^{1}H MRS Monitoring of GABAergic and Glutamatergic Response to 4 Weeks of Antipsychotic Treatment in Medication-naïve First-episode Psychosis Patients

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Target Audience:
Researchers and clinicians with interest in neuropsychiatric disorders and/or in MRS studies of such disorders

Purpose:
Mounting preclinical and clinical evidence implicates dysregulations of the amino acid neurotransmitter systems of GABA and glutamate in the pathophysiology schizophrenia. The purpose of this study was to use the standard J-edited spin-echo difference ^{1}H MRS technique to measure levels of GABA and glutamate+glutamine (Glx) *in vivo* in the medial prefrontal cortex (MPFC) and bilateral dorsal caudate (DCA) of medication-naïve first-episode psychosis (FEP) patients at baseline and then after 4 weeks of treatment with risperidone, a common second-generation antipsychotic medication.

METHODS
Subjects: Twenty-seven non-affective FEP patients, diagnosed by DSM-IV-TR criteria and confirmed by SCID interview, were enrolled into the study. Subjects were excluded if they (a) had any concomitant medical or neurological illness, current substance abuse or history of substance dependence (excluding nicotine), comorbidity of any other axis I disorders; (b) were considered to be at high risk for suicide; or (c) showed psychomotor agitation. Patients were antipsychotic-naïve at baseline and were able to provide written informed consent. Use of psychotropic medications (e.g., benzodiazepines) was not permitted for the duration of the study. Twenty medically healthy subjects, as assessed by the SCID-IV-NP, served as the normal comparison group.

Treatment and ^{1}H MRS Measurements: Following baseline assessments, the FEP patients were treated with risperidone for 4 weeks, with antipsychotic doses adjusted based on clinical judgment. Serum risperidone levels were obtained to verify medication compliance, and response to treatment was defined as a reduction of at least 25% on the total score of the positive and negative syndrome scale (PANSS) after 4 weeks of treatment. Levels of GABA and Glx in the MPFC and bilateral DCA of all the participants were obtained at baseline and after 4 weeks of treatment using the standard J-editing technique. GABA and Glx peak areas were derived by frequency-domain spectral fitting and expressed as ratios relative to the area of synchronously acquired unsuppressed voxel tissue water (W).

RESULTS
Compared to the matched healthy control (HC) subjects, the FEP patients had significantly higher baseline MPFC GABA/W ($p = 0.04$) and Glx/W ($p = 0.02$) [**Fig. 1**], as well as higher baseline DCA GABA/W ($p = 0.04$) and Glx/W (0.04). After 4 weeks of treatment with risperidone, differences in GABA/W and Glx/W between FEP patients and HC seen at baseline vanished for both brain regions (all p-values > 0.5). These results are shown graphically in **Figure 1** for the MPFC.

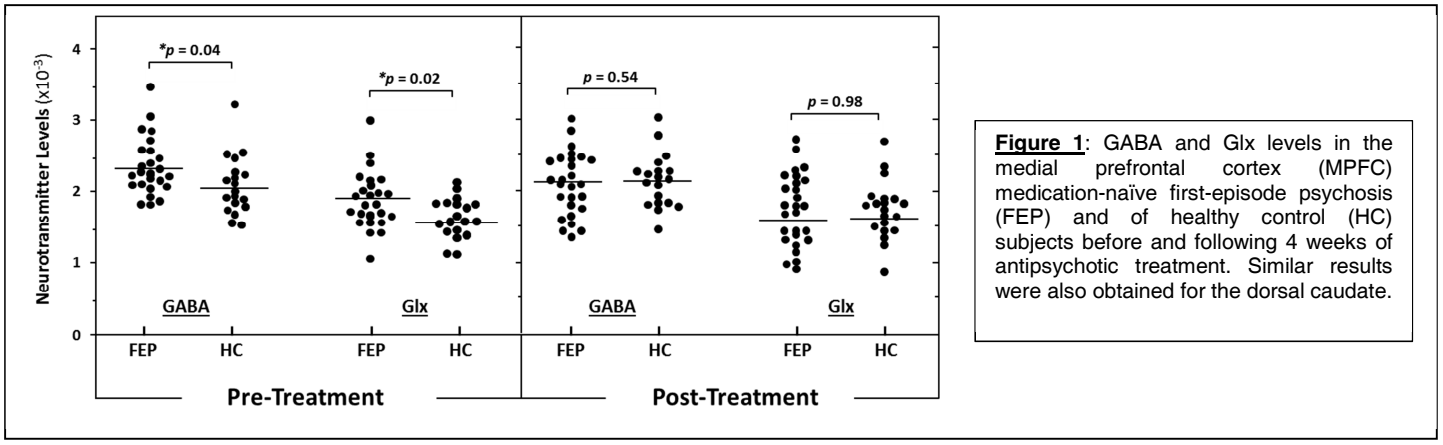

Figure 1: GABA and Glx levels in the medial prefrontal cortex (MPFC) medication-naïve first-episode psychosis (FEP) and of healthy control (HC) subjects before and following 4 weeks of antipsychotic treatment. Similar results were also obtained for the dorsal caudate.

DISCUSSION
In this pilot study, we found regional elevations of both GABA/W and Glx/W in antipsychotic-naïve FEP subjects, which normalized following 4 weeks of antipsychotic treatment (e.g., **Fig. 1**). Our finding of baseline elevations of Glx in medication-naïve FEP patients is in excellent agreement with most prior MRS measurements of glutamatergic compounds in medication-naïve, unmedicated or minimally medicated patients with SZ[1-7]. On the other hand, our finding of baseline elevations of GABA in the present cohort of medication-naïve FEP patients is not only novel, but it is also in apparent contradiction to *postmortem* brain data, which have generally reported GABA deficits in SZ[8]. Since the present study has shown that the effect of antipsychotic treatment is to decrease or normalize both Glx and GABA levels (Fig. 1), a potential source of the discrepancy between the present *in vivo* MRS and prior *postmortem* brain measures of GABA could be that *postmortem* data might be confounded by long periods of exposure to antipsychotics.

CONCLUSION
The presented results are consistent with the growing body of evidence suggesting that schizophrenia, specifically in medication-naïve and unmedicated patients, is characterized by abnormal elevations of both GABA and glutamatergic compounds, and that a potential mechanism of action of antipsychotics is to decrease or normalize the levels of both neurotransmitters.

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