Topics in Translational Neuroscience

9th MHeNs one-day workshop for PhD students

When the brain is under attack: Auto-antibodies and neurotransmitters as key player in neurological and psychiatric diseases

April 15th, 2015
Maastricht, The Netherlands
Venue: Maastricht University
The aetiology of primary psychotic disorders, such as schizophrenia, is thought to be heterogeneous (van Os J. and Kapur, 2009; Phillips and Kupfer, 2013). The treatment is mainly symptomatic. Patients with schizophrenia or bipolar disorder and their family members, however, are recognized to have a higher prevalence of auto-immune diseases (eg. Eaton et al., 2010; Eaton et al., 2006; Gibney and Drexhage, 2013). It is therefore hypothesized that autoimmune processes are involved in causing these diseases in a subgroup of patients. Since synaptic functioning is thought to be disturbed in primary psychotic disorders, synaptic antigens, such as N-methyl-D-aspartate receptor (NMDAR) or voltage-gated potassium channel (VGKC) complex proteins, would be prime targets for antibodies causing psychotic disorders. Over the last decade it has become clear that antibodies to synaptic proteins, such as the NMDAR and VGKC complex proteins (LGI1, CASPR2) can cause autoimmune forms of encephalitis (Dalmau et al., 2008; Vincent et al., 2011; Creten et al., 2011; Zandi et al., 2011). The patients often present with psychiatric symptoms, including psychosis, aggression, anxiety, and depression. In most reported cases prominent neurologic symptoms, such as seizures and movement disorders, develop as well (Dalmau et al., 2011). In the patients without clear neurologic features, however, screening for antibodies is not performed and therefore the number of patients with isolated psychiatric symptoms is likely to be underestimated (Kayser et al., 2013).

To advance this important area, highly synergistic approaches from different disciplines are needed and for this, the TTN workshop is ideal. This day will bring together experts to enhance fruitful collaboration of different disciplines. In the morning and early afternoon the different talks, from experts in schizophrenia, cognition, neurology and immunology will present an overview of the key aspects which are relevant to this topic. In the afternoon, small groups will first prepare and then present their assessments of the strengths, as a part of interactive plenary discussions. Expert moderators, with different scientific backgrounds ranging from immunology to neurology, and psychiatry will be present to support and stimulate the discussions. The aim of the workshop is to create a platform of new scientists who will work together to tackle questions which can be answered only in synergy.

### PROGRAM

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<td>09.00 - 09.20</td>
<td>Registration / coffee</td>
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<td>09.20 – 09.30</td>
<td>Introduction Dr. Pilar Martinez PhD</td>
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<td>09.30 – 10.15</td>
<td>Prof. Jim van Os MD, PhD: <em>Does schizophrenia exist?</em></td>
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<td>10.15 - 11.00</td>
<td>Prof. Therese van Amelsvoort MD, PhD: <em>Cognitive impairment and psychosis: does it matter and what can we do about it?</em></td>
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<td>11.00 - 11.15</td>
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<td>11.15 - 12.00</td>
<td>Mario Losen PhD / Pilar Martinez PhD: <em>Autoimmunity and antibody effector functions</em></td>
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<td>12.00 – 13.00</td>
<td>Lunch (MPR) (UNS 50, 1.142A)</td>
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Workgroups

Group 1
Ehsan Pishva
Bianca de Greef
Syenna Schievink
Carmen Schiweck
Marion Levy

Group 2
Maurice Sopacua
Zuzana Kasanova
Lisa Lebherz
Iris Lange
Mark van den Hurk

Group 3
Renske Uiterwijk
Majed Aldehri
Simone Crivelli
Artemis Iatrou
Inga Koneczny

Group 4
Elfi Vergaelen
Pim Heckman
Marina Mané Damas
Britt Mossink

Propositions:
1. Autoantibodies are more likely to have an effect in neuropsychiatric diseases if they are targeting neuronal membrane proteins than if they are targeting intracellular antigens
2. In a subgroup of psychotic patients the disease is caused by neuronal autoantibodies
3. Antibodies can only reach the brain when the blood brain barrier function is impaired (e.g. due to trauma or inflammation)
4. All psychiatric patients should be screened for the presence of neuronal autoantibodies in the blood and cerebrospinal fluid.
5. Considering the relationship between ion channel dysfunction and clinical manifestations, it is a valid hypothesis that autoantibodies against ion channels cause schizophrenia like symptoms.

Moderators:
Pilar Martinez, PhD / Mario Losen, PhD / Peter Molenaar, PhD / Carolin Hoffmann, PhD student / Wim Buurman, Professor / Marc De Baets, Professor

Background literature:

Therese van Amelsvoort, MD PhD, is a psychiatrist and professor in transitional psychiatry, with a special interest in understanding biological mechanisms underlying psychosis and neurodevelopmental disorders with an emphasis on the transition from adolescence into adulthood. She trained as a psychiatrist at the Institute of Psychiatry in London, obtained her PhD at the University of Amsterdam, and subsequently obtained a Veni and a Vidi to investigate dopaminergic and cholinergic mechanisms in psychosis.

Abstract
Psychotic disorders usually emerge during late adolescence and in early adulthood. Although hallucinations, delusions and thought disorder can be successfully treated, cognitive impairments, probably the most disabling characteristics of the disease, are untouched by currently available antipsychotics. Cognitive dysfunction is estimated to occur in the majority of patients with psychosis, often precedes the onset of other symptoms, and persists even after other symptoms have been effectively treated. It has been found that indices of cognitive deficits are much better predictors of functional outcome than indices from any other symptom domain. Furthermore, the severity of cognitive deficits is predictive of poorer medication compliance, overall treatment adherence, and increased tendency for relapse in first-episode patients. Overall, the widespread use of the atypical antipsychotics has not offered clinical relevant cognitive benefits for patients with schizophrenia, implying a need for directive treatments for enhancing cognition. Over recent years there has been a search for cognitive enhancing interventions, both pharmacologically and non-pharmacologically. In this talk an overview of these will be given.

Frank Leypoldt, MD PhD was born in Braunschweig, Germany in 1976. He started his medical education in 1996 in Hamburg with internships in Toronto, Canada and Bern, Switzerland and graduated in 2004 at the medical faculty, University of Hamburg, Germany. He finished a master in molecular biology and a doctoral thesis in developmental neurobiology. During his residency at the Department of Neurology, University Hospital Hamburg-Eppendorf, he subspecialized in neuroimmunology and worked scientifically with Roland Martin at the Institute of Neuroimmunology and Clinical Multiple Sclerosis Research and Tim Magnus at the Research Group Experimental Research in Stroke and Inflammation. In 2012 he started a research fellowship at Josep Dalmaus Lab in Barcelona. In 2014, he returned to Germany to a faculty position at the Christian-Albrechts-University Kiel, Germany for Autoimmune Diagnostics at the Institute of Laboratory Medicine and he holds the position of a senior attending at the Department of Neurology, University Hospital Schleswig-Holstein, Kiel.
His clinical and scientific interest for many years has been the evolving field of synaptic encephalitis. He has coordinated the current German, Swiss and Austrian Guidelines on Paraneoplastic neurologic diseases and contributed some internationally recognized publications in peer-reviewed journals. He is one of the coordinators of the German Research on Autoimmune Encephalitis (GENERATE) network.

Abstract

Anti-NMDA receptor encephalitis and synaptic autoimmunity - Lessons learned from nature

Ten years ago, Josep Dalmau and colleagues described a small case series of women with subacute development of psychotic symptoms followed by generalized encephalopathy. All were found to harbour a previously unknown ovarian teratoma. He later discovered autoantibodies directed against the N-terminal domain of the ionotropic glutamate receptor N-methyl-D-aspartate-receptor (NMDAR) in their cerebrospinal fluid and serum. This newly discovered disorder has since been referred to as anti-NMDAR encephalitis and has been found to be the most the second most common form of acute or subacute autoimmune encephalitis after acute disseminated encephalomyelitis (ADEM).

Since then, numerous other encephalitic syndromes associated with autoantibodies targeting synaptic components have been discovered in quick succession and termed “synaptic encephalitides”. The advances in understanding pathophysiology, epidemiology and spectrum of this group of diseases has taught scientists and clinicians a lesson and introduced a new paradigm in central nervous system autoimmunity.

My talk will introduce and summarize clinical symptoms, diagnostic techniques, spectrum of autoantibodies, pathophysiology and treatment of synaptic encephalitides.

Jim van Os, MD, PHD, MRCPSYCH is Professor and Chairman of the Department of Psychiatry and Psychology at Maastricht University Medical Centre, Maastricht, The Netherlands, and Visiting Professor of Psychiatric Epidemiology at the Institute of Psychiatry, London, UK. He trained in Psychiatry in Casablanca (Morocco), Bordeaux (France) and finally at the Institute of Psychiatry and the Maudsley/Bethlem Royal Hospital in London (UK) and after his clinical training was awarded a three-year UK Medical Research Council Training Fellowship in Clinical Epidemiology at the London School of Hygiene and Tropical Medicine. In 1995, he moved to Maastricht University Medical Centre.

He is on the editorial board of European and US psychiatric journals such as Acta Psychiatrica Scandinavica, European Psychiatry, Psychological Medicine, Schizophrenia Research, Schizophrenia Bulletin, Early Intervention in Psychiatry, Epidemiology and Psychiatric Sciences, Psychosis Journal, The Journal of Mental Health and the Journal of Psychiatry and Neurological Sciences. He is also an Academic Editor at PLoS ONE.

In 2011, he was elected member of the Royal Netherlands Academy of Arts and Sciences (KNAW); he appears on the 2014 Thomson-Reuter Web of Science list of the world’s ‘most influential scientific minds’ of our time.
Jim van Os is coordinator of a €12M EU FP7 IP project on gene-environment interactions in schizophrenia, and is also active in clinical gene-environment interaction research in depression and bipolar disorder.

He was a member of the Psychosis Group of the influential DSM-5 Task Force, and was co-chair of the APA DSM/ICD conference Deconstructing Psychosis.

He is Director of Psychiatric Services at Maastricht University Medical Centre and runs a service for treatment-resistant depression and first episode psychosis.

**Contribution to research**

Prof. van Os has strived to contribute to the area of brain-mind interplay in a non-reductionist fashion, focusing on the distribution of mental states in the population as related to mental ill-health, and the gene-environment interactions underlying these. He has developed the hypothesis that expression of mental ill-health can be traced to variation in normal mentation, establishing experiential and aetiological links between normal and pathological mental states. Novel diagnosis-free methods of measuring mental states in the flow of daily life can help us understand the symptoms of madness as something that has its origins in normal mentation, that people can monitor and learn to understand and control.

In his recent paper in Nature (2010), he has argued that contextual neuroscience, focusing on the constant interactions between person and context, is the most appropriate way to conduct science in order to find solutions for patients with mental disorders. His current areas of interest include the clinical, cognitive and genetic epidemiology of bipolar disorder, schizophrenia and depression, in particular the study of variation in overlapping dimensions of these disorders in the general population and the underlying cognitive factors and gene-environment interactions driving this variation. Treatment studies focus on novel mobile health (mHealth) applications in the early treatment of mental disorders, novel diagnostic paradigms based on Experience Sampling mental state circuitries, implementation of recovery based services in routine mental health settings, and aspects of patient-professional carer communication.

**Recent publications:**

List of Participants

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