

29th Friedrich Merz Visiting Professorship Award Symposium

November 20, 2019 – Frankfurt am Main

Prof. Dr. Brenda Penninx, Department of Psychiatry, Amsterdam UMC / VU Amsterdam

“Precision medicine in psychiatry: wishful thinking or reality?”

Program:

Venue: Department of Psychiatry, Psychosomatic Medicine and Psychotherapy (Lecture Hall), University Hospital Frankfurt, Heinrich-Hoffmann-Str. 10, 60528 Frankfurt am Main

08.30 – 09.00 Registration

09.00 – 09.15 Welcome Address

Session 1:

09.15 – 09.30 Andreas Reif, Goethe-University Frankfurt am Main: Introduction to the topic

09.30 – 10.15 Brenda Penninx, VU Amsterdam – Subtypes of depression & treatment approaches: modulation of neuroinflammation

10.15 – 11.00 Elisabeth Binder, MPI for Psychiatry, Munich – Subtypes of depression with respect to stress axis and life events

Coffee break

Session 2

11.30 – 12.00 Martijn Arns, University of Utrecht – EEG and ECG Based Response Predictors in Depression: Time for Personalized Medicine or Treatment Stratification?

12.00 – 12.30 Marion Leboyer, Université Paris-Est – Towards precision medicine: what are the stratification tools to identify homogenous inflammatory subgroups?

12.30 – 13.00 Barbara Franke, Donders Institute, Nijmegen – Neurobiological research in ADHD – Opportunities for personalized medicine?

Lunch Break

Session 3

14.00 – 14.30 Daniel J. Müller, University of Toronto – Pharmacogenomics as a use case of personalized medicine in psychiatry

14.30 – 15.00 Christiaan Vinkers, VU Amsterdam – Childhood Trauma and depression: neurobiological mechanisms and treatment opportunities

15.00 – 15.30 Kamilla Miskowiak, University of Copenhagen – Targeting cognition to improve psychosocial function in mood disorders: where are we and where do we go?

Coffee Break

Session 4

16.00 – 16.30 Mark J. Millan, Institute de Recherché de Servier Paris – Towards Individualized Interventions for Neurodegenerative Disorders: Novel Therapeutic Strategies

16.30 – 17.00 Andreas Meyer-Lindenberg, ZI Mannheim – Environmental risk mechanisms for depression

17.00 – 17.15 Andreas Reif & Brenda Penninx: Wrap-Up and concluding remarks

Abstract Book

Prof. Dr. Brenda Penninx, Department of Psychiatry, Amsterdam UMC / VU Amsterdam

“Precision medicine in psychiatry: wishful thinking or reality?”

Prof. Dr. Brenda W.J.H. Penninx, Department of Psychiatry, Amsterdam UMC / Vrije Universiteit
Amsterdam (NL)

Subtypes of depression & treatment approaches: modulation of neuroinflammation

The burden on society due to major depressive disorder is undisputable. Depression ranks second on the WHO's disease burden index. Part of this large burden is due to a course pattern that is more chronic than often assumed, and treatments that do not lead to complete remission in all patients. Precision psychiatry is aimed towards finding more specifically which pathophysiological mechanisms are underlying depression and how this could inform treatment strategies. This is necessary in order to reduce the huge heterogeneity in symptom patterns, etiology and pathophysiology seen in depression. Within the Netherlands Study of Depression and Anxiety (NESDA, n=2981), trying to better understand the heterogeneity of depression is one of the main goals. Using NESDA data, we found that immuno-metabolic dysregulations vary as a function of depression heterogeneity: they map more consistently to “atypical” behavioral symptoms reflecting altered energy intake/expenditure balance (hyperphagia, weight gain, hypersomnia, fatigue and leaden paralysis). Several intervention studies further suggest that the presence of immuno-metabolic dysregulations may moderate the antidepressant effects of standard or novel (e.g. anti-inflammatory) therapeutic approaches. I will finally elicit questions to be answered by future research and will describe how the immuno-metabolic depression dimension could be used to dissect depression's heterogeneity and potentially to match subgroup of patients to specific treatments with higher likelihood of clinical success.

Prof. Dr. Elisabeth Binder, Max-Planck-Institute for Psychiatry, Munich (D) / Emory University School of Medicine, Atlanta (US):

Subtypes of depression with respect to stress axis and life events

Stress and traumatic experiences in childhood and adulthood are among the strongest risk factors for the later development of psychiatric diseases, especially anxiety and depression disorders. But not everyone suffers from adverse outcomes following such experiences. A better understanding of the factors influencing stress resistance or susceptibility to stress could reveal new prevention and treatment strategies for psychiatric disorders. In this lecture, such a mechanism will be examined. The chaperone protein FKBP5 is closely involved in the regulation of the stress response. A large number of studies have shown that genetic variants in the gene coding for this protein moderate the impact of childhood trauma on risk for number of adult psychiatric diseases. In a series of experiments, a possible mechanism for this gene x environment interaction could be identified. A genetic and epigenetic disinhibition of FKBP5 transcription must come together to increase the risk. This increased FKBP5 production then alters a number of signaling pathways via protein-protein interactions that are important for neuronal function, such as BDNF, tau proteins, and calcineurin. Patients with genetically and epigenetically disinhibited transcription of FKBP5 may represent a transdiagnostic subgroup of patients. These patients could benefit from treatment with small molecule antagonists of FKBP5, which have shown promising results in reducing stress consequences in animal experiments. Before disease onset, individuals carrying this dual risk could benefit from specific interventions in the course of development to prevent disease.

Prof. Dr. Martijn Arns, Research Institute Brainclinics, Nijmegen / Department of Experimental Psychology, Utrecht University, Utrecht (NL):

EEG and ECG Based Response Predictors in Depression: Time for Personalized Medicine or Treatment Stratification?

In depression (MDD) treatment there is a clear need for novel treatments, biomarkers and individualized treatment approaches. One of the most promising and most widely investigated biomarkers for antidepressant treatments is the EEG. Most EEG biomarkers however, still lack robustness and reproducibility and suffer significant publication bias as highlighted in a recent meta-analysis (Widge et al., 2018). Therefore, large controlled validation studies are needed with a focus on robustness, replication and clinical relevance.

In this presentation results will be presented from the largest EEG Biomarker study to date, the international Study to Predict Optimized Treatment in Depression (iSPOT-D), where 1008 MDD patients were randomized to Escitalopram, Sertraline and Venlafaxine. Drug-class specific (Arns et al., 2016) and drug-specific (Arns, Gordon & Boutros, 2015) biomarkers, as well as non-replications (Arns et al., 2015) will be highlighted as well as preliminary data from a prospective feasibility trial.

Furthermore, data will be presented on repetitive Transcranial Magnetic Stimulation (rTMS) treatment in MDD on EEG and clinical predictors (Krepel et al., 2018; 2019). The efficacy of rTMS is thought to be mediated through a frontal-vagal pathway, including structures such as the DLPFC and sgACC. A new method called Neuro-Cardiac-Guided TMS (NCG TMS), exploits the network connectivity in this frontal vagal pathway, as a target engagement approach (Iseger et al., 2019). In addition, co-activation of these structures (e.g. using psychotherapy) enhance clinical response to rTMS (Donse et al., 2017). Stimulation of pre-frontal areas using TMS results in downstream activation of the vagal nerve, with subsequent heart-rate deceleration, only for specific and individualized locations (Iseger et al., 2017; 2019). Preliminary results on its potential for individualizing rTMS stimulation locations and possible better clinical outcomes will be presented.

Finally, clinical implications and implementations will be discussed from a 'treatment stratification' perspective, which might be a more realistic goal relative to 'personalized medicine' perspective.

Prof. Dr. Marion Leboyer, Department of Psychiatry, University Paris-Est-Créteil, Fondation FondaMental, Créteil (F):

Towards precision medicine: what are the stratification tools to identify homogenous inflammatory subgroups?

Psychiatric disorders are heterogeneous overlapping disorders needing valid biomarkers to define homogeneous subgroups leading the way to Precision medicine, as in cancer or cardiovascular settings. Identification of clinical and biological signatures further dissected in animal models will help the discovery of mechanism-based treatments. As of yet, there are different visions about this phenotypic approach. By splitting or lumping: we may either identify trans-nosographical dimensions that cut across diagnostic categories and/or, at the other extreme of the vision, we will identify very precise sub-phenotypes.

Among existing biological pathways that should help to foresee homogenous subgroups, immune dysfunction, now clearly recognized as being associated with psychiatric disorders, offer different type of biological markers at central, peripheral or gut levels. In that respect, we will describe three pathways, with inflammation as a common denominator, leading to specific subgroups according to (i) auto-immunity against brain receptors, (ii) re-activation of human endogenous retro-virus, or (iii) gut dysbiosis, all of them constituting targets for immuno-modulatory treatments.

The combination of serum auto-antibodies against brain receptor (e.g., against NMDA-R or LGI1) leading to synaptic dysfunction, clinical syndromes defined by minor neurological symptoms and lasting psychiatric mood or psychotic symptoms, clear electroencephalography (EEG) abnormalities (e.g., intermittent rhythmic delta and theta activity, spike-wave discharges), magnetic resonance tomography (MRI) pathologies (e.g., juxtacortical white matter lesions), or [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) changes (e.g., different hypometabolic or hypermetabolic areas) define what is now known as “auto-immune psychosis” (Ellul et al, 2017; Pollack et al, 2019). These subgroups could be treated by immunoglobulin and anti-inflammatory drugs (Lenox et al, 2019). Another example of subgroup comes from the identification of activation by different types of infections during key developmental periods of Human Endogenous Retrovirus (HERV) type W leading to the production of Envelop protein (ENV) which have neurotoxic and pro-inflammatory actions, associated with elevated serum levels of C-Reactive Protein. Auto-immune psychosis, cutting across bipolar and schizophrenia, very likely define a subgroup which could be treated with antibodies neutralizing the ENV protein (Perron et al, 2008, 2012). Last example comes from the identification of blood markers of increased gut permeability, associated to dysbiosis in different psychiatric and neurodevelopmental disorders. For example, in autism, patients with gastro-intestinal symptoms have been shown to have serotonin abnormalities, increased gut permeability and abnormal metagenomic profile. In each case, animal models can be used to precisely identify the underlying mechanisms and to test the efficacy of treatment before trying to test it in humans.

Prof. Dr. Barbara Franke, Departments of Human Genetics and Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen (NL):

Neurobiological research in ADHD – Opportunities for personalized medicine?

Psychiatry is the last discipline in medicine where diagnosis is solely based on interviews and observation - no biomarkers to support diagnostics or inform about the prognosis of a patient are available. Furthermore, pharmacological treatment for those disorders is so far largely based on drugs identified based on serendipitous findings, few - if any - of the drugs used were developed based on a mechanistic understanding of the disorders.

Through technological innovations and international collaboration, we are finally starting to identify the biological underpinnings of psychiatric disorders. Our increasing possibilities also help us start to understand the brain substrates and genetic architecture of ADHD. Does this new knowledge bring us any closer to a clinical application of biological information in the diagnosis or treatment of ADHD? In this presentation, I will discuss recent progress in the neurobiological research on ADHD, in particular in the areas of genetics and brain imaging, and the potential ways in which such information may inform (personalized) medicine.

Prof. Dr. Daniel J. Müller, Department of Psychiatry, University of Toronto (CAN):

Pharmacogenomics as a use case of personalized medicine in psychiatry

Antidepressants and antipsychotics are essential components in treatment of most psychiatric disorders. Unfortunately, lengthy trials are often required before the optimum medication treatment is found. The underlying reasons for this large inter-individual variability in terms of treatment response are not fully understood. Important factors that influence medication dose, response and adverse effects include age, gender, patient compliance, type of symptoms, co-morbidity, and to a significant extent: genetic factors. This presentation will 1) review the clinical validity and utility of pharmacogenetic studies in psychiatry; 2) discuss current guidelines and recommendations (e.g., CPIC, DPWG); and 3) present results of own studies evaluating treatment outcome in psychiatric care after genetic information (e.g., CYP2D6 and CYP2C19) was provided to more than 350 physicians.

There is growing consensus among experts that genetic information, when adopted thoughtfully, will result in improved treatment for many psychiatric gene-drug pairs. However, utility remains restricted to specific gene-drug pairs and multi-gene test require specific validation. Our own research has shown that variation in genes - mainly involved in the metabolism of psychotropic drugs (pharmacokinetics) - are associated with plasma drug levels, treatment response, and onset of adverse effects. With respect to our pre-emptive genetic testing program in more than 11,000 patients, we received supportive responses from physicians who enrolled patients in our study. Notably, the vast majority of patients reported improvement in patient treatment outcome.

There is emerging evidence that pre-emptive genetic testing will improve treatment for numerous gene-drug pairs commonly used in psychiatry. While pharmacogenetic testing has become readily available and is offered routinely in many institutions of the world, both care providers and patients are poorly prepared to these new opportunities and proper education remains of utmost importance. This presentation will provide an important update in this regard and present those gene-drug pairs which ready to be used in psychiatric practice.

Prof. Dr. Christiaan Vinkers, Department of Psychiatry and Anatomy & Neurosciences, Amsterdam
University Medical Center (NL):

Childhood Trauma and depression: neurobiological mechanisms and treatment opportunities

There are few experiences as common and consequential for depression as childhood trauma (CT, abuse or neglect before 18). CT results in a clinically distinct and severe forms of psychopathology which emerge earlier in life and have worse treatment outcomes. Even though CT-related psychopathology is common, our understanding of the underlying mechanisms is limited and targeted treatments are lacking. Why are the effects of CT so persistent and far-reaching? CT by definition occurs during a vulnerable period early in life crucial for stress system development. Recent work from my group and others has made clear that dynamic functionality of stress systems is key to an adequate and coordinated stress response. Thus, the multi-layer interplay between stress systems is pivotal to understand CT in health and disease. In this presentation, I will discuss recent developments in the neurobiological research on CT-related stress system dynamics at the level of epigenetics, structural and functional brain networks, and the HPA-axis. Moreover, I will discuss how this integrated stress dynamics framework may help to develop new (personalized) interventions aimed to reverse the biological and psychological sequelae of excessive stress due to CT.

Prof. Dr. Kamilla Miskowiak, Department of Psychology, University of Copenhagen (DK):

Targeting cognition to improve psychosocial function in mood disorders: where are we and where do we go?

Cognitive impairment across memory, attention and executive function is a core dimension of neuropsychiatric disorders that impedes recovery and contributes to socio-occupational disability, the largest socio-economic burden of these disorders. Cognition is therefore a strategic treatment target to improve the lives of people with neuropsychiatric disorders and reduce the associated societal costs. In mood disorders, there are no clinically available efficacious treatments for cognitive impairments. This is partially a result of major methodological challenges in this relatively new field, including lack of consensus on how to screen for entry into cognition treatment trials and how to define efficacy outcomes. In this talk, Dr Miskowiak will outline some of these challenges and the first consensus-based methodological recommendations by the International Society for Bipolar Disorders (ISBD) Targeting Cognition Task Force for cognition trials. She will also highlight future perspectives for the methodology and design of cognition trials, including investigation of the neuro-circuitry targets of cognitive enhancement. Specifically, she will outline the most consistent neuronal correlates of cognitive impairments and – improvements and present a new framework to explain some apparently conflicting findings. This will lead to a discussion of the next steps for investigation of treatment-related modulation of activity the identified neuro-circuitries as surrogate markers of pro-cognitive effects.

Prof. Dr. Mark J. Millan, Centre for Therapeutic Innovation in Neuropsychiatry, Institute de Recherché de Servier, Paris (F):

Towards Individualized Interventions for Neurodegenerative Disorders: Novel Therapeutic Strategies

Despite the persistent obsession with ensuring homogeneity of lab animals, a rich ethological literature emphasizes individual differences in cognition, behaviour, personality, and vulnerability to stress and other risk factors for brain disorders in many species, from fish to birds (think blue tits and milk bottles) and rodents to primates. Humans are also primates and we are no different. The diversity of “healthy” subjects, the heterogeneity of patients with a “common” brain disorder, and the importance of considering each patient as unique were recognized as long ago as the Hippocratic canon and the Ayurvedic creeds. Hence, by analogy to another en vogue buzz word, translational (“improving the link between preclinical and clinical research”), the notion of “personalized” medicine is less of a conceptual revolution than a procedural refinement inasmuch as we now have access to a broader suite of animal models (and model animals), diagnostic tools, biomarkers, and potential therapeutic interventions.

As regards the latter, a remarkable range of preventative and treatment measures are (becoming) available for adaptation to specific patient needs, including: altered nutrition and lifestyle: cognitive-style therapies; brain stimulation; robotic and digital. This mainly applies to symptom relief, but also to efforts to prevent or stall the progression of diseases like “depression(s)”, despite that fact that the nature of pathology is not entirely clear. Nonetheless, the most striking progress towards “individualized (even “precision”) medicine is occurring for neurodegenerative disorders with the emergence of oligonucleotide (RNA and DNA) therapeutics such as antisense (ASO), silencing RNA, modulators of DNA transcription and gene replacement. These strategies are being evaluated across the life-span for discrete, genetically-defined sub-classes of neurodevelopmental disease and neurodegenerative disorders of aging. Effective treatment (and prevention) of spinal muscular atrophy disease in children has been demonstrated using both gene replacement (Onasemnogene abeparvvec) and ASOs that modify RNA-splicing (Nuniserin) to increase the level of functional protein (“Survival Motor Neuron”). The ultimate in individualized medicine (n = 1) has just (Oct 9, 2019, NEJM) been documented with a custom-designed ASO (Milasen) that improves the condition of a child suffering from Batten disease. This ASO was launched within 1 year of contact with the patient and exemplifies the immense promise of this approach: correspondingly, major programmes are underway for disorders like Huntington’s disease (HD), amyotrophic lateral sclerosis (ALS) and closely-related frontotemporal dementia (FTD).

However, things are not that simple as they might seem. First, despite the suppression of neurotoxic proteins in human patients and encouraging clinical signals, robust proof of efficacy is still awaited for HD and ALS/FTD. Second, for ALS, more than a dozen, different mutated genes are known and some of them, like C9ORF72, have functionally-distinct mutations. Third, the precise link between targeted genes and disorders is not fully clear: hence, it is uncertain if the option of reducing total protein (easy, works in all patients) or only the mutated protein (tough, sub-populations of patients) is the most apt. Fourth, owing to “genetic modifiers” and environmental factors, the same mutation can have different outcomes between patients. Hence, even in this “ideal” field for codification, precision medicine presents challenges, and there may be an array of “n=1, 2 or half a dozen” patient classes out there: sadly, it is impossible to help them all rapidly, even ignoring the huge costs (in the millions) of therapy. Finally, thanks

to improving patient stratification with novel biomarkers, it may eventually be possible to consider such individualized strategies for much more common (>90%) idiopathic forms of neurodegenerative disorders of aging, including Alzheimer and Parkinson disease.

Focusing on “personalized”, RNA/DNA-driven medicine for rare and discrete pathologies is truly important and provides a springboard for attacking non-familial forms of neurodegenerative (and other brain) disorders. However, we must not ignore the crucial need to address far more ubiquitous threats to the mental (and physical) health (of our own and other species): accelerating climate change, catastrophic loss of biodiversity, escalating environmental destruction and a grave loss of ecosystem services, in particular when coupled to urban decay, migration, poverty, obesity and poor early-life education. Socioeconomic resources are limited, so a balance must be found to advance in parallel on both these complementary fronts (the individual and the universal) for the sake of ourselves and our co-inhabitants of this planet.

« People vary so much anyway » G. Millan, 13. 08. 2019

Prof. Dr. Andreas Meyer-Lindenberg, Zentralinstitut für Seelische Gesundheit, Mannheim (D):

Environmental risk mechanisms for depression

The size and burden of depression should ideally prompt a strategy of preemption and early intervention. Large interindividual variability points to the opportunity and necessity of precision prevention. On the neuroscientific side, this leads to the question of brain mechanisms of risk and resilience for this common and disabling disorder. The social environment plays an especially important role in risk, but the impact on the brain is just coming into focus. In this presentation, we review emerging evidence that combines epidemiology, social psychology and neuroscience to identify neural mechanisms of variable interindividual response to social risk factors for depression. We focus on exposures that have a presumed social component such as urbanicity, migration/refugee status and social status. We propose a specific risk and resilience circuit mediating these effects that links perigenual cingulate cortex to subcortical structures such as ventral striatum and amygdala as well as dorsolateral and anterior medial prefrontal cortex. We then discuss recent research identifying interindividual variability to three environmental resilience factors: social interactions, non-exercise activity, and urban green space. Social risk factors have a converging impact on structure and function of key nodes in this circuits, while resilience factors strengthen it. Understanding this neurobiology is helpful in designing and targeting preventive strategies through a better understanding of specific exposures contributing to resilience.