35.3 CHILDHOOD EXPOSURE TO GREEN SPACE – A NOVEL RISK-DECREASING MECHANISM FOR SCHIZOPHRENIA?

Kristine Engemann1, Carsten Bocker Pedersen1, Constantinos Tsiriggiannis1, Preben Bo Mortensen1, Jens-Christian Svenning1

1Aarhus University

Background: Schizophrenia risk has been linked to urbanization but the underlying mechanistic link remains unknown. Less green space in urbanized areas, where schizophrenia risk is high, could point to green space as an important factor. Green space is hypothesized to positively influence mental health and could mediate schizophrenia risk through noise and particle pollution removal, stress relief or other unknown mechanisms. However, the effect of green space on schizophrenia risk has not been disentangled from that of urbanization and it is unclear if different measures of green space associate differently with risk.

Methods: We used satellite data from the Landsat program to quantify green space for Denmark in 30 x 30m resolution for the years 1985–2013. The effect of quantity and heterogeneity of green space and urbanization at place of residence on schizophrenia risk was estimated using cox regression from a longitudinal population-based sample of the Danish population (943 027 persons). Schizophrenia risk was controlled for a range of individual and socioeconomic characteristics that may confound the effect of green space including age, sex and parental education, salary, and employment status.

Results: Living at the lowest amount of green space was associated with a 1.52-fold increased risk of developing schizophrenia compared to persons living at the highest level of green space. This association remained after adjusting for known risk factors for schizophrenia: urbanization, age, sex, and socioeconomic status. The strongest protective association was observed during the earliest childhood years and closest to place of residence.

Discussion: We found green space to decrease schizophrenia risk independent of urbanization - consequently pointing to green space as a new environmental risk factor for schizophrenia development. This study supports findings from other studies highlighting the natural environment as an important factor for human health, and points to a new methodological framework that combines epidemiological studies with big data approaches.

35.4 A PUBLIC HEALTH APPROACH TO THE PREVENTION OF PSYCHOSIS

Robin Murray1, Marta Di Forti1, Evangelos Vassos1, Antonella Trotta1, Harriet Quigley1, Olesya Ajnakina1, Diego Quattrone1, Giada Tripoli1, Victoria Rodriguez1, Craig Morgan1

1Institute of Psychiatry, Psychology & Neuroscience, King’s College London

Background: The main attempt to prevent the development of psychosis has been through clinics for people at clinical high risk. Such an approach is useful for research but can never reach the majority of individuals who will become psychotic. Biological markers could be used to identify individuals with unusual vulnerabilities e.g. those with copy number variations such as VCFS. However, identifying the with such markers is unlikely to impact on the majority of cases, and as yet no useful interventions are available. How therefore to prevent psychosis?

Methods: Data will be presented from 3 studies of first onset psychosis (FEP) which used similar methods of ascertainment and assessment of cases and controls; AESOP and GAP from South London and the EU-GEI across 16 sites in 5 European countries.

Results: The identified risk factors for psychosis were the polygenic risk score for schizophrenia, childhood abuse, living in a city, being from an ethnic minority, drug abuse, adverse life events. Clearly, reducing some of these (e.g. urbanicity or migration) is not within the powers of psychiatrists. The GAP study showed that the polygenic risk score accounted for the greatest variance in caseness; those with scores in the highest quintile were 7 times more likely to be a psychotic case than those in those lowest quintile. The GAP study also gave estimates of the population attributable fraction (PAF): these indicated that if no one was exposed to child abuse and use of high potency cannabis, then 16% and 24% respectively of psychosis in South London could be prevented. The EU-GEI study showed striking differences in the incidence of psychosis between Northern and Southern Europe; data will be prevented concerning the contribution of risk factors, especially cannabis use, to this.

Discussion: The knowledge that schizophrenia is the extreme of a continuum of psychosis has important implications for prevention. Preventive approaches to hypertension or obesity do not focus on identifying individuals carrying biological markers; rather they encourage members of the general population to take exercise and reduce their calorie intake. A similar approach should be adopted for psychosis. In the long-term attempts to reduce risk factors should be made e.g. addressing psychotogenic aspects of city living or by decreasing discrimination of ethnic minorities. This will be difficult. However, an obvious place to start is by attempting to influence society’s patterns of consumption of high-potency cannabis. Unfortunately, public policy in the US and certain other countries appears to be moving in the opposite direction with increases in consumption and potency. Are these countries sleep-walking to more psychosis?

Plenary

36. INVESTING IN RECOVERY – AN ECONOMIC AS WELL AS MORAL IMPERATIVE

David McDaid
London School of Economics and Political Science

Overall Abstract: ‘Recovery’ is a key concept in mental health policy around the globe. The World Health Organization has called for ‘a recovery-based approach that puts the emphasis on supporting individuals with mental disorders and psychosocial disabilities to achieve their own aspirations and goals’. Investing in evidence-based actions to help foster recovery should therefore be core to any system of support for anyone experiencing schizophrenia or other severe mental health problems. While there is clearly a moral imperative to maximise opportunities for recovery, the economic case for action can also be compelling and complementary. However, the opportunity to make an economic argument to support investment in recovery is not always taken, and even when made it is often too narrow in ambition and scope to have a major influence policy and practice. This presentation will highlight examples of the economic potential of recovery-focused services in health, employment, education and housing services. It will look at strengths and weaknesses in the way in which economic evidence is presented to policy makers, including the extent to which implementation challenges have been considered. It will argue that in making the economic case for recovery it is just as vital to look at the role of the messenger as well as the message that is being communicated.

Plenary

37. THE GUT MICROBIOME: A KEY REGULATOR OF NEURODEVELOPMENT AND BEHAVIOUR

John Cryan
University College Cork

Overall Abstract: The brain-gut-microbiota axis is emerging as a research area of increasing interest for those investigating the biological and physiological basis of neurodevelopmental, age-related and neurodegenerative disorders.
The routes of communication between the gut and brain include the vagus nerve, the immune system, tryptophan metabolism, via the enteric nervous system or by way of microbial metabolites such as short chain fatty acids. These mechanisms also impinge on neuroendocrine function at multiple levels. Studies in animal models have been key in delineating that neurodevelopment and the programming of an appropriate stress response is dependent on the microbiota. Developmentally, a variety of factors can impact the microbiota in early life including mode of birth delivery, antibiotic exposure, mode of nutritional provision, infection, stress as well as host genetics. At the other extreme of life, individuals who age with considerable ill health tend to show narrowing in microbial diversity. Stress can significantly impact the microbiota-gut-brain axis at all stages across the lifespan. Recently, the gut microbiota has been implicated in a variety of conditions including obesity, autism, schizophrenia and Parkinson’s disease. Moreover, animal models have been key in linking the regulation of fundamental brain processes ranging from adult hippocampal neurogenesis to myelination to microglia activation by the microbiome. Finally, studies examining the translation of the effects from animals to humans are currently ongoing. Further studies will focus on understanding the mechanisms underlying such brain effects and developing nutritional and microbial-based intervention strategies.

**Concurrent Symposia**

38. DO NMDAR ANTIBODIES CAUSE SCHIZOPHRENIA?

Belinda Lennox

*University of Oxford*

**Overall Abstract:** NMDAR antibodies have been described in association with some people with schizophrenia. However the finding is still controversial, and in particular some groups describe equal prevalence of antibodies in patients with schizophrenia as other disease controls, or in healthy control subjects. This symposium includes the leading academics undertaking research in this area and will discuss the hot topics in the area, reviewing the latest evidence from a range of perspectives. This will include comparison of testing methods for NMDAR antibodies, discussion of functional effects of NMDAR antibodies with relevance to schizophrenia, an update on prevalence studies of antibodies in psychosis and at risk mental states, and clinical data on the experience of screening patients for NMDAR antibodies in psychiatric hospitals. The discussant is Sarosh Irani, associate professor in neurology at the University of Oxford, who led the first European case series description of NMDAR antibodies.

38.1 IMPACT OF ANTI-NMDA RECEPTOR AUTOANTIBODIES FROM PSYCHOTIC PATIENTS ON THE GLUTAMATE SYNAPSE

Laurent Groc*,1

1*CNRS, University of Bordeaux*

**Background:** The flourishing identification of circulating autoantibodies against neuronal receptors in neuropsychiatric disorders has fostered new conceptual and clinical frameworks. However, their putative presence in different diseases, as well as in healthy subjects, has raised questions about detection reliability and pathogenic role.

**Methods:** Using a combination of single molecule-based imaging approaches, cell calcium imaging, and single-cell electrophysiological recordings, we investigated in hippocampal networks the impact of autoantibodies against glutamate NMDA receptor (NMDAR-Ab) on several aspects of the glutamate synapse.

**Results:** We ascertain the presence of circulating autoantibodies against glutamate NMDA receptor (NMDAR-Ab) in about 20% of psychotic patients diagnosed with schizophrenia and very few healthy subjects. NMDAR-Ab from patients and healthy subjects do not compete for binding on native receptor. Strikingly, NMDAR-Ab from patients, but not from healthy subjects, specifically alter the surface dynamics and nanoscale organization of synaptic NMDAR and its anchoring partner the EphrinB2 receptor. Functionally, only patients’ NMDAR-Ab prevent long-term potentiation at glutamatergic synapses while leaving NMDAR-mediated calcium influx intact. Furthermore, we unveil that NMDAR-Ab from first episode psychotic patients produced similar effects.

**Discussion:** By taking advantage of the single molecule imaging and complementary ensemble approaches, we unveil that NMDAR-Ab from psychotic patients (schizophrenic and first episode) profoundly alter NMDAR synaptic transmission and NMDAR-dependent synaptic functions, supporting a pathogenetically relevant role.

38.2 NEURONAL AUTOANTIBODIES IN PSYCHOSIS: ENOUGH ABOUT PREVALENCE, WHAT’S THE RELEVANCE?

Thomas Pollak*,1

1Institute of Psychiatry, Psychology & Neuroscience, King’s College London

**Background:** One source of controversy in the emerging field of autoimmune psychiatry concerns varying prevalence estimates of neuronal surface autoantibodies (NSAbs) in psychiatric disorders, particularly psychotic disorders. Differences in assay methodology and patient selection may contribute to varying case-control estimates.

I will argue that the field needs to move beyond small n prevalence studies, to address the question of the relevance of NSAbs in psychotic disorders, and namely the following questions:

1) Does the presence of NSAbs offer any aetiopathological insights into psychosis i.e. by associating with other disease-relevant biomarkers?
2) Do NSAbs shape the clinical phenotype of psychotic disorders?
3) Do NSAbs have a predictive role in psychotic disorders, in terms of treatment response or course of illness?

**Methods:** To address this issue, we have undertaken measurement of NSAbs using multiple immunoassays in a cohort of individuals at ultra-high risk for psychosis, and another first episode psychosis cohort. Associations between NSAb seropositivity and phenotype, outcome and biomarkers including structural MRI were explored.

**Results:** NSAbs were detected at rates of between 1% and 9% of cases in both cohorts, depending on assay used. Live CBAs detected significantly more NMDAR and GABA-AR IgG antibodies than did fixed CBAs. Rates in cases were not significantly different from controls, regardless of assay. Nevertheless in UHR subjects NSAbs, and NMDAR Abs in particular, showed clear aetiological and phenotypic relevance, associating with cognitive function (poorer verbal memory and IQ), more severe psychopathology and increased volumes of key limbic areas. Significant interactions with a marker of blood-brain barrier integrity offered further aetiopathological insights. NSAbs detected by both fixed and live CBAs demonstrated phenotypic associations and interactions with BBB status, suggesting both assays can detect phenotypically relevant antibodies in the UHR context. In FEP subjects, no such associations were noted. GABA-A receptor antibodies, which have been proposed as NSAbs with emerging disease-relevance, showed no phenotypic associations. Data on the predictive utility of NSAbs in UHR and FEP subjects will be presented.

**Discussion:** With appropriately fine-grained phenotyping and careful consideration of moderating biological factors and assay variation, clear disease-relevance of NSAbs could be established in UHR subjects but not in FEP subjects. In particular, NMDAR antibodies may have important biomarker potential in the at-risk mental state.

The failure to establish clear disease-relevance in previous psychiatric cohorts may reflect a genuinely irrelevant antibody but could also be due any of the following: