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Glutamatergic metabolites among adolescents at risk for psychosis

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ABSTRACT

Proton-Magnetic Resonance Spectroscopy (^{1}H-MRS) may serve as an important tool for identifying biomarkers that aid the understanding of early psychosis, as development of this condition may be associated with metabolite concentration changes that reflect an alteration in glutamatergic mechanisms. The current study explored ^{1}H-MRS metabolite concentrations in the striatum and anterior cingulate cortex (ACC) as potential biomarkers of psychosis-risk symptom severity. In a sample of 12 adolescents at clinical high-risk for psychosis, the subclinical symptom of grandiosity significantly correlated with glutamate in the ACC. Striatal glutathione, a marker of oxidative stress linked to the glutamatergic system, significantly correlated with grandiosity. Anterior cingulate glutathione significantly correlated with grandiosity and disorganized communication. These findings suggest that within a small sample of young people at clinical high-risk, glutamatergic metabolites are correlated with symptomatology generally predictive of conversion to psychosis. These mechanisms may serve as relevant biomarkers for facilitating prediction of symptom severity and providing insight into the etiology of early psychosis.

1. Introduction

The phase of risk for psychosis is characterized by sub-threshold psychotic symptoms, which are associated with psychological distress and need for services. Assessment of psychosis-risk generally relies on self-report and structured interview measures, which have limited accuracy (Cannon et al., 2008; Correll et al., 2010; Fusar-Poli et al., 2013; Kline and Schiffman, 2014; Simon et al., 2011). Such self-report approaches could be improved through the discovery of biologically-based markers. Consistent with national research priorities (Cuthbert and Insel, 2013), a biomarkers approach has the potential to help illuminate the neural mechanisms of psychosis development in an effort to refine clinical prediction criteria, while also reducing bias inherent in self-report and clinical approaches (Keshavan et al., 2005). Thus, a major goal for the field of psychosis-risk research is to increase accuracy in early detection in order to identify individuals who are at most imminent risk of developing a full psychotic disorder. A fuller understanding of brain-behavior relationships carries the additional potential to identify empirically derived treatment targets.

Traditional theories of biological contributors to psychosis tend to focus on the role of dopamine (e.g., Laruelle and Abi-Dargham, 1999; Laruelle et al., 1999; Laruelle et al., 2005; Howes and Kapur, 2009). Psychosis onset, however, has also been linked to hypofunctioning of the glutamatergic N-methyl-D-aspartate receptor (NMDAR; Olney and Farber, 1995), and recent hypotheses incorporate both theories, such that NMDAR hypofunction and glutamatergic pathway disruption is posited to contribute to dopaminergic dysregulation and eventual development of psychosis (Schwartz et al., 2012).

A recent meta-analysis suggests consistent elevations of glutamatergic metabolites across various brain regions in individuals with psychosis compared to healthy controls (Merritt et al., 2016). The authors describe elevations in glutamate, glutamine, and a combination of both signals (Glx) across the basal ganglia, thalamus, and medial temporal lobe. Specific patterns for the different stages of psychotic illness were also reported. For example, elevations in medial frontal Glx levels were observed for individuals at risk for psychosis (Merritt et al., 2016).

A closer look at the psychosis-risk glutamate + glutamine literature reveals notable gaps in research and understanding. The review article from Merritt et al. (2016) refers to the psychosis-risk studies as a combination of clinical high-risk (CHR) and familial risk studies. Upon

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further examination, the majority of these studies identify individuals as being at psychosis-risk based on genetic loading (e.g., having a first- or second-degree relative with schizophrenia; see supplemental materials in Merritt et al. (2016)). Only five prior studies (two of which were from overlapping samples) have examined glutamate + glutamine in symptomatic individuals who met interview-defined psychosis-risk criteria. Of these few studies, only one focused on the basal ganglia. In 2011, de la Fuente-Sandoval and colleagues identified elevated glutamate levels in the striatum of participants at clinical high-risk (CHR) for psychosis compared to controls, a population on the psychosis continuum for whom little work in this area has been conducted. A follow-up of these participants suggested further elevations in striatal glutamate in the seven patients who converted to psychosis (de la Fuente-Sandoval et al., 2013). The authors, while acknowledging their small sample size, reported that their pilot study suggests that glutamate levels may be elevated for individuals who develop psychosis. Despite promising group differences, the relation between striatal glutamate and symptom severity was not significant in that study. Better understanding the link between glutamate and symptom severity within a clinical high-risk group may offer insight into the link between the NMDAR system and psychosis-risk.

Another metabolite that is implicated in psychosis development through NMDAR hypofunctioning is glutathione (GSH), an antioxidant (Do et al., 2000; Fournier et al., 2014; Kantrowitz and Javitt, 2010; Matsuzawa et al., 2008; Steullet et al., 2006; Olney and Farber, 1995). The oxidized form of glutathione modulates NMDAR (Kantrowitz and Javitt, 2010), and a glutathione deficit has been interpreted as one potential causal factor for the hypofunction of NMDAR in schizophrenia (Do et al., 2000; Steullet et al., 2006). In addition to the traditional measurement strategy through plasma, glutathione can also be measured via in vivo Proton Magnetic Resonance Spectroscopy (^{1}H-MRS; see Kantrowitz and Javitt, 2010; Matsuzawa et al., 2008; Terpstra et al., 2005; Wood et al., 2009; Xin et al., 2016). Despite the possible relevance to the developmental course of psychosis, there are no studies examining glutathione in a clinical high-risk population.

In addition to group comparisons between those with psychotic illness and controls on glutamatergic metabolites, a small number of previous studies have identified associations between psychotic symptom severity and glutamatergic metabolites with mixed findings (see Table 1). Despite this growing body of research, whether associations may emerge during the clinical high-risk phase of psychotic illness is unknown, as too few studies to date have reported on psychotic symptom severity among samples at CHR in relation to ^{1}H-MRS metabolites for a reliable conclusion to be made (see supplementary materials in Merritt et al. (2016)).

The current study examined the hypothesized association between ^{1}H-MRS-measured glutamatergic markers and psychosis-risk symptoms in adolescents at clinical high-risk. We selected the anterior cingulate cortex (ACC) and the striatum as areas of interest, given their relevance to dopamine synthesis (Howes et al., 2011) and the glutamatergic system (Schwartz et al., 2012). Specifically, the prefrontal cortex communicates directly with the limbic system and both brain regions are implicated in one of several glutamatergic pathways (Schwartz et al., 2012). In a recent review, Poels et al. (2014) note elevated levels of glutamatergic metabolites in the medial frontal cortex and the basal ganglia. Both of these brain regions are represented in our study given our focus on the ACC and the striatum. Higher levels of glutamate in the striatum and ACC were expected to correlate with higher levels of positive psychosis-risk symptom severity. The combined signal of glutamate and glutamine (i.e., Glx) in both brain regions was also hypothesized to share a positive correlation with psychosis-risk symptom severity. Based on prior ^{1}H-MRS studies with individuals in more advanced stages of illness, glutathione (GSH) in the ACC and the striatum was hypothesized to share a negative correlation with symptom severity.

2. Methods

2.1. Participants

Participant data was collected via the Institutional Review Board-approved Maryland Early Intervention: Strive for Wellness/Youth FIRST programs at the University of Maryland School of Medicine, Division of Child and Adolescent Psychiatry, and the University of Maryland, Baltimore County. We scanned 12 participants at clinical high-risk for psychosis between the ages of 12 and 23 (see Table 2). To be eligible for the current study, participants met criteria for a psychosis-risk syndrome, had no contra-indications to MRI, and were receiving mental health treatment.

2.2. Procedures

Participants provided consent to complete the study (if under 18, minors provided assent and their legal guardian[s] provided consent) before participating. All participants completed a brief safety screen that assessed for any metal objects in or on the body that would prevent them from safely completing the MRI procedure.

2.3. Measures

2.3.1. Structured interview for psychosis-risk syndromes (SIPS)

The clinician-administered SIPS assesses the following symptom groupings: positive (hallucinations, delusional ideas, etc.), negative (anhedonia, avolition, etc.), disorganized (odd behavior, bizarre thinking, etc.), and general (sleep disturbance, motor disturbances, etc.) symptoms (Miller et al., 2002). SIPS ratings are based on a 7-point

Table 1
Literature on symptom severity correlations with glutamatergic metabolites among psychosis-risk.

Authors	*Sample*	*Metabolite & location*	*Symptom correlate*
de la Fuente-Sandoval et al. (2011)	UHR	Associative-striatal Glu	(ns) SIPS positive, negative, disorganized, & general sx
Egerton et al. (2014)	UHR	↓L thalamic Glu	↑ Total positive sx
Fusar-Poli et al. (2011)	ARMS	ACC Glu	(ns) CAARMS, PANSS
Keshavan et al. (2009)	Genetic risk	R/L caudate Glx	(ns) Chapman schizotypy scores
Liemburg et al. (2016)	UHR	PFC Glx	(ns) PANSS
Natsubori et al. (2014)	UHR	mPFC Glx	(ns) PANSS
Stone et al. (2010)	ARMS	↑L striatal [18F]DOPA uptake ↓hippocampal Glu	↑Abnormal beliefs ↑Disordered speech (trend)
Tandon et al. (2013)	Genetic risk	↑R/L caudate Glx	↑Sum (positive + disorganized sx)
Yoo et al. (2009)	High genetic risk	ACC, L dlPFC, & L thalamus Glx	(ns) PANSS & BPRS

Note: UHR = ultra high risk; ARMS = at-risk mental state; CAARMS = Comprehensive Assessment for At-Risk Mental States; ns = not significant; PANSS = Positive and Negative Symptom Scale; BPRS = Brief Psychiatric Rating Scale; sx = symptoms; Glu = glutamate; Gln = glutamine; Glx = glutamate + glutamine; (m/dl)PFC = (medial/ dorsolateral) prefrontal cortex; R/L = average of right and left region metabolite level; R = right hemisphere; L = left hemisphere.