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 latest evidence from a range of perspectives. This will include comparing research in this area and will discuss the hot topics in the area, reviewing conceptual and clinical frameworks. However, their putative presence 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.

**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  
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**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-Ah) 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, significantly 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 pathologically relevant role.

### 38.2 NEURONAL AUTOANTIBODIES IN PSYCHOSIS: ENOUGH ABOUT PREVAlENCE, WHAT’S THE RELEVANCE?*

Thomas Pollak*1  
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**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 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 aetiopathological 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:
1) Inadequately fine-grained phenotyping of subjects
2) Ignoring the important moderating role of BBB permeability
3) Choosing subjects at 'too late' a stage of illness
4) Inadequately sensitive antibody detection assays

38.3 ONGOING GERMINAL CENTRE REACTIONS CONTRIBUTE TO N-METHYL-D-ASPARTATE RECEPTOR (NMDAR) ANTIBODY PRODUCTION IN NMDAR-ANTIBODY ENCEPHALITIS

Mateusz Makuch1, Robert Wilson1, Adam Al-Diwani*,1, James Varley1, Anne-Kathrin Kienzler1, Jennifer Taylor1, Patrick Waters1, Isabel Leite1, Belinda Lennox1, Sarosh Irani1

1University of Oxford

Background: Immunoglobulin G (IgG) against the NR1-subunit of the N-methyl-d-aspartate (NMDAR) receptor mediates NMDAR-antibody encephalitis (NMDAR-Ab-E). This multi-stage illness presents with an acute severe psychiatric syndrome, alongside other neurological features, similar to human and animal NMDAR antagonist models. The disease is associated with an ovarian teratoma in around 20% of cases. The cellular immunity underlying this disease is not well understood. While antibody-modifying immunotherapies often promote disease resolution, the illness can be refractory to these treatments correlating with sub-optimal outcomes.

NR1-IgG can be detected several years after clinical resolution, which may be via ongoing germinal centre reactions or the establishment of antibody-secreting cells as long-lived plasma cells in bone marrow niches. Two divergent models implicate use of differing immunotherapies to target these cells. Here we investigate the contribution of ongoing germinal centre reactions to disease progression, potentially informing disease mechanisms and guide targeted immunotherapy.

Methods: We hypothesised that recurrent antigen-driven germinal centre reactions would be associated with active generation of NR1-specific IgM and IgG and NR1-specific circulating B cells. We validated a NR1-IgM cell based assay establishing specificity cut-offs by screening healthy and disease control cohorts alongside a previously collected NMDAR-Ab-E cohort (n=46). Following this we went on to explore the temporal evolution of NR1-IgG and NR1-IgM titres in a prospective cohort (n=12).

To investigate the lymphocyte characteristics, we stimulated ovarian teratoma lymphocytes and peripheral blood mononuclear cells (PBMCs) from multiple time points under varying cytokine conditions to understand whether these circulating cells showed capacity for NR1-IgG and IgM generation.

Results: We found a 43% prevalence rate of NR1-IgM in the historic cohort. We then confirmed that NR1-IgM binding was specific by its selective depletion after anti-IgM precipitation but not with protein G. In the prospective cohort, we noted often high titres of IgM (up to 1:500) most commonly early in the disease but persisting for around 2 years. NR1-IgM levels varied in titre alongside NR1-IgG spikes. Consistently, culture experiments of patient lymphocytes (PBMCs and tumour-derived) produced varying degrees of NR1-IgM and NR1-IgG under conditions associated with B cell proliferation. The NR1-IgG levels correlated with serum NR1-IgM titres suggesting these circulating B cells made a proportional contribution to serum levels.

Discussion: Ongoing germinal centre reactions likely contribute much of the circulating NR1-specific B cell population in NMDAR-Ab-E. Autoimmunisation at these centres represents an as yet unexplored therapeutic target in this and potentially other autoimmune encephalopathies. Regional specificity of these reactions including lymph nodes draining sources of NR1-antigen require further direct evaluation.

38.4 PREVALENCE OF ANTI-NEURONAL ANTIBODIES IN PATIENTS ADMITTED WITH FIRST EPISODE OF PSYCHOSIS AND THEIR CLINICAL OUTCOMES

James Scott*,1, David Gillis2, Alex Ryan1, Hethal Hargovan2, Stefan Blum1
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Background: Anti-neuronal antibodies are associated with psychosis although their clinical significance in first episode of psychosis (FEP) is undetermined. This study examined the prevalence of anti-neuronal antibodies in patients admitted to hospital for treatment of their first episode of psychosis and described clinical presentations and treatment outcomes of those who were antibody positive.

Methods: Between July 2013 and May 2015, all consenting patients aged between 12 and 50 admitted for their first episode of psychosis to three mental health hospitals in Queensland, Australia, were tested for anti-neuronal antibodies in serum. Antibody positive patients were referred for neurological and immunological consultation and treatment.

Results: During the study, 154 FEP patients were admitted with their first episode of psychosis and 113 consented to participate. Six patients were found to have anti-neuronal antibodies; (anti-NMDAR antibodies [n = 4], VGKC antibody [n = 1], antibody against uncharacterised antigen [n = 1]). Of these, five received immunotherapy, leading to complete resolution of psychosis in four.

Discussion: A small, but significant subgroup of patients with first episode psychosis have anti-neuronal antibodies detectable in serum and evidence of central nervous system autoimmune pathology. Early identification of these patients and referral for appropriate treatment is critical to optimise recovery.

39. VIRUSES AND SCHIZOPHRENIA: IMPLICATIONS FOR PATHOPHYSIOLOGY AND TREATMENT

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Overall Abstract: The viral hypothesis of schizophrenia posits that viral infections disrupts cortical circuits that give rise to schizophrenia psychopathology. Prenatal viral exposure during key neurodevelopmental periods, either through direct effects on fetal brain or exposure to exogenous maternal cytokines and other chemokines, have been implicated. In addition, abnormal activation of dormant neuro-viruses have been linked to the pathophysiology of schizophrenia. Activation of dormant viruses has potentially important treatment implication for therapies, such as valacyclovir, that suppress viral activity. Among the viruses that have been mostly frequently associated with schizophrenia include herpes simplex virus type 1 (HSV1) and Epstein-Barr virus (EBV). The purpose of this symposium is to focus on the role of viruses in the pathophysiology of schizophrenia and results of antiviral treatment trials in this illness. Diana Perkins will present data from the North American Prodrome Longitudinal Study (NAPLS2) which is an eight-site observational study of predictors and mechanism of conversion to psychosis and is comprised of a cohort of 763 individuals at clinical high risk for developing psychosis. This paper examines methylation of promoter regions of genes associated with gene expression and reports that 10 markers correctly classified individuals who converted to psychosis. The SIRT1 gene, that is upregulated with HSV, was among the predictive markers.