diffusivity (MD) was significantly increased in the hippocampal part of the cingulum in unmedicated patients (n=40) compared to healthy controls (n=41). Longitudinal analyses showed no changes in FA, MD, RD or white matter macrostructure in healthy controls over time, and no changes in patients after six weeks of treatment with risperidone.

**Discussion:** With state of the art data-processing methods we only found small areas of white matter integrity deficits in our predominantly medication-naive patients. This is consistent with prior reports of limited white matter alterations at disease onset that may progress with illness duration. Our data suggests that a short-term course of antipsychotic medication may not alter white matter microstructure, but studies with longer follow-up durations will be important to determine long term effects of antipsychotic medications.

**O6.7. COMMON NEUROANATOMICAL ABNORMALITIES IN FIRST EPISODE PSYCHOSIS ACROSS SEVERAL INDEPENDENT SAMPLES**

Sandra Vieira\(^1\), Cristina Scarpazza\(^1\), Benedicto Crespo-Facorro\(^2\), Diana Tordesillas-Gutierrez\(^2\), Victor Ortiz-Garcia de la Foz\(^2\), Esther Setien-Suero\(^2\), Floor Scheepers\(^3\), Qiyong Gong\(^4\), Tiago Reis Marques\(^1\), Robin Murray\(^1\), Anthony David\(^1\), Paola Dazzan\(^1\), Andrea Mechelli\(^1\)

\(^1\)Institute of Psychiatry, Psychology and Neurosciences, King’s College London; \(^2\)Marqués de Valdecilla University Hospital, Instituto de Investigación Valdecilla, CIBERSAM; \(^3\)University Medical Center Utrecht; \(^4\)School of Public Administration, Sichuan University

**Background:** Structural abnormalities in first episode psychosis (FEP) tend to be subtle and widespread. Most studies investigating structural abnormalities in this clinical population have used small samples, and therefore may be under-powered. In addition, most studies have examined participants at a single research site, and therefore the results may be specific to the local sample investigated. Consequently, findings from existing studies have often been heterogeneous. This study aimed to overcome these issues by testing for neuroanatomical abnormalities in individuals with FEP relative to healthy controls that are expressed consistently across five independent datasets.

**Methods:** Structural Magnetic Resonance Imaging data were acquired from a total of 572 patients with FEP and 502 age and gender comparable healthy controls (HC) at five sites - London (UK), Utrecht (Netherlands), Chengdu (China) and two independent sites at Santander (Spain). Voxel-based morphometry (VBM) as implemented in Statistical Parametric Mapping software (SPM12) was used to investigate differences in gray matter volume (GMV) between the two groups. The statistical analysis was carried out using an analysis of variance (ANCOVA), with diagnostic group and scanning site as factors, and age and gender as covariates of no interest. Neuroanatomical alterations in patients with FEP relative to HC common to the five datasets were identified by comparing the total FEP group against the total HC group, and then using the inclusive masking option (at p<0.05 uncorrected) to identify those regions that survived the comparison between FEP and HC within each dataset. Individual clinical scores from each site were normalised and then used to examine their association with GMV in the total sample. Statistical inferencias were made at p<0.05 after family-wise error correction for multiple comparisons.

**Results:** Relative to HC, FEP showed a widespread pattern GMV reduction in fronto-temporal regions bilaterally, including the gyrus rectus, orbitofrontal, temporal, fusiform, precentral and lingual gyri, anterior cingulate and insula as well as in the parietal lobe in the precuneus gyrus. The largest GMV reduction was found in the left gyrus rectus which is part of the inferior frontal lobe. Negative correlations were found between this region and positive symptoms severity (r=-.2, p<.001) and duration of illness (r=-.1, p<.012), but not with negative symptoms (r=0, p=.991). Patients also showed GMV increases in the temporal gyrus bilaterally, left inferior frontal gyrus and right cerebellum relative to HC.

**Discussion:** This study identified a common pattern of fronto-temporal-parietal reductions in five independent FEP samples; in addition, some of these reductions were more pronounced in patients with more severe positive symptoms and longer duration of illness. This pattern of results suggests the presence of symptom- and stage-dependent neuroanatomical alternations in FEP that are expressed above and beyond site-related differences in recruitment criteria and scanning parameters.

**O6.8. GLUTAMATERGIC DYSFUNCTION AND TREATMENT RESPONSE IN MINIMALLY TREATED AND CHRONIC SCHIZOPHRENIA PATIENTS**

Elias Mouchlianitis\(^1\), Lucy Yanes\(^2\), Erica Barry\(^2\), Krishna Patel\(^2\), Katie Wong\(^1\), Lilla Porfy\(^1\), Sukhi Shergill\(^1\)

\(^1\)Institute of Psychiatry, Psychology and Neuroscience, King’s College London

**Background:** Glutamatergic dysfunction as a result of NMDA receptor hypofunction has been implicated in antipsychotic treatment-resistant schizophrenia, however its nature in very early stages and chronic stages of the disease is still unknown. Data on glutamate and treatment response are currently limited in two separate studies, one in first-episode patients (Egerton et al., 2012) and one in chronic patients (Mouchlianitis et al., 2016). Here we acquired proton magnetic resonance spectroscopy measures from a large sample of minimally treated first episode and chronic schizophrenia patients, and a group of matched healthy controls. Both first-episode and chronic schizophrenia groups were further stratified by treatment response. This allowed us to investigate glutamatergic dysfunction in both early and later stages of the diseases in relation to treatment-response.

**Methods:** We acquired proton magnetic resonance spectroscopy (1H-MRS) at 3 Tesla from bilateral anterior cingulate cortex (ACC) from 170 participants. 137 participants with a diagnosis of schizophrenia (according to ICD-10 criteria) and 33 healthy controls matched for age, sex, and socioeconomic background consented to participate in this study. The patient sample included 95 minimally treated first-episode patients, with illness duration less than 36 months, of which 65 has shown good response and 26 have shown persistent psychotic symptoms; and a group of 42 chronically-ill patients with illness duration over 3 years. The chronic group was classified into 21 antipsychotic treatment-resistant patients and 21 antipsychotic treatment-responsive patients. 1H-MRS data were analyzed using a standard basis function within LC-Model. Our primary measure was glutamate to creatine ratio (Glu/Cr) and its correlation to N-Acetylaspartic acid to creatine ratio (NAA/Cr).

**Results:** The main new finding is that first-episode patients with persistent psychotic symptoms show significantly higher Glu/Cr and NAA/Cr correlation R(23)=0.76, P<0.001 compared to first-episode patients in remission R(65)=0.43, P<0.00, Fisher’s r-to-z, Z=1.97, P=0.05, effect size d=0.48. Compared to healthy controls (who did not show any Glu/Cr to and NAA/Cr correlation R(33)=0.24, P<0.33) the FEP-resistant group showed a significant difference, Z=2.6, P<0.005, representing a large effect size of d=0.87 but not the FEP-responsive group, Z=0.97, P=0.17. Remarkably, when we examined first-episode patients with antipsychotic exposure of less than 6 months, we found an extremely high correlation in the non-responsive group R(5)=0.95, P=0.01, compared to the responsive-group, R(20)=0.44, P<0.05, which reflected a large effect size of d=0.99. Chronically-ill resistant patients showed a significant correlation R(21)=0.48, P<0.05 and responsive trend-level correlation R(21)=0.41, P<0.07, but neither group differed from healthy controls.

**Discussion:** Our study provides the first 1H-MRS evidence for acute metabolic perturbations in glutamatergic neurotransmission in minimally treated schizophrenia patients with persistent psychotic symptoms. These

Abstracts for the Sixth Biennial SIRS Conference

Downloaded from https://academic.oup.com/schizophreniabulletin/article-abstract/44/suppl_1/S92/4957294 by guest on 26 July 2018
are absent in later stages of the disease for both treatment-resistant and treatment-responsive patients. It is likely that neurodegenerative processes resulting from excitotoxicity due glutamatergic dysfunction are most impactful within the first few months from illness onset. Our data point to the urgent need to identify reliable biomarkers for the prediction of antipsychotic treatment-response and the development of novel interventions to address glutamatergic perturbations at the beginning of their illness.

**O7. Oral Session: Pharmacology**

**O7.1. MIDBRAIN DOPAMINE NEURON ACTIVITY CONTROLS THE EFFECTS OF REPEATED KETAMINE ON STRIATAL DOPAMINERGIC FUNCTION**

Michelle Kokkinou* 1, Oliver Howes2
1 Medical Research Council, London Institute of Medical Sciences; 2 Medical Research Council, London Institute of Medical Sciences, King’s College London

**Background:** Schizophrenia is a chronic debilitating disorder which affects about 21 million people worldwide (WHO 2017). Elevated pre-synaptic striatal dopamine synthesis capacity is a robust neurochemical alteration seen in patients with schizophrenia compared to controls, with a large effect size Cohen’s d=0.79 (Howes et al., 2012). Ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist induces psychotomimetic effects in healthy human (Krystal et al., 1994, Stone et al., 2007) and exacerbates psychotic symptoms in patients with schizophrenia (Lahti et al., 1991). For these reasons, it has been used to model the neurochemical alterations seen in schizophrenia such as dopaminergic over-activity (Usun et al., 2013, Kokkinou et al., 2017). However, the effect of sub-chronic ketamine on dopamine synthesis capacity in vivo is not known. Here we investigated the effect of sub-chronic ketamine on striatal dopamine synthesis capacity in vivo using Positron Emission Tomography (PET) imaging and on locomotor activity in the mouse. Moreover, via a chemogenetics approach (Roth 2016) we explored the role of midbrain dopamine neuron activity in mediating ketamine-induced effects.

**Methods:** All procedures were conducted under licence in accordance with the UK Animals (Scientific Procedures) Act of 1986. Mice received a sub-anaesthetic dose of ketamine or an equivalent volume of saline for five consecutive days. Locomotor activity was assessed in the open field test. Moreover, mice received a dynamic 3,4-dihydroxy-6-[(18F)-fluoro-L-phenylalanine Positron Emission Tomography (PET) scan to assess striatal dopamine synthesis capacity in vivo. Data were analysed using an extended Patlak graphical analysis approach (Walker et al., 2013). Further midbrain dopamine neurons were transduced with an adeno-associated virus vector expressing Gi-coupled (hM4Di) inhibitory receptors under the control of the dopamine transporter (DAT) promoter in DATCre positive mice. Standard immunohistochemistry was used to label dopamine neurons and mCherry expression in dopamine neurons was confirmed using confocal microscopy. Two weeks following the stereotaxic injection of the viral construct, mice received clozapine N-oxide (CNO) to study the effects of inhibiting dopamine neuron firing on locomotor activity and striatal dopamine synthesis capacity in the sub-chronic ketamine model. Data were analysed by two-tailed independent samples t-tests, one-way ANOVA and repeated measures two-way ANOVA followed by Bonferroni post hoc tests where appropriate. p<0.05 was considered statistically significant.

**Results:** Sub-chronic ketamine treatment significantly increased striatal dopamine synthesis capacity (p<0.05, effect size=1.2) and induced locomotor sensitization (p<0.01). hM4Di-mCherry viral construct was successfully transduced in midbrain dopamine neurons with over 98% specificity. Chemogenetic inhibition of midbrain dopamine neurons prevented the ketamine-induced elevation in striatal dopamine synthesis capacity (p>0.05, effect size=0.64) and locomotor sensitization (p>0.05).

**Discussion:** Our data show that sub-chronic ketamine results in the elevation in striatal dopamine synthesis capacity and locomotor sensitization and that these effects require midbrain dopamine neuron activation. Furthermore, our data are in support of the hypothesis that NMDA receptor hypofunction on GABAergic interneurons leads to disinhibition of glutamatergic projections and subsequently increase in dopamine neuron activity and dopamine synthesis capacity in projection targets such as the striatum.

**O7.2. BREAKTHROUGH ON ANTIPSYCHOTIC MAINTENANCE MEDICATION IN A CLINICAL COHORT**

Jose Rubio*, 1 Christoph Correll2, Anil Malhotra3, Majnu John2, John Kane1
1 Northwell Health; 2 Zucker Hillside Hospital

**Background:** Antipsychotic drugs are effective in reducing the severity of psychotic symptoms both in the short and long term, and in reducing risk of relapse. However, some patients may develop a relapse of their psychotic symptoms despite continued antipsychotic treatment. Arguably, this phenomenon would be best studied in patients treated with long-acting injectable (LAI) formulations, where the dates of exposure can be confirmed, removing the potential confounder of non-adherence. The characterization of this phenomenon can add important knowledge about the intrinsic efficacy of antipsychotic drugs, potential mechanisms involved in the decrement of their efficacy, and the underlying pathophysiology of psychosis that is not modulated via primarily dopaminergic mechanisms. Despite the implications of this clinical phenomenon, research on breakthrough on antipsychotic maintenance medication (BAMM) in models not confounded by non-adherence has been limited. To date, little is known about the incidence and predictors of BAMM in clinical populations.

**Methods:** We extracted data from a cohort of individuals with a psychotic disorder who were initiated on their first LAI treatment between 2010 and 2015 in the injection clinic at The Zucker Hillside Hospital (New York, USA). We defined BAMM as hospitalization during the period of continuous treatment with LAI, which we used as the primary outcome. LAI treatment was considered continuous for each treatment episode if it was administered following the manufacturer’s recommendations for the first 2 months, and until there was a delay in the administration that would have required additional oral supplementation according to the manufacturer instructions (typically >1.5 times the scheduled interval of administration). We measured the cumulative incidence and time to BAMM in individuals with continuous LAI administration, and conducted univariate and multivariate analyses of covariates.

**Results:** A total of 291 episodes of continuous treatment were observed. Of those, 44 (15.1%) led to hospitalization associated with greater odds of hospitalization during continuous antipsychotic treatment. The median time to hospitalization was 204.5 days. In the multivariate analysis, the number of hospitalizations prior to onset of LAI treatment (5 vs 2, OR=2.75; 95% CI=1.60–4.72) and time since last hospitalization (4 vs 24.8 weeks, OR 0.70; 95% CI=0.53–0.91) were significantly associated with greater odds of hospitalization during continuous antipsychotic treatment. Individuals who were hospitalized despite continuous treatment were more likely to subsequently be treated with clozapine or ECT (18.2% vs 0, OR=4.93; 95% CI=1.25–19.40). We conducted a multivariate Cox regression analysis for time to hospitalization and a sensitivity analysis comparing BAMM with individuals that completed 2 years of continuous antipsychotic maintenance with LAI antipsychotic. The median time to hospitalization was 204.5 days. In the multivariate analysis, the number of hospitalizations prior to onset of LAI treatment (5 vs 2, OR=2.75; 95% CI=1.60–4.72) and time since last hospitalization (4 vs 24.8 weeks, OR 0.70; 95% CI=0.53–0.91) were significantly associated with greater odds of hospitalization during continuous antipsychotic treatment. Individuals who were hospitalized despite continuous treatment were more likely to subsequently be treated with clozapine or ECT (18.2% vs 0, OR=4.93; 95% CI=1.25–19.40). We conducted a multivariate Cox regression analysis for time to hospitalization and a sensitivity analysis comparing BAMM with individuals that completed 2 years of continuous treatment without being hospitalized and the results were consistent.

**Discussion:** In a clinical cohort, a meaningful proportion of patients with a psychotic disorder treated with LAs were hospitalized, despite confirmed continuous treatment. The median time to this event occurred about 7 months after onset of LAI treatment, suggesting that these patients had been stable and had reached steady state antipsychotic levels prior to hospitalization. Patients with a more active illness at the time of initiation of LAI treatment were more likely to relapse. These data suggest that more