sham) and Slow Crossing group (p=0.049 vs sham). Contrarily, von Frey assessment did not indicate signs of heterogeneity in the PSNL-group. We conclude that the MCAS is a valid method to assess behavioral signs of neuropathic pain, induced by PSNL. Furthermore, the MCAS was able to reveal two subgroups in the PSNL-group, unrecognized by reflex-based von Frey measurements.

Keywords: Mechanical Conflict-Avoidance System, Neuropathic Pain, Reflex-Based Preclinical Pain Test.
Tryptophan depletion in Parkinson’s disease patients treated with deep brain stimulation of the subthalamic nucleus: effects on mood and motor functions. Study design

Anne Mulders¹, Albert Leentjens², Yasin Temel¹

Departments of ¹Neurosurgery, ²Psychiatry and Neuropsychology, Maastricht University Medical Center, Maastricht, the Netherlands

Background: While deep brain stimulation of the subthalamic nucleus (STN DBS) is known to improve motor symptoms in Parkinson’s disease (PD), it has also been shown to induce severe psychiatric side effects such as depression in a number of patients (8-25%). The underlying mechanisms of psychiatric side effects following STN DBS in PD are unknown. Preclinical research suggests that postoperative depression is mediated through the serotonin (5-HT) system (Tan et al., 2012; Temel et al., 2007). Additionally, dysfunction of the 5-HT system is implied in the pathophysiology of PD, suggesting that PD patients may be inherently predisposed to the development of mood disorders. The current study hypothesizes that postoperative depression in PD patients is the result of an STN DBS induced decrease in 5-HT activity in an already lowered and vulnerable 5-HT state in PD.

Objective: To assess the effect of a temporary reduction in serotonin availability on mood and behavior in PD patients treated with STN DBS in order to identify risk factors for psychiatric side effects of STN DBS.

Study design: This study is a double blind intervention paradigm with a placebo controlled, randomized cross-over design, investigating the effect of tryptophan (TRP) depletion on mood and behavior in 30 PD patients treated with STN DBS. TRP depletion is a commonly used method to achieve a temporary and reversible reduction in 5-HT activity in the brain. There will be two separate days of testing in which the patient will drink an amino acid mixture to accomplish the TRP depletion or a control placebo drink. The patient will be assessed at three time points during the day: (1) at baseline, before TRP depletion/placebo with stimulation ON; (2) after TRP depletion/placebo with stimulation ON; and (3) after TRP depletion/placebo with stimulation OFF. Mood state will be estimated using the Profile of Mood States (POMS) and the Emotional Responsiveness Task (IAPS). Impulsivity will be assessed with an anti-cue reaction time task, and motor function will be examined with the MDS-UPDRS part III.

Study status: Four patients have been included.

References
Do age and hippocampal subfield volume influence pattern separation performance?

Lisa Müller-Ehrenberg¹, Frans Verhey¹, Alexander Sack², Ed Gronenschild¹, Heidi Jacobs¹,²

¹School of Mental health and Neuroscience, Faculty of Health, Medicine and Life Science, Maastricht University
²Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University

Ageing is associated with alterations in cognitive performance, most notably in episodic memory. These aging-associated memory changes are experienced as debilitating. A hallmark feature of episodic memory is pattern separation (PS), the ability to form similar temporal-spatial information into distinct, non-overlapping representations. This process is dynamically at odds with pattern completion, the ability to merge similar representations of the same information into one representation. With ageing there is a tendency towards pattern completion over separation. The brain structures critically involved in pattern separation are hippocampal subfields CA3, CA4 and dentate gyrus, while the CA1 is crucial for pattern completion. Previous work suggested that pattern separation ability declines around 40 years of age, however, whether structural hippocampal changes associated with pattern separation changes including middle-aged individuals remains unknown. This study aimed at investigating with ultra-high field 7T MR-imaging how PS-performance is associated with hippocampal subfield volume across three age groups: 15 young (20-30y), 17 middle-aged (40-50y) and 16 old (60-75y) participants. All participants performed a previously validated PS-task during MR-scanning. High-resolution T1-weighted anatomical images (0.7mm isotropic) were acquired, as well as task and resting-state fMRI. The high resolution allowed for accurate segmentation of hippocampal subfields using Freesurfer version 6.3. Hippocampal subfield volumes were corrected for head size. We investigated whether age and group, respectively, predicted PS-performance and whether this association was modulated by hippocampal subfield volume, using multiple linear regression. There was a significant main effect of age. Neither of the hippocampal subfield volumes was significantly associated with PS-performance. Moreover, there was no significant interaction between group and subfield volume on PS-performance. Thus, the only predictors for PS-performance were age and group, with older age and group, respectively, being associated with worse performance. These findings suggest that hippocampal structural changes may not contribute as much to PS-performance and highlights the need for investigating functional brain activation in the hippocampal subfields and on a whole-brain network level.

Keywords: Pattern separation, Ageing, Hippocampal subfields.
MicroRNAs in susceptibility to traumatic stress


School for Mental Health and Neuroscience, Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands.

Department of Toxicogenomics, Maastricht University, Maastricht, The Netherlands.

Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht, The Netherlands.

Research Centre for Military Mental Healthcare, Ministry of Defence, Utrecht, The Netherlands.

Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands.

Department of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Department of Clinical Genomics, Maastricht University Medical Center, Maastricht, The Netherlands.

Traumatic stressors are important and prevalent risk factors for mental health disorders, such as post-traumatic stress disorder (PTSD). People differ strikingly in their susceptibility to develop PTSD after traumatic stress, however the exact underlying biological mechanisms of differential susceptibility are unknown. The identification of biomarkers that distinguish between persons at high and low risk of developing PTSD following trauma exposure would enable more effective preventive strategies and early interventions.

Epigenetic mechanisms have been proposed to underlie the relationship between exposure to traumatic stress and the susceptibility to develop PTSD. Recent evidences suggest that microRNAs (miRNAs) are key epigenetic players in mental health disorders. Furthermore, numerous studies demonstrated the high potential of miRNAs as promising non-invasive biomarkers for different health outcomes. We therefore aimed to identify miRNA candidates associated with differential susceptibility to develop PTSD after traumatic stress exposure in humans and mice. We examined circulating miRNA profiles in serum samples at 6 months after a 4-month deployment period from selected subjects (n=24) based on three polarized groups (susceptible subjects, unsusceptible subjects and control subject without robust exposure to stress, n=8 per group) out of a large prospective Dutch military cohort. Upon applying next generation high-throughput sequencing of small RNA libraries, we identified 42 miRNAs that were differentially expressed in the serum of susceptible persons (i.e. with PTSD after trauma exposure). We are currently performing studies using the social defeat mouse model in order to validate our human results in the blood samples of these mice. The results of our pilot study suggest that profiles of circulating miRNAs in human serum might provide biomarker candidates and possibly mechanistic information relevant to PTSD.

Keywords: Post-traumatic stress disorder, Epigenetics, microRNA.
Locus Coeruleus imaging at ultra-high field MRI

Priovoulos Nikos\textsuperscript{a}, Dimo Ivanov\textsuperscript{b}, Heidi Jacobs\textsuperscript{a,b}, Kamil Uludag\textsuperscript{b}, Frans Verhey\textsuperscript{a}, Benedikt Poser\textsuperscript{b}

\textsuperscript{a}School for Mental Health and Neuroscience, Maastricht University
\textsuperscript{b}Department of Cognitive Neuroscience, Maastricht University

The Locus Coeruleus (LC) is a small brainstem structure that is the source of noradrenaline in the cortex and is thought to modulate attention and memory. LC imaging in vivo is commonly performed with a T1-weighted Turbo Spin Echo (TSE) sequence, an approach that suffers from several drawbacks. The purpose of this study was to optimize in vivo LC imaging using ultra-high field (UHF) MRI and to translate this back to the 3 T to facilitate clinical applications. We developed a high-resolution Magnetization Transfer (MT) sequence for LC imaging in both 7 and 3 T and compared its performance to a TSE sequence. Preliminary results indicate that LC imaging can be achieved with a MT sequence in both 7 and 3 T at higher resolution than the TSE, while retaining similar signal-to-noise and contrast-to-noise ratio. Furthermore, we investigated whether the currently disputed source of contrast in the LC region with a TSE sequence relates to MT effects or elongated T1 due to increased iron concentration. Preliminary results indicate that the contrast in the LC area is due to MT effects. Overall, in this study we managed to image the LC for the first time at 7 T and at an increased resolution compared to the current state-of-the-art. Additionally, our results provide insight on the contrast behavior in the LC region that can possibly be used to quantify atrophy in the region.
Monoclonal gammopathy of undetermined significance polyneuropathy (MGUSP) is a slowly progressive disease with differential effects in individuals, ranging from mild foot numbness and minor imbalance to severe neuropathic pain and sensory and motor dysfunction. International consensus regarding assessment and treatment of patients with MGUSP is lacking, due to repeated use of suboptimal outcome measures, small trial sizes and low numbers of treated patients, the indolent disease course needing a longer follow-up period to capture relevant changes, or the possibility that administered treatments were not aggressive enough. The IMAGiNe study will result in a unique collection of prospectively collected and highly standardized clinical data, and a biobank from a large population of well-defined patients with MGUSP. The main objective is to describe in detail the variation in clinical subtypes, clinical disease course, past and current practice of treatment, antibody titres, and clinical picture at the various levels of assessing outcome. The study group aims to define the clinical and biological determinants, and predictors of this variation in subtypes, disease activity, treatment response and outcome. The study is an international, multi-centre, prospective, observational cohort study having a follow-up duration of 3 years (assessments at 0/3/6/12/24/36 months). The coordinating centres are the Maastricht University Medical Centre+ and University Medical Centre Utrecht, both in the Netherlands. Patients ≥18 years fulfilling the international criteria for MGUSP are eligible. Exclusion is primarily based on concomitant diseases influencing peripheral nerve function. We aim to recruit at least 250 patients in the Netherlands, the United Kingdom, France, and Italy. Centres recruiting at least 10 patients may participate in the study. The following study parameters will be of interest: weakness ((Rasch Transformed) Medical Research Council sum score), sensation ((Rasch Transformed) Modified INCAT Sensory Sum Score), activity and participation (MGUSP Rasch-built Overall Disability Scale), ataxia (Modified International Cooperative Ataxia Rating Scale, Scale for the Assessment and Rating of Ataxia), quality of life (EuroQol EQ-5D health Questionnaire), and pain (Pain-Intensity Numerical Rating Scale).

Keywords: MGUSP, outcome measures.
The expression of OPRM1 and GluR1 in the spinal cord after surgery affects the nociceptive behaviour

Roel van Reij MSc¹², Daisy Hoofwijk MD¹, Bart Rutten MD PhD², Gunter Kenis PhD², Wolfgang Buhre MD PhD¹, Bert Joosten, PhD¹, Nynke van den Hoogen MSc¹²

¹Department of Anaesthesiology and Pain Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands.
²School for Mental Health and Neuroscience (MHeNs), Faculty of Health, Medicine and Life Sciences, Maastricht University Medical Centre, Maastricht, the Netherlands.

Introduction: Chronic postsurgical pain (CPSP) is a common problem affecting between 10 and 60% of the patients undergoing surgery. Single nucleotide polymorphisms (SNPs) might play a crucial role in the development of CPSP. A systematic literature search showed a strong association for SNPs in the OPRM1 gene and the GluR1 gene in CPSP. However, the exact role of OPRM1 and GluR1 gene products in the development of postsurgical pain is unclear. A pre-clinical pilot study was performed to investigate the effects of acute postsurgical pain on expression of OPRM1 and GluR1.

Methods: Pain behaviour was measured as paw withdrawal threshold to mechanical stimuli (Von Frey filaments). Immunohistochemistry was performed on transverse spinal cord sections (L4 and L5) from naïve, adult animals (n=4), as well as 1 day after (n=3) and 5 days (n=3) after unilateral hind-paw incision. The mean intensity of staining in the Region Of Interest (ROI), superficial dorsal horn lamina I to III, and the area fraction (area with intensity above background threshold within the ROI) were analysed.

Results: Hind-paw incision resulted in increased mechanical sensitivity to von Frey filaments 1-5 days after incision. A significant decrease in OPRM1 mean grey value and area fraction was noted at 1 day after incision compared to preoperative tissue. Furthermore, both the mean grey value and the area fraction of OPRM1 and GluR1 were significantly increased 5 days after incision.

Conclusion: Hind-paw incision induces changes in OPRM1 and GluR1 expression within the superficial dorsal horn. These changes in expression seem linked to the behavioural recovery after incision.

Keywords: Chronic Postsurgical Pain, Immunohistochemistry, Behavioural testing.
Vitamin D₃ supplementation reduces antibody titers against the Epstein-Barr Virus nuclear antigen 1 (EBNA-1) in relapsing remitting multiple sclerosis

Linda Rolf¹,²*, Anne-Hilde Muris¹,², Amandine Matthias³, Renaud Du Pasquier³, Inga Koneczny¹, Giulio Disanto⁴, Jens Kuhle⁵, Jan Damoiseaux⁶, Joost Smolders²,⁷, Raymond Hupperts¹,²

¹School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, the Netherlands; ²Academic MS Center Limburg, Zuyderland Medical Center, Sittard, the Netherlands; ³Laboratory of neuroimmunology, University Medical Center Vaudois (CHUV), Lausanne, Switzerland; ⁴Neurocenter of Southern Switzerland (NSI), Ospedale Civico, Lugano, Switzerland; ⁵Department of Neurology, University Hospital Basel, Basel, Switzerland; ⁶Central Diagnostic Laboratory, Maastricht University Medical Center, Maastricht, the Netherlands; ⁷Department of Neurology, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands.

Background: In search for the trigger of multiple sclerosis (MS) two environmental risk factors have consistently been identified: Epstein-Barr virus (EBV) infection and vitamin D insufficiency. Moreover, there may be an interaction between these risk factors. The objective of this study was to investigate the effect of high dose vitamin D₃ supplementation on antibody levels against the EBV nuclear antigen 1 (EBNA-1) in patients with relapsing remitting (RR-) MS, and to assess potential targets of vitamin D in order to gain more insight into the underlying mechanism.

Methods: This study was part of the SOLAR(IUM) trial (NCT01285401), a randomized controlled trial in which relapsing remitting (RR) MS patients received either high dose vitamin D₃ (n=30) supplementation (14000 IU/day) or placebo (n=23) during 48 weeks. Pre- and post-supplementation 25(OH)D levels, anti-EBNA-1, anti-viral capsid antigen (VCA) and anti-cytomegalovirus (CMV) immunoglobulin G (IgG) levels were measured in blood. Furthermore, the effect of vitamin D₃ supplementation on the EBV viral load and the amount of EBV-specific CD8⁺ cytotoxic T cells was explored, as well as a direct effect of vitamin D on anti-EBNA-1 IgG secreting B cells in vitro.

Results: The median antibody level against EBNA-1, but not VCA and CMV, significantly reduced in the vitamin D₃ supplemented arm (526 (368 – 1683) - 455 (380 – 1148) U/mL) compared to the placebo arm (432 (351 – 1280) - 429 (297 – 1290 U/mL; p=0.023). The proportion of EBV-specific CD8⁺ T cells was not affected. Results of further explorative analyses will be presented.

Conclusion: Our results show that high dose vitamin D₃ supplementation selectively reduces anti-EBNA-1 IgG levels in patients with RRMS. This observation may either support an interaction between vitamin D and EBV in MS or reflect a better immune regulation by vitamin D in general.

Keywords: EBV, multiple sclerosis, vitamin D.
Deep brain stimulation in refractory epilepsy: a novel role for white matter?

F.L.W.V.J. Schaper¹, B Plantinga², A Noecker⁵, C McIntyre⁵, L. Wagner⁴, A.J. Colon⁴, P.A. Boon⁴, L. Ackermans², G. Hoogland², R.P.W. Rouhl¹, Y. Temel²

Introduction: Therapy response to deep brain stimulation (DBS) of the anterior nucleus of thalamus (ANT) for refractory epilepsy varies highly among patients. There is thus a strong need for improving therapy response. Optimization of the DBS target region may improve clinical outcome for refractory epilepsy patients. The ANT functions as a key grey matter structure in the Circuit of Papez and is surrounded by fibers of the mammillothalamic tract (MMT). We tested the hypothesis that the end of the MMT can be used as a potential landmark or functional target in DBS for epilepsy.

Objective: To investigate whether the locations of the active contacts in respect to the mammillothalamic tract relate to DBS therapy response.

Patients & procedures: We analyzed the active contact locations of 11 refractory epilepsy patients treated with DBS of the ANT at the MUMC+. Therapy response was assessed at 1-year follow up by two neurologists and defined as >50% reduction in seizure frequency compared to baseline. We classified 5 patients as responders and 6 patients as non-responders. Using fused pre-operative MRI and post-operative CT, we calculated the shortest distance of the active contacts of the DBS lead to the end of the MMT. The locations of the active contacts were then plotted in 3D space with the end of the MMT as the origin for every individual patient. The volume of tissue activation (VTA) was calculated and plotted in the same 3D space.

Results: In responders to DBS of the ANT for epilepsy, the shortest distance of the active contacts to the end of the MMT in 3D space is 42% smaller (R: 3.6 mm vs NR: 6.2 mm, p = 0.02). This is mostly caused by a 1.6 mm difference in the dorsoventral direction (R: 2.2 mm vs NR: 3.8, p = 0.02). VTAs were similar in both groups but overlapped more prominently at the end of the MMT in responders compared to non-responders.

Conclusion: We propose the end of the MMT as an anatomical landmark for targeting the ANT and as a novel functional target for DBS in refractory epilepsy. Experimental animal studies targeting white matter for DBS in epilepsy are warranted.
The applicability of corneal confocal microscopy in (possible) small fiber neuropathy

Maurice Sopacua¹, Janneke GJ Hoeijmakers¹, Ingemar SJ Merkies¹,², Catharina G Faber¹.

¹Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands.
²Department of Neurology, St. Elisabeth Hospital, Willemstad, Curaçao.

According to international criteria, the diagnosis small fiber neuropathy (SFN) is based on clinical symptoms in combination with a reduced intraepidermal nerve fiber density (IENFD) in skin biopsy and/or abnormal temperature threshold testing (TTT). The sensitivity of skin biopsy is moderate to good, although IENFD is normal in about 12% of patients with SFN complaints. Furthermore, TTT is a widely available diagnostic tool, but this test lacks specificity. Corneal confocal microscopy (CCM) has been described and is used in clinical practice as an objective, non-invasive diagnostic tool to detect small nerve fiber damage in patients with diabetes mellitus. This study examines the applicability of CCM in patients with possible SFN, and the value of CCM as an additional diagnostic tool in SFN.

We will include 20 healthy participants and 200 patients referred for possible SFN. All patients referred to our center for possible SFN will undergo routine diagnostics for SFN, including determination of IENFD and TTT, as well as CCM as part of the regular patient care. Corneal nerve fiber density (CNFD), branch density (CNBD), fiber length (CNFL), and the tortuosity coefficient (CNFT) will be determined in all participants. Preliminary results will be presented.
**Stress-induced aggression in mice and evidence for preventive effects of drugs with pro-neurogenetic activity**


Several lines of evidence suggest that stress, serotonin deficiency and suppressed neurogenesis may be the factors of aggression. In the present work we have used two different paradigms of stress, pharmacological treatments and mice with deficient serotonin synthesis in the brain, in order to address these issues. Tryptophanhydroxylase-2 (TPH2) null mutant mice (Tph2−/−) are characterized by increased aggressive behaviour in baseline conditions, while naïve heterozygous mice (Tph2+/-) lack such behavioural changes. In the present study, Tph2+/- male mice were subjected to a 5-day predator stress followed by the resident-Intruder test. In comparison to their wild type littermates, non-stressed Tph2+/- mice showed no changes in parameters of aggressive, dominant-like and social behaviours. However, stressed Tph2+/- mice displayed elevated measures of aggressive behaviour, such as reduced latency of the first attack and increased duration of fighting behaviour. In contrast to Tph2+/- mice, wild type mice subjected to predator stress showed a significant reduction in the measures of aggressive behavior, such as an increased latency of the first attack, reduced number and duration of attacks. These data suggest that predator stress evokes opposing effects on aggressive behaviour dependently on congenital Tph2 levels. HPLC measurements of monoamines revealed a strong positive correlation between aggressiveness and serotonin turnover rate in striatum in stressed wild type animals (Tph2+/-), while in naïve Tph2+/- mice there was a correlation between aggressiveness and serotonin turnover rate in prefrontal cortex. Therefore, it can be assumed that heterozygous animals use serotonin to process the situation of resident-intruder test through different brain areas. In another study, male Balb/c mice were subjected to a 3-week ultrasound radiation in 20-45 kHz frequencies ranges, which was recently shown to evoke emotionally negative state and affective disturbances. It was found that this challenge has induced aggressive-like changes. We have also studied a potential anti-aggressive effect of a 2-week administration of two pro-neurogenetic substances with different mechanisms of action, a new analogue of dimebon DF302 and thiamine (vitamin B1) at the doses of 40 mg/kg/day and 200 mg/kg/day respectively, in this paradigm. Both compounds were previously shown to counteract stress-induced suppression of neurogenesis. Aggressive behaviour was evaluated in the resident-Intruder test. It was found that mice subjected to a three-week ultrasound exposure, had significantly decreased latency of attacks, and significantly increased number and duration of attacks, in comparison to the control group. At the same time, mice treated with DF302 and thiamine displayed no changes in the measures of aggressive behaviour, as compared with the control non-stressed group. To sum up, first, stress of various origins can precipitate or result in the excessive aggression. Second, the substances that increase neurogenesis can prevent these negative effects of the stress on aggressive behaviour.
High field imaging of neurometabolite networks in epilepsy

Tamar van Veenendaal¹, Desmond Tse², Tom Scheenen³, Dennis Klomp⁴, Paul Hofman¹, Rob Rouhl³, Marielle Vlooswijk⁵, Albert Aldenkamp⁶, Walter Backes¹, Jacobus Jansen¹

¹Departments of Radiology and Nuclear Medicine, Maastricht University Medical Center; ²Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University; ³Department of Radiology and Nuclear Medicine, Radboud University Medical Center; ⁴Department of Radiology, University Medical Center Utrecht; ⁵Department of Neurology, Maastricht University Medical Center, ⁶Epilepsy Center Kempenhaeghe, Heeze

Introduction: In patients with localization-related epilepsy, aberrant in vivo neurometabolite concentrations (GABA, glutamate, N-acetylaspartate) have been shown[1,2]. Although localization-related epilepsy has traditionally been considered a focal disease, many structural abnormalities have been found beyond the epileptic zone, suggesting that these patients have brain anomalies beyond the epileptic focus. Patients also often have cognitive and other problems indicative of an effected network. In this study, we assess global neurotransmitter variations and their mutual relations, and propose the concept of ‘neurometabolite networks’.

Methods: Twenty healthy participants and nine patients with localization-related epilepsy were included. Five of the healthy participants were included twice, with an interval of one week, to assess reproducibility. Each participant underwent 7T MR scanning (Siemens Magnetom), comprising a T1-weighted image and a MR spectroscopic imaging (MRSI) image. Average NAA, glutamate, and GABA concentrations (relative to creatine) were computed in 26 brain regions, which were considered connected if the concentrations showed a significant correlation over the healthy participants.

Results: The neurotransmitter concentrations can be measured reliably in 24 out of 26 brain areas, with coefficients of variation <20% for GABA and glutamate, and <15% for NAA. In twelve healthy participants, data were available in these 24 brain areas. In these participants, forty percent of the regions showed a significant correlation for the glutamate and NAA concentrations, while this was only five percent for the GABA concentrations.

Discussion: A spatial relation between NAA and glutamate concentrations of different regions was shown, suggesting a network of these neurometabolites. For GABA, no substantial correlations were found, suggesting that the GABA network is not organized. Currently, studies are being performed to evaluate differences between these networks in healthy participants and patients with epilepsy.

Keywords: epilepsy, MR spectroscopic imaging, network dysfunction.

References
Effect of modifiable risk factors on brain connectivity and cognition in hyperglycaemia measured with advanced MRI

L.W.M. Vergoossen¹, W.H. Backes¹, M. Schram², and J.F.A. Jansen¹ on behalf of the Maastricht Study.

¹Department of Radiology, Maastricht University Medical Center;
²Department of Medicine, Maastricht University Medical Center.

Introduction: Type 2 Diabetes Mellitus (T2DM) is a common metabolic disorder, characterized by chronic hyperglycemia, while Impaired Glucose Metabolism (IGM) is regarded as a pre-diabetic condition. T2DM and IGM are both hyperglycaemic conditions and are associated with accelerated cognitive decline. The rate of cognitive decline is likely increased relative to normal ageing due to cerebrovascular and neurodegenerative changes. Affected cognitive domains concern mainly the areas of learning, memory and processing speed. In subjects with Normal Glucose Metabolism (NGM), an unhealthy lifestyle is associated with brain alterations indicative of vascular dysfunction. To obtain a better insight in processes underlying cognitive decrements in hyperglycaemic conditions, it can be beneficial to investigate disturbances in both the structural and functional brain network organization, which are reflections of the white matter integrity and gray matter vitality, respectively, and relate these to lifestyle measures.

Aim: The aim is to investigate the mechanisms underlying cognitive decline in T2DM and IGM, and the effect of modifiable risk factors, including physical inactivity and visceral fat accumulation.

Methods: In a cross-sectional study, three homogeneous groups, NGM, IGM, and T2DM, matched on age, sex and education will be selected from ‘The Maastricht Study’ database. For these subjects, evaluations of macrostructural MRI, cognitive performance, physical activity, and visceral fat accumulation are available. Furthermore, advanced brain connectivity measures will be calculated by using self-developed automated quantitative image processing pipelines. Structural connectivity (SC) will be assessed by performing tractography on diffusion MRI (dMRI) data. Functional connectivity (FC) will be investigated using resting-state functional MRI (rs-fMRI) time-series data. Additionally, the FC-SC correlation will be calculated as a measure of functional-structural coupling, which is proposed as an early imaging biomarker of brain tissue changes.

Hypotheses: It is hypothesized that: 1) Macrostructural and cerebral connectivity measures is abnormal in hyperglycaemic conditions (compared to NGM), with T2DM more severe than IGM. 2) Modifiable risk factors, in particular physical inactivity and visceral fat accumulation, have an amplifying effect on brain alterations associated with hyperglycaemia. 3) The coupling between functional and structural connectivity could possibly serve as an early biomarker of brain alterations associated with cognitive decrements in hyperglycaemia.

Keywords: T2DM, IGM, MRI, cognition, modifiable risk factors.
Constructing a reward-related Quality of Life function in daily life -a proof of concept study-

Simone J. W. Verhagen and Philippe A. E. G. Delespaul

1Department of Psychiatry and Neuropsychology, Maastricht University

Mental healthcare needs person-tailored interventions and experience sampling method (ESM) can provide monitoring of personal processes in daily life. Intuitively, good QoL is improved by spending most time on rewarding experiences. ESM treatment interventions can use this information to coach patients to find a realistic, optimal balance of reward in daily life. The purpose of the present study is two-fold: operationalizing a measure of momentary reward-related Quality of Life (rQoL) and testing its feasibility.

rQoL combines the frequency of engaging in specific environments or ‘behavior setting’ (i.e. meaningful context) with the momentary mental state (i.e. positive affect). High rQoL occurs when high frequency situations are combined with high mental states or low frequency is limited to low mental states. Monte Carlo simulations (MCs) were used to assess the sampling characteristics that allow reliable assessment of rQoL: various definitions of behavior setting, several cut-off scores, sample sizes for virtual subjects or real subjects with low-, average- and high variability in behavior setting. Finally, MCs were used to assess whether rQoL is distinct from positive affect.

The rQoL definition is feasible. MCs drawn from an aggregated sample of 1058 valid ESM observations (virtual subjects) demonstrated that behavior settings defined by ‘Who-What’ contextual information are most informative. At least 100 ESM observations are needed for reliable assessment when using virtual subjects. In individual subjects, behavior setting defined by ‘Who-What-Where’ combinations is probably best. Small sample sizes are only feasible for the low behavior setting variation subjects. Last, rQoL is distinct from mere positive affect. Future research should explore other options in defining rQoL, use different populations and pilot it’s meaningfulness as treatment intervention.

Keywords: reward; experience sampling method; quality of life; positive affect; behavior setting.
Blood-brain barrier function: The key to successful cognitive aging?

Inge Verheggen¹, Martin van Boxtel², Frans Verhey³, Walter Backes⁴

School for Mental Health and Neuroscience, department of Psychiatry and Neuropsychology, Maastricht University

A potential initiating factor of age-related cognitive decline is blood-brain barrier (BBB) breakdown. The BBB separates circulating blood from the brain tissue, thereby maintaining a healthy environment for neuronal cells. Previous studies suggest that BBB breakdown can cause several age-related pathological brain changes, such as small vessel disease, protein deposits, inflammation and neuronal death. These brain changes can then eventually lead to cognitive decline.

At baseline, we will implement an innovative dynamic contrast-enhanced (DCE) MRI scan, which for the first time enables us to detect even subtle BBB leakage. We will only include participants who have previously completed the MAastricht Aging Study, in which they were cognitively followed over a period of 12 years (1993-2005). We will also conduct our own measurements of cognitive performance at baseline and follow-up, so that we will have information on cognitive performance over the past 23 years. We will use this information to investigate the relationship between BBB leakage and age-related cognitive decline. BBB leakage has already been associated with a diagnosis of dementia and we now wish to investigate whether a connection between BBB leakage and cognitive decline can already be discovered within the range of normal aging.

At both baseline and follow-up, we will also implement regular MRI scans to measure other age-related brain changes. We will use this information to investigate whether BBB leakage at baseline can give an accurate prediction of increase in age-related brain changes at follow-up. This will support the claim that BBB leakage is an initiating factor of age-related pathological brain changes.

Our eventual aim is that our DCE MRI scan can predict who is vulnerable to age-related cognitive disorders and who is not, and that this will lead to improved diagnosis, treatment and prevention.

Keywords: MRI, BBB, cognitive aging.
Characterization of stroke patients visiting outpatient follow-up care

Marianne Vruwink¹,², Bert Lenaert¹,²,³, Rudolf Ponds¹,², Caroline van Heugten¹,²,³

¹Limburg Brain Injury Center, Maastricht University, the Netherlands
²Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, the Netherlands
³Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, the Netherlands

Introduction: Stroke is a common cause of death and disability. Many of the surviving patients have to deal with the long term consequences of stroke. The MUMC offers outpatient follow-up care for early detection and treatment of these effects.

Methods: Patients (N=91) who visited between January-May 2015 the outpatient clinic for the first time were included. The questionnaires: CLCE-24 (cognitive failures), HADS (depression & anxiety), FSS (fatigue), USER-P (participation) and CSI (caregiver burden) were used as part of regular care to assess long term functioning. The demographic and questionnaires data were retrieved from the electronic patient records.

Results: The average age of the patients was 70.7 (±12.5) years and 52.7% were male. Patients suffered an ischaemic stroke (85.7%), haemorrhage (7.7%) or TIA (6.6%). The visit to the clinic took place 6.9 (±2.7) months after the stroke. Patients reported on average 4.2 (±3.9) cognitive problems and 2.6 (±2.6) emotional problems (CLCE-24). 83.3% and 88.1% of the patients experienced at least one problem in the cognitive and emotional domains. The mean FSS score was 4.2 (±1.4) and in 63.4% of the patients fatigue affected daily functioning. The mean HADS anxiety and depression score was 5.8 (±4.2) and 5.4 (±4.7). 29.3% of the patients showed a potential depressive disorder; the same percentage of patients showed a potential anxiety disorder. The mean USER-P restriction score was 74.6 (±26.8) and 70.9% of the patients experienced at least one restriction in daily life. The most common restrictions were in household (45.1%), transportation (41.8%) and physical exercise (40.7%). The mean score of the CSI, that was mainly completed by partner (49.5%) or family member (17.6%), was 4.2 (±3.8); 19.1% of the primary caregivers experienced overburden.

Discussion: The results show that six months post-stroke, a significant proportion of the patients experience negative long term consequences; in the majority of the patients fatigue and participation restriction affected their functioning. Since recovery may take up to 2-3 years, a longer period for follow-up would be desirable to determine the long term effects of stroke. Additionally, rehabilitation treatment can be considered.

Keywords: brain injury, stroke, follow-up care.
Brain serotonin and the mediation of early life stress

M. T. Weidner1,2, C. Auth2, J. Waider2, A. G. Schmitt2, D. van den Hove1,2, K.-P. Lesch2,1

1Dept. of Psychiatry and Neuropsychology, Maastricht Univ., Maastricht, Netherlands;  
2Ctr. of Mental Hlth., Univ. of Wuerzburg, Wuerzburg, Germany

The epigenetic mediation of events that occur early in development is a widely discussed phenomenon. However, the underlying molecular mechanisms remain somewhat diffuse. In recent years, the programming of the hypothalamic-pituitary-adrenal (HPA) axis via glucocorticoid receptors was identified as an important factor in this process. The serotonin (5-HT) system has been suggested as another vital factor in this respect. Moreover, various studies show an effect of corticosteroids on number and functionality of 5-HT receptors. This goes together with various findings linking changes in the 5-HT system to early life stress exposure. To further elucidate the role of 5-HT in developmental programming by early life stress, we employed a B6.Tph2 mouse line. Mice of this line were bred towards a constitutive knock out of the tryptophan hydroxylase 2 (Tph2) gene. Tph2 is the rate-limiting enzyme of the serotonin synthesis in the brain. Tph2−/− animals of this line have been shown to be completely depleted of 5-HT in the brain. For our experiments, we exposed animals of this line to maternal separation, a well-established model of early life stress. Using this paradigm, all pups of a litter, regardless to sex and genotype, were separated from their mother for 3 hours per day. This separation is repeated from postnatal day 2 to postnatal day 15. After this period of stress exposure, the animals were allowed to grow up under normal conditions. From postnatal day 60 onwards, male and female offspring were tested in diverse behavioural tasks to assess motor activity (open field), anxiety-like behaviours (dark-light-box, open field, elevated plus maze) as well as aggressive behaviour (resident-intruder test). Following the behavioural screening, brains were harvested for molecular analyses. We found several effects of a genotype-by-environment interaction on the display of anxiety-like behaviours and aggression. In particular, in Tph2−/− animals we observed a different level of coping following maternal separation. These findings seen in the light of the observed molecular changes provide more insight into the role of brain 5-HT in the mediation of early life stress.
Diminished mentalizing as a mediator between reported childhood abuse and outcome in nonaffective psychotic disorder

Jonas Weijers¹,²*, Peter Fonagy³, Elisabeth Eurelins-Bontekoe⁴, Fabian Termorshuizen¹, Wolfgang Viechtbauer², Jean-Paul Selten¹,².

¹Rivierduinen Institute for Mental Health Care, Leiden, the Netherlands.
²Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands.
³Research Department of Clinical, Educational, and Health Psychology, University College London, London, United Kingdom.
⁴Dept. of Clinical Psychology, Health, and Neuropsychology, Leiden University, Leiden, the Netherlands.

Objective: Reported childhood abuse (RCA) has been linked to the severity of clinical symptoms and social dysfunction in non-affective psychotic disorder (NAPD). Diminished mentalizing ability may be one of the mechanisms accounting for this effect. This study examined whether impaired mentalizing mediates the effect of RCA on positive symptoms, negative symptoms, and social dysfunction.

Method: Ninety NAPD patients were examined with regard to RCA, mentalizing impairment, positive symptoms, negative symptoms, and social dysfunction. RCA was measured using the Childhood Experience of Care and Abuse interview. Additionally, the Social Functioning Scale and the Positive and Negative Syndrome Scale were used. The Hinting Task was used to measure mentalizing impairment.

Results: RCA was related to severity of positive symptoms and negative symptoms, but not social dysfunction. RCA was also related to mentalizing impairment. Mentalizing impairment was related to negative symptoms, but not to positive symptoms or social dysfunction. Diminished mentalizing partially mediated the relation between RCA and negative symptoms.

Conclusion: Diminished mentalizing due to parental abuse may be one of the pathological mechanisms accounting for the severity of negative symptoms in NAPD.

Keywords: Childhood abuse, mentalizing, psychosis.
Vascular genetic biomarkers associated with Alzheimer’s disease related neuropathological changes and longevity: First report from a South Asian ageing population

Printha Wijesinghe¹, Shankar SK², Yasha TC², Catherine Gorrie³, Dhammika Amaratunga⁴, Yoo-Hun Suh⁵, Harry W.M. Steinbusch⁶, K. Ranil D. de Silva¹,*

¹Interdisciplinary Center for Innovation in Biotechnology & Neuroscience, Genetic Diagnostic & Research Laboratory and Human Brain Tissue and DNA Repository, Dept. of Anatomy, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka
²Dept. of Neuropathology, National Institute of Mental Health & Neurosciences, Bangalore, India
³School of Medical and Molecular Biosciences, University of Technology Sydney, Sydney, Australia
⁴Nonclinical Biostatistics, Janssen Research & Development (retired), Raritan, USA
⁵Dept. of Pharmacology, College of Medicine, Seoul National University, Seoul, South Korea
⁶Dept. of Translational Neuroscience, Faculty Health, Medicine & Life sciences, Maastricht University, Maastricht, Netherlands

Background: To the best of our knowledge this is the first autopsy and genetic study, representing a South Asian ageing population that has intended to investigate vascular genetic risk factors; apolipoprotein E (APOE), angiotensin converting enzyme (ACE), methylenetetrahydrofolate reductase (MTHFR C677T) and Factor V Leiden (G1691A) associated with sporadic Alzheimer’s disease (AD) and human longevity, and the potential co-existent of cerebrovascular lesions underlying cerebral hypo-perfusion theory in sporadic AD which have been found to be inconclusive.

Objectives: In ageing autopsy brains (1) to identify vascular genetic biomarkers associated with AD related neuropathological changes and life expectancy, and (2) to find potential coexistent cerebrovascular lesions associated with AD related neuropathological changes.

Methods: Postmortem brain samples from 76 elderly subjects (≥50yrs) were used to study genetic polymorphisms encoding for APOE, ACE, MTHFR and FVL; intracranial atherosclerosis of the circle of Willis (IASCW), and microscopic infarcts in deep white matters. From this cohort 50 brains (≥60yrs) were subjected to neuropathological diagnosis using histopathological/ immunohistochemical techniques.

Results: The ε4 allele of the APOE and MTHFR T allele were significantly associated with Thal β amyloid (Aβ) phase ≥1 and presence of cerebral amyloid angiopathy (CAA) with the odds 6-7 and 10-2, respectively. Potential coexistent cerebrovascular lesions identified with AD related neuropathological changes were white matter hyperintensities (WMHs) and CAA (P < 0.05) compared to large vessel pathology- IASCW. ACE DD genotype was identified as a longevity associated genotype [15/23 (65%), P = 0·04] as opposed to ACE ID genotype [22/29 (76%), P = 0·004] and APOE ε4 allele [11/19 (58%)] which were frequent among young decedents who died between 50 and 69 years.

Conclusions: APOE ε4 allele and MTHFR T allele could be considered as vascular genetic biomarkers for Aβ accumulations in ageing brains, justify further studies in folic acid supplementation as a preventative approaches against vascular Aβ accumulations due to MTHFR polymorphism. ACE ID genotype could be considered as vascular genetic biomarker for reduced life expectancy as opposed to ACE DD genotype which shows a selective beneficial effect on human longevity.

Keywords: vascular genetic biomarkers, sporadic Alzheimer’s disease, human longevity.
Intravoxel Incoherent Motion Imaging in Cerebrovascular Disease: Reproducibility and Scan Time Reduction

S.M. Wong¹,³, W.H. Backes¹,³, C.E. Zhang²,³,⁴, J.E.A. Staals²,⁴, P.A.M. Hofman¹,³, R.J. van Oostenbrugge²,³,⁴, C.R.L.P.N. Jeukens¹ and J.F.A. Jansen¹,³

¹Radiology, Maastricht University Medical Center, Maastricht, Netherlands
²Neurology, Maastricht University Medical Center, Maastricht, Netherlands
³School for Mental Health and Neuroscience (MHeNs), Maastricht, Netherlands
⁴School for Cardiovascular Diseases (CARIM), Maastricht, Netherlands

Introduction: Intravoxel Incoherent Motion imaging (IVIM), a diffusion-weighted imaging technique, can measure brain perfusion and diffusion properties simultaneously.¹ The perfusion volume fraction f provides information on the microvasculature and has already shown promising results in assisting stroke assessment in cerebrovascular disease.² However, IVIM measures are affected by partial volume effects of cerebral spinal fluid (CSF). Therefore, Inversion Recovery (IR)-IVIM was proposed to suppress the CSF signal.³ Unfortunately, IR-IVIM is accompanied with long scan times. Clinical feasibility of IR-IVIM was investigated by studying 1) the reproducibility of IR-IVIM and 2) the effect of fewer diffusion-sensitizing directions to reduce scan time in patients with cerebrovascular disease.

Methods: IR-IVIM imaging (3T) was performed on two days in 16 patients (age 66±9 years) with cerebrovascular disease. Diffusion was measured in three directions: right-left (RL), anterior-posterior (AP) and feet-head (FH) (scan time: ~5 min. per direction). The trace was obtained combining all three directions (~15 min.) and employed to calculate the reproducibility of f using the coefficient of variation (CV), indicating the day-to-day variations. To study the effects of scan time reduction, inter-direction CVs of f between the trace and unidirectional measurements were calculated and compared with the day-to-day variations of f. The investigated regions had different diffusion properties: the entire normal appearing white matter (NAWM), cortex and the corpus callosum (CC).

Results: Day-to-day variations of f (CVs ≤5.0%) were low in all regions. The inter-direction CVs between the FH direction and trace (≤9.8%) were larger than the day-to-day variations of f (≤5.0%) in all regions. For other directions, the inter-direction CVs with the trace (≤2.4%) was in the same range as the day-to-day variations of f (≤2.9%) in the NAWM and cortex. In the CC the inter-direction CVs with the trace (≥9.8%) were larger than the day-to-day variations of the trace (≤5.0%).

Discussion and Conclusion: Good reproducibility was observed for IR-IVIM for f. IR-IVIM measurement utilizing a single diffusion-sensitizing direction is not advised when investigating anisotropic tissue (e.g. CC). However, for large tissue regions, scan time reduction can be realized by using a single diffusion-sensitizing direction (AP or RL, not FH).

Keywords: diffusion weighted MR imaging; microvasculature; cerebrovascular disease;

References
Hydropathic topology of an ion channel’s pore

Markos N. Xenakis\textsuperscript{1,2}, Ronald Westra\textsuperscript{1}, Patrick Lindsey\textsuperscript{2}

\textsuperscript{1}Maastricht University, Dep. Of Data Science & Knowledge Engineering
\textsuperscript{2}Maastricht University, Dep. of Clinical Genomics

Voltage-gated sodium (NaV) channels are fundamental components of excitable membranes and serve as pharmacological targets for several diseases. Although molecular dynamics (MD) provides a phenomenological framework to study functional aspects of NaV channels, principles underlying their functional architecture remain elusive. Here we report the hydropathic topology of the bacterial voltage-gated sodium ion channel (NavAb) at the pre-open state\textsuperscript{[1]} encoding the spatial organization of mass and hydropathicity around the molecule's pore. Starting from a symmetry argument, we investigated the cumulative behavior of the zero-th and first hydropathic moment\textsuperscript{[2]} across pore points by utilizing an atomic hydropathic scale\textsuperscript{[3]}. We found that the mean cumulative effect captures a structural transition from the S6 pore-forming helices to the voltage-sensor domain (VSD), while a pseudo-symmetric topology dichotomizing the molecule's pore arose. Interestingly, the distribution of critical points across the molecule's pore was found to peak around functionally important regions of the pore. Our results suggest that the modeling methodology presented here may enrich our fundamental understanding of the functional architecture underlying an ion channel's pore, and provide insight into hydropathic binding sites across the pore.

\textbf{Keywords}: ion channel, hydropathicity, topology.

\textbf{References}:

Estimating the proportion of patients with an indication for clozapine in Dutch ambulatory care

Yvonne van der Zalm1,2, Raphael Schulte3,4, Jan Bogers1,4, Machteld Marcelis2,5, Iris Sommer6, Jean-Paul Selten1,2

1Rivierduinen Psychiatric Institute, Leiden, The Netherlands
2School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands
3Mental Health Service Noord-Holland Noord, Alkmaar, The Netherlands
4Dutch Clozapine Collaboration Group, Castricum, the Netherlands
5Institute for Mental Health Care Eindhoven (GGzE), Eindhoven, The Netherlands
6University Medical Center Utrecht, Brain Center Rudolf Magnus, Department of Psychiatry, Utrecht, The Netherlands

Background: Clozapine is the preferred treatment for patients with treatment-resistant psychosis. The proportion of patients with Non-Affective Psychotic Disorder (NAPD) in Dutch ambulatory care that uses clozapine or could benefit from a treatment with this drug is unknown.

Objectives: The objectives of this study are to determine, per team of approximately 150 patients, the proportion of patients on clozapine and to estimate the proportion with an indication for this drug.

Method: Nineteen teams of four psychiatric institutes participated. The Nurse Practitioner (NP) of each team identified the patients already on clozapine. Next, using a decision tree, he assessed whether the remaining patients had an indication for this drug, by type of indication. Subsequently, the NP and responsible psychiatrist of each team discussed the cases with a possible indication and reached consensus.

Results: A total of 2217 patients was assessed. The proportion of patients in each team that was on clozapine ranged from 8.4 to 34.4%. (mean: 22.9%). The proportion of patients considered to have an indication for this drug ranged from 1.7 to 15.5% (mean: 7.0%). There was no significant correlation between those two proportions (r=-.22; p=.36).

Conclusion: The findings suggest that the decision to prescribe clozapine is more often driven by personal preferences than by guidelines.

Keywords: Clozapine, outpatients, indications.
Screening for anti-neuronal autoantibodies in plasma from the Netherlands Study of Depression and Anxiety (NESDA)

Shenghua Zong1, Carolin Hoffmann1, Marina Damas1, Peter Molenaar1, Gerard van Grootheest2, Mario Losen1, Brenda W.J.H. Penninx2, Pilar Martinez Martinez1 *

1Division Neurosciences, School for Mental Health and Neurosciences, Maastricht University, Maastricht, The Netherlands;
2GGZ inGeest and Department of Psychiatry, EMGO+ Institute and Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

Objective: To study the presence of autoantibodies targeting brain receptors in depression and related disorders. Because antibody tests are difficult to perform routinely at the moment, we surmise that autoimmunity is underdiagnosed in depression. To answer this question, we have obtained samples (n=2240) from the Netherlands Study of Depression and Anxiety (NESDA). We propose to identify the presence of autoantibodies targeting several brain ion channels/membrane receptors in the plasma. We expect to be able to (i) identify different anti receptor/channel antibodies, (ii) define autoimmunity subgroups of patients with depression spectrum disorders, and (iii) analyse the correlation between autoantibodies and specific clinical characteristics. The results of the proposed study will provide insight into the role of autoantibodies in neuropsychiatric syndromes, help to identify subgroup of patients with autoimmunity and help to develop new treatment strategies based on immunosuppression.

Methods: 2240 plasma samples from depression and related disorders and healthy individuals from NESDA have been tested by immunohistochemistry (IHC) on rat brain tissue. The rat brain IHC results were considered positive when staining patterns were observed in the hippocampus. Scores were given according to the intensity of the staining. Images are evaluated by two independent observers. Scores are classified as (0) negative, (1, 2, 3, 4) positive and (?) borderline.

Results: 106 samples were found positive for staining in the hippocampus, scoring from 1 to 4, 251 samples were considered borderline, indicating ambiguous reactivity. In the 106 positive samples analysed, 8 scored ≥ 3, and four different hippocampal patterns were observed.

Interpretation: We are currently investigating the possible correlation between the autoantibodies and specific clinical characteristics. The positive samples identified by IHC are being tested by immunoprecipitation and cell based assay to identify the antigens that the autoantibodies are targeting. Finally, the study of other plasma samples from the same patients at different times will be of interest to confirm the presence of the autoantibodies.
**Tinnitus suppression with high frequency stimulation of the rat medial geniculate body**

**Gusta van Zwieten**\textsuperscript{ab}, Jasper V Smit\textsuperscript{ab}, Mark LF Janssen\textsuperscript{c}, Ali Jahanshahi\textsuperscript{bd}, Robert J Stokroos\textsuperscript{ab}, Yasin Temel\textsuperscript{bd}

\textsuperscript{a}Department of Ear Nose and Throat/Head and Neck Surgery, Maastricht University Medical Center, Maastricht, The Netherlands;
\textsuperscript{b}Department of Neuroscience, School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands;
\textsuperscript{c}Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands;
\textsuperscript{d}Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands.

**Introduction:** Tinnitus can be a disabling symptom, as it can lead to insomnia, anxiety, depression and even suicide in severe cases. Currently, there is no effective standard therapy. Neuromodulation is a promising treatment modality in tinnitus. The medial geniculate body (MGB) of the thalamus is a key structure in tinnitus pathophysiology.

**Objectives:** Here, we assessed the effect of deep brain stimulation of the MGB in a rat model of chronic noise-induced tinnitus.

**Materials and methods:** A within-subject design was used. 12 male Sprague Dawley rats underwent bilateral DBS electrodes implantation at the start of the experiment. Tinnitus was induced by unilateral noise exposure. Hearing thresholds were determined before and after noise trauma with auditory brainstem responses. Gap-induced pre-pulse inhibition of the acoustic startle (GPIAS) response testing was used for tinnitus assessment during four main conditions: 1) baseline stimulation off, 2) baseline HFS on, 3) post noise trauma stimulation off and 4) post noise trauma HFS on. After noise trauma, two additional stimulation paradigms were tested, namely "post HFS" (stimulation off after 30 minutes of HFS) and "during low-frequency stimulation (LFS)". Anxiety and locomotion related side-effects of HFS were evaluated in the elevated zero maze and open field.

**Results:** ABR measurements demonstrated preserved hearing thresholds of the contralateral ear. GPIAS for tinnitus assessment showed significant chronic tinnitus development after noise-trauma at the 16 kHz frequency bands. HFS caused a significant decrease of the gap:no-gap ratios of 16 kHz and 20 kHz after tinnitus induction. A persistent effect on tinnitus suppression was found directly after HFS was turned off, but no effect was found of LFS on the gap:no-gap ratios of the acoustic startle response. No side-effects were found during HFS.

**Conclusion:** These results show that chronic tinnitus can be suppressed with bilateral HFS of the MGB in this rat model. Optimal stimulation parameters need to be investigated, as well as the effect of stimulation on hearing function. Clinically, the MGB is accessible with stereotaxy and might therefore be an applicable DBS target if an invasive treatment is considered in severe and refractory tinnitus patients.

**Keywords:** Tinnitus, deep brain stimulation, neuromodulation.
LIST OF PARTICIPANTS
## Division 1 = Cognitive Neuropsychology and Clinical Neuroscience
## Division 2 = Mental Health
## Division 3 = Neuroscience

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<tr>
<th>Name</th>
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<tr>
<td>Alahmari Mohammed</td>
<td>Division 3</td>
<td><a href="mailto:m.alahmari@maastrichtuniversity.nl">m.alahmari@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Aldehri Majed</td>
<td>Division 3</td>
<td><a href="mailto:m.aldehri@maastrichtuniversity.nl">m.aldehri@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Amelsvoort Therese</td>
<td>Division 2</td>
<td><a href="mailto:t.vanamelsvoort@maastrichtuniversity.nl">t.vanamelsvoort@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Argyrousi Elentina</td>
<td>Division 3</td>
<td><a href="mailto:e.argyrousi@maastrichtuniversity.nl">e.argyrousi@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Banning Leonie</td>
<td>Division 1</td>
<td><a href="mailto:leonie.banning@maastrichtuniversity.nl">leonie.banning@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Barkhuizen Melinda</td>
<td>Division 3</td>
<td><a href="mailto:m.barkhuizen@maastrichtuniversity.nl">m.barkhuizen@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Barnes Devon</td>
<td>Other</td>
<td><a href="mailto:devon.barnes@hotmail.co.uk">devon.barnes@hotmail.co.uk</a></td>
</tr>
<tr>
<td>Bartels Sara Lauren</td>
<td>Division 1</td>
<td><a href="mailto:sara.bartels@maastrichtuniversity.nl">sara.bartels@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Beek, van Maarten</td>
<td>Division 3</td>
<td><a href="mailto:m.vanbeek@maastrichtuniversity.nl">m.vanbeek@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Berendschot Tos</td>
<td>Division 3</td>
<td><a href="mailto:t.berendschot@maastrichtuniversity.nl">t.berendschot@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Berk Lotte</td>
<td>Division 1</td>
<td><a href="mailto:lotte.berk@maastrichtuniversity.nl">lotte.berk@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Bertens Christian</td>
<td>Division 3</td>
<td><a href="mailto:Christian.Bertens@mumc.nl">Christian.Bertens@mumc.nl</a></td>
</tr>
<tr>
<td>Beucken, van Twan</td>
<td>Other</td>
<td><a href="mailto:t.vandenbeucken@maastrichtuniversity.nl">t.vandenbeucken@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Bischoff Peggy</td>
<td>Other</td>
<td><a href="mailto:p.bischhoff@maastrichtuniversity.nl">p.bischhoff@maastrichtuniversity.nl</a></td>
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<td>Bohler Sacha</td>
<td>Other</td>
<td><a href="mailto:s.bohler@maastrichtuniversity.nl">s.bohler@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Bos Isabelle</td>
<td>Division 1</td>
<td><a href="mailto:isabelle.bos@maastrichtuniversity.nl">isabelle.bos@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Boxtel, van Martin</td>
<td>Division 1</td>
<td><a href="mailto:martin.vanboxtel@maastrichtuniversity.nl">martin.vanboxtel@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Briëde Jacco</td>
<td>Division 3</td>
<td><a href="mailto:j.briere@maastrichtuniversity.nl">j.briere@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Capponi Rachelle</td>
<td>Division 3</td>
<td><a href="mailto:secr-neuroscience@maastrichtuniversity.nl">secr-neuroscience@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Christie Hannah</td>
<td>Division 1</td>
<td><a href="mailto:hannah.christie@maastrichtuniversity.nl">hannah.christie@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Cinar Ozan</td>
<td>Division 2</td>
<td><a href="mailto:ozan.cinar@maastrichtuniversity.nl">ozan.cinar@maastrichtuniversity.nl</a></td>
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<tr>
<td>Crivelli Simone</td>
<td>Division 3</td>
<td><a href="mailto:s.crivelli@maastrichtuniversity.nl">s.crivelli@maastrichtuniversity.nl</a></td>
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<td>Crommenacker, van Tom</td>
<td>Other</td>
<td><a href="mailto:t.vandencrommenacker@maastrichtuniversity.nl">t.vandencrommenacker@maastrichtuniversity.nl</a></td>
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<tr>
<td>Dam Alieske</td>
<td>Division 1</td>
<td><a href="mailto:alleske.dam@maastrichtuniversity.nl">alleske.dam@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Damas Marina</td>
<td>Division 3</td>
<td><a href="mailto:m.damas@maastrichtuniversity.nl">m.damas@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Deckers Kay</td>
<td>Division 1</td>
<td><a href="mailto:kay.deckers@maastrichtuniversity.nl">kay.deckers@maastrichtuniversity.nl</a></td>
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<tr>
<td>Domen Patrick</td>
<td>Division 2</td>
<td><a href="mailto:p.domen@maastrichtuniversity.nl">p.domen@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Douven Elles</td>
<td>Division 1</td>
<td><a href="mailto:elles.douven@maastrichtuniversity.nl">elles.douven@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Drenten Gerhard</td>
<td>Division 1</td>
<td><a href="mailto:g.drenten@maastrichtuniversity.nl">g.drenten@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Drukker Marjan</td>
<td>Division 2</td>
<td><a href="mailto:Marjan.Drukker@MaastrichtUniversity.nl">Marjan.Drukker@MaastrichtUniversity.nl</a></td>
</tr>
<tr>
<td>Duin, van Esther</td>
<td>Division 2</td>
<td><a href="mailto:eda.vanduin@maastrichtuniversity.nl">eda.vanduin@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Dunker Suryan</td>
<td>Division 3</td>
<td><a href="mailto:suryan.dunker@mumc.nl">suryan.dunker@mumc.nl</a></td>
</tr>
<tr>
<td>Eijkenboom Ivo</td>
<td>Other</td>
<td><a href="mailto:ivo.eijkenboom@maastrichtuniversity.nl">ivo.eijkenboom@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Erdag Ece</td>
<td>Division 3</td>
<td><a href="mailto:ece.erdag@maastrichtuniversity.nl">ece.erdag@maastrichtuniversity.nl</a></td>
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<tr>
<td>Faber Karin</td>
<td>Division 1</td>
<td><a href="mailto:c.faber@mumc.nl">c.faber@mumc.nl</a></td>
</tr>
<tr>
<td>Foulquier Sebastien</td>
<td>Other</td>
<td><a href="mailto:s.foulquier@maastrichtuniversity.nl">s.foulquier@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Franken Glenn</td>
<td>Division 3</td>
<td><a href="mailto:g.franken@maastrichtuniversity.nl">g.franken@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Freeze Whitney</td>
<td>Division 1</td>
<td><a href="mailto:w.freeze@maastrichtuniversity.nl">w.freeze@maastrichtuniversity.nl</a></td>
</tr>
<tr>
<td>Gavilanes Danilo</td>
<td>Division 3</td>
<td><a href="mailto:danilo.gavilanes@mumc.nl">danilo.gavilanes@mumc.nl</a></td>
</tr>
<tr>
<td>Geraerts Anouk</td>
<td>Division 1</td>
<td><a href="mailto:anoukgeraerts@live.nl">anoukgeraerts@live.nl</a></td>
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<td>Goossens Lies</td>
<td>Division 2</td>
<td><a href="mailto:lies.goossens@maastrichtuniversity.nl">lies.goossens@maastrichtuniversity.nl</a></td>
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<td>Gorgels Theo</td>
<td>Division 3</td>
<td><a href="mailto:theo.gorgels@mumc.nl">theo.gorgels@mumc.nl</a></td>
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<td>Division 1</td>
<td><a href="mailto:bianca.greef@mumc.nl">bianca.greef@mumc.nl</a></td>
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<td>Gruters Angelique</td>
<td>Division 1</td>
<td><a href="mailto:angelique.gruters@maastrichtuniversity.nl">angelique.gruters@maastrichtuniversity.nl</a></td>
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<td>Guloksuz Sinan</td>
<td>Division 2</td>
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<td>Hamers Marcella</td>
<td>Division 3</td>
<td><a href="mailto:m.hamers@maastrichtuniversity.nl">m.hamers@maastrichtuniversity.nl</a></td>
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<td>Handels Ron</td>
<td>Division 1</td>
<td><a href="mailto:ron.handels@maastrichtuniversity.nl">ron.handels@maastrichtuniversity.nl</a></td>
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<td>Heckman Pim</td>
<td>Division 3</td>
<td><a href="mailto:pim.heckman@maastrichtuniversity.nl">pim.heckman@maastrichtuniversity.nl</a></td>
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<td>Hellebrekers Danique</td>
<td>Division 1</td>
<td><a href="mailto:danique.hellebrekers@maastrichtuniversity.nl">danique.hellebrekers@maastrichtuniversity.nl</a></td>
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Maastricht University
School for Mental Health and Neuroscience [MHeNs]
Faculty of Health, Medicine and Life Sciences
Universiteitssingel 40
6229 ER Maastricht [NL]
T +31(43) 388 10 21
E secr-mhens@maastrichtuniversity.nl

For more information contact our office or visit the website at:
www.maastrichtuniversity.nl/mhens