2. We performed a systematic literature search on long-term treatment effects, risks and monitoring of antipsychotic medication in schizophrenia.
Results: 1. In NFBC1966 in midlife, higher lifetime doses of antipsychotics were associated with alterations in brain morphometry, poorer neurocognition, and poorer clinical outcomes. Clinical follow-up was inadequate even in half of the schizophrenia cases. In therapeutic community cohort, maximal development of psychosocial care reduced the mean dose of antipsychotics in acute psychosis ward from 370 mg/day as chlorpromazine equivalents into 160 mg/day. 2. In the literature review, three main cornerstones in the high quality longitudinal use of antipsychotic medication were: a) high, evidence-based pharmacological quality, b) optimal adjuvant psychosocial therapies, c) sophisticated long-term prescription, monitoring and follow-up practices to minimize nonadherence and psychiatric and somatic failures.
In sum, antipsychotics are effective for acute and mid-term psychosis in prevention of relapses and excess mortality. Long term antipsychotic use especially in high doses may include major iatrogenic harms, as also poorly monitored withholding or discontinuing. When aiming for an optimal benefit-risk ratio and for balancing symptomatic, functional and somatic outcomes, the goal is to aim for lower ranges of effective dosing, as well as choosing an appropriate antipsychotic agent that causes minimal side effects, and to combine adjuvant psychosocial interventions in the treatment. The often recommended personalized smallest effective dose is not so simple but still a realistic strategy in current relapse prevention practices, where doses often are too large for safety reasons.
Discussion: Cohort-based register studies are useful in examining long-term medication effects although they contain a risk of residual confounding due to their observational design. However, randomized controlled trials in long, over 3–7 years of follow-up, are unrealistic.
The systematic literature review demonstrates major open or conflicting questions in risk-benefit ratio related to long-term outcomes. Nonadherence and attrition are key problems in sustained antipsychotic medication. Standardized prescription and monitoring practices (not so much studied) might improve medication adherence and also outcomes. Current clinical guidelines advise us based on studies from first years of schizophrenia. There are only few and weak patient-level predictors of successful tapering and discontinuation of antipsychotic medication.
In the future, clinical follow-up of medication can be improved by structured follow-up and planned continuity. Life span view of antipsychotic medication stresses careful documentation of doses, responses and harms, longitudinal planning and realization of medication as part of the whole treatment program, as well as individualized and tailored selection, dosing (dose as low as possible or minimal effective dose) and follow-up by a well-trained team.

S231. THE ROLE OF DOPAMINERGIC AND GLUTAMATERGIC NEUROTRANSMISSION IN DELUSIONAL IDEATION AND SENSORY INFORMATION PROCESSING OF PATIENTS WITH SCHIZOPHRENIA IN COMPARISON TO HEALTHY HUMAN PARTICIPANTS

Wolfgang Strube*[,1], Graziella Quattrocchi[2], Simon Little[2], Louise Marshall[3], Alkomiet Hasan[1], Sven Bestmann[2]
[1]*University of Munich, LMU;* [2]*Sobell Department, UCL;* [3]*Wellcome Trust*

Background: The primary aim of this study was to generate neurobiological evidence regarding the impact of dopaminergic and glutamatergic neurotransmission on reasoning biases related to delusional ideation in patients with schizophrenia associated with impaired processing of sensory information. The proposed respective roles of these neurotransmitter systems have been encapsulated in the so-called dopamine- and glutamate-hypotheses of schizophrenia. From a behavioural perspective both reduced glutamate and enhanced dopamine levels are currently discussed as critical contributing factors to generate aberrant beliefs (glutamate) during information sampling and to generate confidence or expected precision (dopamine) during action selection. Hence, by modulating levels of glutamate and dopamine in the brain we hypothesized to induce reported impairments of patients with schizophrenia related todelusional ideation.
Methods: The study consisted of three aligned experiments: In the first two experiments a prospective interventional drug study was conducted with n=192 participants employing a randomized, placebo-controlled, double-blinded design on two parallel testing-groups, receiving either dopaminergic or glutamatergic neuromodulators: Experiment I: either 2.5mg haloperidol (D1/D2-receptor antagonist; HAL), 2.5mg bromocriptine (D2-receptor agonist; BRO), or placebo (PLC-1). Experiment II: either 120mg Dextromethorphan (NMDA-receptor antagonist, DXM), 250mg D-Cycloserine (NMDA-receptor agonist, CYC), or placebo (PLC-2). In the third experiment n=45 patients with schizophrenia (SZ) and n=45 healthy control participants (HC) matched for gender, age and IQ were investigated. All experiments employed a computerized (Matlab, Cogent) version of the Beadstask (Huq, Garety et al. 1988). In total participants processes 60 Beadstask trials subdivided into three levels of difficulty: (I) easy trials with a bias of 80–90% for one predominant bead color in a sequence, (II) difficult trials (60–70% bias), and (III) ambiguous trials (no bias, 50% likelihood). Additionally, the task consisted of three parts that were presented in a fixed order: an easy draws-to-decision condition, an easy probability estimates condition, and a difficult draws-to-decision condition.
Results: In accordance with foregoing studies, SZ patients showed significantly less draws to decision compared to HC (all $p \leq 0.038$). Explorative analysis across experimental conditions further revealed no significant differences for participants receiving DXM (NMDA-receptor antagonist) compared SZ patients (all $p \geq 0.090$), but obtained less draws to decision in the DXM group than all other groups. Whereas following HAL intervention the number of draws increased significantly compared to any other experimental group (all $p \leq 0.048$). Analyzing the probability estimates condition we quantified changes of probability estimates on an individual subject level whenever there was a change of bead color in a sequence (so called disconfirmatory evidence score, DES). In case of easy and difficult trial types we observed significantly higher DES scores in participants with SZ compared to HC ($p \leq 0.003$) and again obtained no differences between SZ and DXM ($p=0.037$).
Discussion: Our findings are supportive for a hypothesized relationship between neurotransmitter state alterations of glutamate and dopamine in patients with schizophrenia and the delusional ideation. Future analysis will focus on developing a computational behavioral model of cognitive processing of the Beadstask, implementing our neurobiological findings in order to further disentangle the neurobiological underpinnings of delusional ideation in patients with schizophrenia.

S232. ALPHA7 NICOTINIC RECEPTOR AGONISTS REVERSE THE HYPERDOPAMINERGIC STATE IN THE MAM MODEL OF SCHIZOPHRENIA

Gilda Neves*[,1], Anthony Grace[1]
[1]*University of Pittsburgh*

Background: Most investigations into the pharmacology of schizophrenia have revolved around dopaminergic and glutamatergic neurotransmission; however, one neurotransmitter that has not received adequate attention is the cholinergic system. Indeed, several post-mortem, genetic and epidemiologic studies link specifically the alpha7 nicotinic receptor (nAChR) to schizophrenia, and the potential use of alpha7 modulators as a treatment strategy is an active field of research. Nevertheless, studies to date have been limited to normal animals rather than on a validated neurodevelopmental model of schizophrenia. Moreover, knowledge about the differential impact of orthosteric and allosteric modulators in vivo is lacking. Thus, we investigated the effects of alpha7 nAChR modulation on dopamine