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Striatal metabolic alterations in non-psychotic adolescent offspring at risk for schizophrenia: A ^{1}H spectroscopy study

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ABSTRACT

In vivo proton (^{1}H) Magnetic Resonance spectroscopy (^{1}H MRS) has shown abnormalities in young first-episode patients with schizophrenia. It is unclear whether these abnormalities reflect trait related vs. state related alterations in schizophrenia. We compared young first-degree relatives of schizophrenia patients and healthy controls using ^{1}H MRS. We hypothesized alterations in the ^{1}H MRS metabolites *N*-acetyl aspartate (NAA) and glutamate in corticostriatal and thalamic brain regions. We obtained multi-voxel, short-TE ^{1}H MRS measurements at 1.5 Tesla in 40 consenting adolescent offspring at risk for schizophrenia (HR), and 48 age matched healthy controls (HC). Absolute levels of NAA, phosphocreatine plus creatine (PCr + Cr), choline-containing compounds (GPC + PC), myo-inositol and glutamate plus glutamine (Glu + Gln) were obtained from the seven different anatomical brain areas (nominal voxel size of 4.5 cm^3 each) and corrected for tissue voxel composition. HR subjects showed NAA ($p = .0049$), PCr + Cr ($p = 0.028$) and GPC + PC ($p = 0.0086$) reductions in the caudate compared with HC subjects. Male HR subjects had significant Glu + Gln reductions compared to male HC subjects ($p = .0022$). HR subjects had increased NAA in prefrontal white matter. NAA levels in the prefrontal white matter and Glu + Gln levels in the inferior parietal/occipital region were both increased in HR without psychopathology compared with HC subjects. Lower NAA, PCr + Cr and GPC + PC levels may reflect an overall reduction in cellular processes in the caudate of HC subjects, perhaps related to decreases in cell density, or synaptic overpruning. Further studies are needed to examine the pathophysiologic significance of these observations, and their potential predictive value for schizophrenia related psychopathology that may emerge in these at risk relatives during adolescence and early adulthood.

1. Introduction

Proton (^{1}H) magnetic resonance spectroscopy (^{1}H MRS) is a noninvasive approach to investigate neurochemistry in the living human brain. ^{1}H MRS has been widely used to investigate *in vivo* neurochemical integrity in major psychiatric disorders such as schizophrenia. Much of the research has focused on two important metabolites. *N*-acetyl-aspartate (NAA), one of the most abundant ^{1}H MRS metabolites, has been variously thought to be a marker of functioning neuroaxonal tissue that includes functional aspects of the formation and/or maintenance of myelin (Chakraborty et al., 2001). NAA is present in axons, dendrites and synaptic terminals and increases during the first several years of brain development in grey matter. This provides additional evidence that NAA does not merely reflect the number of neurons but is a marker of functioning neurons, or in the context of development a marker of dendritic and synaptic proliferation (Pouwels et al., 1999). Glutamate (Glu), another highly "visible" MRS metabolite, is of

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importance in schizophrenia because of the currently widely held view that abnormal Glu neurotransmission might underlie the pathophysiology of this illness (Goff and Coyle, 2001; Javitt and Zukin, 1990). Glutamate is synthesized in presynaptic neurons from glutamine; astrocytes take up Glu from extracellular compartments and convert to glutamine (Gln), which is in turn transported back to the presynaptic neurons (Magistretti and Pellerin, 1999).

In schizophrenia, reductions in NAA have been observed in cortical brain regions such as frontal and temporal lobes primarily in chronic treated patients (Keshavan et al., 2000; Steen et al., 2005). At the other extreme, NAA reductions have also been reported in childhood-onset of schizophrenia, which is consistent with greater severity of symptoms in these patients. However, the evidence supporting lower NAA levels at least in frontal areas is weaker in treatment-naive first-episode patients with schizophrenia (Keshavan et al., 2000). Stanley et al., (2007) observed an association of lower NAA with an earlier onset age in the prefrontal cortex (PFC) of treatment-naive first-episode patients with schizophrenia, suggesting a neurodevelopmental contribution to this abnormality. The NAA reductions may be seen in subcortical regions as well; a recent study of minimally treated schizophrenia patients showed reduced NAA in caudate (Bustillo et al., 2008).

Due to the complexity in the quantification of glutamate with ^{1}H MRS, results investigating possible alterations in glutamatergic metabolites such as Glu and Gln in schizophrenia are mixed. Stanley et al. (2007) and Bartha et al. (1999) reported no change in prefrontal glutamate levels in treatment-naïve first-episode schizophrenia (Stanley et al., 2007; Ohrmann et al., 2005). Theberge et al. (2003) observed increased glutamine in the left anterior cingulate cortex and thalamus of treatment-naïve first-episode schizophrenia patients. Of interest are the recent reports of large effects of increased Glu and Gln in the left dorsolateral PFC of schizophrenia patients (Olbrich et al., 2008; van Elst et al., 2005; Rusch et al., 2008); however, it is unclear if the appropriate *a priori* knowledge in quantifying the broad underlying signals of macromolecules and lipids was used in these studies because an earlier study by Stanley et al. (2004) showed a significant increase in the macromolecule signal in the left DLPFC of treatment-naïve first-episode schizophrenia patients.

Studies of at-risk populations for developing schizophrenia allow clarification of metabolic alterations that may be related to the consequences of already evident illness versus those related to the underlying vulnerability. Trendworthy decreases in NAA/choline ratios in the anterior cingulate (Keshavan et al., 1997) and NAA concentration reductions in the left thalamus (Yoo et al., 2009) have been observed in genetic high risk relatives. Progressive NAA/choline ratio reductions have also been observed in individuals deemed to be at high clinical risk for schizophrenia (Jessen et al., 2006 Oct). Thus, NAA alterations appear to occur in the premorbid phase of schizophrenia, but the brain regions seem variable. Increased Glu + Gln/PCr + Cr ratios have been reported in right medial PFC in adolescent offspring of schizophrenia patients (Tibbo et al., 2004). Abnormalities in glutamatergic neurotransmission have been implicated in schizophrenia based on clinical, post-mortem and animal model studies (Olney and Farber, 1995). The precise nature of the Glu alterations may be complex, with both reductions in the presymptomatic phase and increases in acute phases of the illness, having been postulated (Keshavan, 1999). Clearly, more data are needed to clarify the nature of MRS metabolic alterations in the premorbid phase of schizophrenia.

Studies of adolescent and young adult offspring of schizophrenia patients (HR) allow us to noninvasively investigate neurobiologic alterations without the potential confounds of state related alterations and medication effects (Keshavan et al., 2005). Specifically, we have seen volume reductions in the basal ganglia (Rajarethinam et al., 2007) and superior temporal cortex (Rajarethinam et al., 2004). Volume changes in the thalamus and PFC (Lawrie et al., 2001) have also been observed. The neurochemical underpinnings of these structural alterations in HR subjects have been sparsely studied.

In this study, we compared young HR offspring and healthy controls using short echo-time (TE), multi-voxel ^{1}H spectroscopy data in HR subjects and healthy control (HC) subjects. In light of the prior literature reviewed above we predicted that HR subjects would have decreased NAA in cortical, striatal and thalamic brain regions. Based on the glutamatergic hypothesis as discussed above we also sought to examine glutamate alterations in these brain regions compared to healthy controls (HC). Specifically, we predicted reductions in glutamatergic metabolites in the HR offspring without symptoms, but increases in those with psychopathology. ^{1}H spectroscopy provides information on other metabolites (described later) which were explored in secondary analyses. We examined the effects of gender (Buckley et al., 1994) and age to address the potential contribution of these measures to the observed spectroscopic changes. Finally, we also examined whether subgroups of HR subjects divided by the presence or absence of psychopathology would differ with regard to these metabolites, and whether the metabolites would correlate with quantitative measures of psychosis related psychopathology such as schizotypy.

2. Experimental/materials and methods

2.1. Subjects

The participants were identified at the Western Psychiatric Institute and Clinic (WPIC), Pittsburgh or related clinical sites. HR subjects were recruited by first approaching patients with schizophrenia with eligible offspring in our outpatient clinical services; we also recruited subjects via advertisements in community locations. Forty individuals (18 males; mean age of 15.6 ± 2.9 years old; age range of 10.6 to 20.2 years old) with at least one parent suffering from schizophrenia or schizoaffective disorder were included in this study (High Risk Offspring; HR). Of the HR subjects, 7 had a family history of depression and bipolar disorder in a first-degree relative, 7 had a family history of depression in either a first or second degree relative, 5 had a family history of bipolar disorder in a 1st or 2nd degree relative, and 1 had a family history of depression and bipolar disorder in a 2nd degree relative. Forty-six healthy controls (HC; 21 males; mean age 15.6 ± 3.7 years old; age range of 10.5 to 21.6 years old) were also recruited from the same neighborhoods as the HR subjects. Of the HR subjects, 32 were right handed, 1 was left handed, and two were ambidextrous (5 HR subjects were missing this data). Of the HC subjects 30 were right handed, 4 were left handed (6 HC subjects were missing this data). Subjects with a DSM-IV diagnosis of a