In Vivo ¹H MRS Assessment of Cortico-Striatal GABAergic and Glutamatergic Dysregulations in Antipsychotic-naïve First-episode Schizophrenia

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INTRODUCTION
One of the most widely investigated neurochemical hypotheses of schizophrenia (SZ) posits neurodevelopmental deficits in the disorder that involve dysregulations of the inhibitory and excitatory amino neurotransmitter systems of γ-Aminobutyric acid (GABA) and glutamate (Glu), respectively. In support of this hypothesis are several ¹H MRS studies[1-7] that have reported increased levels of Glu, glutamine (Gln) or Glu+Gln (Glx) in antipsychotic-naïve, unmedicated or minimally medicated patients with SZ, and in subjects experiencing first-episode psychosis (FEP). In addition, while brain GABA levels have generally been thought to be decreased in SZ based on postmortem evidence[8], this view was recently challenged by an in vivo ¹H MRS study that found significant elevations of cortical GABA in unmedicated SZ patients but normal in an independent cohort of treated subjects[7]. To the best of our knowledge, no prior studies have assessed brain GABA levels in FEP patients. The purpose of this study was to measure and compare, for the first time, brain GABA and Glx levels in antipsychotic-naïve FEP patients and age- and sex-matched healthy control (HC) subjects.

METHODS
Subjects
Twelve non-affective FEP patients (3 females, mean age = 22.58±5.72), diagnosed by DSM-IV-TR criteria and confirmed by SCID interview, were enrolled into the study. Patients 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 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-three HCs (3 females, mean age = 21.00±3.43) assessed by the SCID-IV-NP, served as comparison subjects.

In vivo Brain GABA and Glx Measurements by ¹H MRS
All in vivo brain GABA and Glx spectra were recorded on a 3.0 T GE MR system from a voxel 4.5x2.5x2.0-cm³ in the striatum and a 3.0x2.5x2.5-cm³ voxel in the medial prefrontal cortex (MPFC), comprising the anterior cingulate cortex. Each spectrum was acquired in 13.4 min using the standard J-edited spin echo difference method and an 8-channel phased-array head coil, with TE/TR 68/1500 ms and 512 interleaved excitations. The resulting GABA and Glx peak areas were derived by frequency-domain spectral fitting and expressed as ratios relative to the area of simultaneously acquired unsuppressed voxel tissue water (W).

RESULTS

Compared to the matched HC subjects (Fig. 1), MPFC Glx/W and GABA/W were elevated in FEP patients (p = .002 and p = 0.001, respectively). In the striatum, we found strong trend-level elevations in the FEP group for both Glx/W (p = .052) and GABA/W (p = .076) compared to the HC group (Fig. 1).

DISCUSSION AND CONCLUSION

This pilot study has found regional elevations or trend-level elevations of both GABA/W and Glx/W in antipsychotic-naive FEP subjects, which, along with a recent study that also reported elevations of GABA and Glx in unmedicated patients with SZ but normal in an independent medicated cohort[7], paint a picture in which elevations of the two neurotransmitters are present in medication-naive, first episode psychosis. Our finding of elevations of Glx in medication-naive FEP patients is in general agreement with most prior studies[1-7]. On the other hand, our finding of elevated GABA in this group of patients are novel, and are an apparent contradiction to postmortem data, which have reported deficits of the neurotransmitters in SZ. A potential source of this discrepancy with postmortem markers of elevations of these transmitters in subjects exposed to substantial periods of medication treatment. While the present results still require replication in larger studies, they have provided a compelling rationale for longitudinal investigations of brain GABA and Glx as potential noninvasive biomarkers of SZ.

LITERATURE CITED:

Fig. 1: Levels of Glx and GABA in the medial prefrontal cortex (MPFC) and striatum of first-episode psychosis (FEP) and healthy controls (HC) subjects. *** Highly significant; * trending.