Schizophrenia Research 148 (2013) 59–66

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Brain metabolite alterations in young adults at familial high risk for schizophrenia using proton magnetic resonance spectroscopy

Neeraj Tandon [a], Nicolas R. Bolo [a], Kunal Sanghavi [a], Ian T. Mathew [a], Alan N. Francis [a], Jeffrey A. Stanley [b], Matcheri S. Keshavan [a,*]

[a] Department of Psychiatry, Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, Harvard Medical School, Boston, MA, USA
[b] Wayne State University, Detroit, MI, USA

ARTICLE INFO

Article history:
Received 10 November 2012
Received in revised form 19 May 2013
Accepted 22 May 2013
Available online 20 June 2013

Keywords:
Early psychosis
High risk
Schizophrenia
Spectroscopy

ABSTRACT

Background: Proton magnetic resonance spectroscopy (^{1}H MRS) enables in-vivo measurement of several relevant brain metabolites and has provided evidence of a range of neurochemical abnormalities in schizophrenia, especially in glutamate and N-acetyl-aspartate (NAA). While individuals at high familial risk for schizophrenia (HR) exhibit some neurobiological findings observed in the disorder, ^{1}H MRS findings and their clinical correlates are not well characterized in this population.

Methods: We compared 23 adolescent and young adult offspring of schizophrenia patients with 24 age- and sex-matched healthy controls using ^{1}H MRS. We acquired multi-voxel, short TE ^{1}H MRS measurements at 1.5 T and obtained metabolite concentrations of N-acetyl-aspartate (NAA), combined glutamate and glutamine (Glu + Gln) and choline-containing compounds (GPC + PC) for the left and right thalamus, anterior cingulate gyrus, and caudate. We also assessed the relationship between regional metabolite levels, clinical measures and brain volume in a subset of 16 high-risk and 15 control subjects.

Results: Compared to healthy controls, high-risk subjects showed reductions in NAA levels in all three regions (thalamus, caudate, and anterior cingulate cortex), increases in Glu + Gln in the thalamus and caudate, and increases in GPC + PC in the anterior cingulate. In HR, thalamic Glu + Gln concentration was positively correlated and thalamic NAA inversely correlated with measures of schizotypy. Anterior cingulate GPC + PC and caudate Glu + Gln were significantly correlated with attenuated psychotic symptom severity. Anterior cingulate NAA was correlated with executive function.

Conclusions: Our data suggest the occurrence of metabolic alterations in young relatives of schizophrenia patients similar to those seen in patients with established illness. The observed correlations with cognitive deficits and psychosis-related psychopathology suggest that these metabolic measures may have value as biomarkers of risk for schizophrenia.

1. Introduction

Schizophrenia is a familial disorder characterized by a range of structural and functional brain abnormalities. First-degree relatives of probands with schizophrenia have 10–12 times greater risk of developing the illness in comparison to the general population (Erlenmeyer-Kimling et al, 1995; Tandon et al., 2008) and these 'familial high-risk (HR)' individuals exhibit, to a lesser extent, a number of neurobiological findings noted in persons with schizophrenia (Whyte et al., 2006; Keshavan et al, 2008; Liu et al., 2009; McIntosh et al., 2011). A better understanding of the relationship between the neurobiological and clinical attributes of the familial high-risk group can potentially help elucidate the pathophysiology of the early stages of schizophrenia (Smieskova et al., 2010).

Proton magnetic resonance spectroscopy (^{1}H MRS) is an established neuroimaging method employed to examine neurochemistry in the living brain. The most common metabolites measured in different brain regions by ^{1}H MRS include N-acetylaspartate (NAA, a marker of functioning neural tissue that includes functional aspects of the formation and/or maintenance of myelin, (Moffett et al., 2007), glutamate + glutamine (a marker of glutamatergic metabolism, Sibson et al., 1998; Di Costanzo et al., 2003), choline containing metabolites (GPC + PC, involved in membrane metabolism), and phosphocreatine + creatine (PCr + Cr, involved in energy metabolism, Catani et al., 2001; Hammen et al., 2003). ^{1}H MRS studies at different stages of schizophrenia and of individuals at familial or clinical high-risk for developing schizophrenia reveal a decrement in NAA, increases in Glu + Gln, and variable alterations in GPC + PC in different brain regions, notably in the anterior cingulate, thalamus and caudate

* Corresponding author at: Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, 75 Fenwood Road, Boston, MA 02115, USA. Tel.: +1 2488851057.
E-mail addresses: neerajtandon25@gmail.com (N. Tandon), keshavanms@gmail.com (M.S. Keshavan).

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.05.024

(Nasrallah et al., 1994; Steen et al., 2005; Abbott and Bustillo, 2006; Keshavan et al, 2009; Shirayama et al., 2010; Brugger et al., 2011). Findings are not consistent, however (Uhl et al., 2011), and their clinical correlates are inadequately defined.

In this study, we compared ^{1}H MRS metabolites in various brain regions between adolescent and young adult offspring of schizophrenia probands and healthy controls. Based on previous studies, we hypothesized that in comparison to healthy controls, the familial high-risk subjects would exhibit lower NAA levels and increased Cho and Glx levels (Stone et al., 2010; Brugger et al., 2011) in the anterior cingulate, thalamus and the caudate. We further examined the relationship between metabolites that significantly differed between high-risk subjects and healthy controls on the one hand and clinical and neurobiological attributes linked to likelihood of conversion to psychosis such as schizotypy, cognitive function, attenuated psychotic symptoms, and regional brain volume reductions on the other (Smieskova et al., 2010; Wood et al., 2011; Tandon et al., 2012a).

2. Methods

2.1. Subjects

The study was conducted at Wayne State University, Detroit and was approved by the Wayne State University Institutional Review Board. Subjects were recruited by approaching patients via their treating clinicians (for high risk relatives) or directly through advertisements (for both high risk relatives and healthy controls). All participants signed informed consent following a full explanation of the study. For participants <18 years of age, consent was provided by the parent or guardian and the subjects provided informed assent. Diagnoses of schizophrenia were confirmed in the index relatives using the Structured Clinical Interview for DSM Disorders (SCID, Spitzer et al., 1992). Clinical evaluation of both high-risk relatives (HR) and healthy controls (HC) was conducted by using the SCID supplemented by the Behavioral Disorders section of the Schedule for Affective Disorders and Schizophrenia for Children (K-SADS, Kaufman and Schweder, 2003). Twenty-three offspring of individuals with schizophrenia and 24 age-matched healthy controls, who had complete MRS and structural imaging data, were included. A subset of 16 HR subjects and 15 healthy controls with complete imaging data also received the Structured Interview for Prodromal Symptoms (SIPS, Miller et al., 2002), the Wisconsin Schizotypy Scales (Chapman et al., 1978), and the Wisconsin Card Sorting test (Heaton et al., 1993). None of the HR subjects or healthy controls met criteria for prior cannabis abuse.

2.2. Clinical measures and cognitive assessments

Of the 23 HR subjects, 16 received the Structured Interview for Prodromal Symptoms (SIPS), the Chapman Schizotypy Scales, and the Wisconsin Card Sorting test at baseline. The 19-item SIPS assesses symptoms in four domains (positive, negative, disorganized, and general symptoms) and rates symptom severity on a 0–6 scale on the Scale of Prodromal Symptoms (SOPS), with scores of 3–5 indicating prodromal or attenuated psychotic symptoms. Positive and disorganization symptoms are considered putative prodromal symptoms and are included in the proposed DSM-5 definition of "Attenuated Psychosis Syndrome" whereas negative and general symptoms are not (Tandon and Carpenter, 2012). The sum of the positive and disorganization subscale scores was therefore utilized as a measure of severity of attenuated psychosis. The four Chapman Schizotypy Scales include perceptual aberration, magical ideation, social anhedonia, and physical anhedonia. Of these, perceptual aberration and magical ideation define a positive schizotypy factor that has been found to predict likelihood of psychosis in longitudinal studies of psychosis-prone subjects (Lenzenweger, 1994; Kwapil et al., 2008; Tandon et al., 2012a). Therefore, we utilized the sum of scores on the perceptual aberration and magical ideation scale as the schizotypy score. On the Wisconsin Card Sorting test (Heaton et al., 1993), percentage of perseverative errors was used as a measure of executive function. This has been found to be a sensitive measure of executive cognitive impairment in individuals at increased familial risk for developing schizophrenia (Bhojraj et al., 2010; Kim et al., 2011).

2.3. Spectroscopic imaging ^{1}H MRS

Spectroscopic imaging acquisition methods are described elsewhere (Keshavan et al., 2009) and are briefly summarized here. A 2D, multi-voxel, short-TE ^{1}H MRS acquisition was performed using a 1.5 T GE SIGNA imaging system (LX platform, GE Medical Systems, Waukesha, WI). It combined a point-resolved spectroscopy (PRESS) sequence (Bottomley et al., 1984) with chemical shift imaging (CSI). The region of interest (ROI) defined by the PRESS sequence was 20 mm thick and 142 ± 10 mm × 110 ± 8 mm in-plane. The ROI was parallel to the anterior commissure–posterior commissure line and its inferior limit was at the superior edge of the orbital bone resulting in an ROI encompassing the anterior cingulate gyrus, caudate, thalamus, inferior parieto-occipital cortex, inferior prefrontal cortex, prefrontal white matter and posterior white matter (Fig. 1). CSI was performed with the following parameters: 240 × 240 mm^2 FOV divided into 16 × 16 phase-encoding steps or voxels with nominal dimensions 15 × 15 × 20 mm^3, TR = 1500 ms, TE = 30 ms, BW = 2.5 kHz, 2048 data points.

For spectroscopic processing, the CSI grid was shifted to align with anatomical landmarks using 3DICSI (Zhao et al., 2005) and the sub-ROIs were selected. The CSI data set of 1024 complex data points was zero filled to 2048 data points, and then exported for processing with LCModel (Provencher, 1993). Figs. 2 and 3 show LCModel graphical output best-fit spectra. Data from four HR subjects and two healthy controls were rejected from further analysis based on the following criteria: Cramer–Rao lower bound values above 20% for NAA, Cr + PCr, Cho, or Glx, (Jansen et al., 2006; Helms, 2008) or LCModel warnings indicating a failure to fit a spectrum. Data rejection was required due to noise and artifacts likely caused by inadequate water suppression or field homogeneity adjustment. Freesurfer and FSL tools (Dale et al., 1999; Smith et al., 2004) were used to segment each ROI into cerebral-spinal fluid, gray matter and white matter. The grey and white matter tissue and CSF voxel content values, along with the appropriate correction factors, were incorporated into the calculation of absolute metabolite values (Stanley, 1995). Absolute concentrations in units of millimoles per liter (mM) were obtained by applying the water-scaling method in LCModel (Provencher, 1993), which scales the model metabolite peak signal area per proton to the unsuppressed water signal area per proton from the voxel using the following formula:

$$F_{scale} = S_{met} \times [H_2O]_{voxel}/S_{H2O})$$

where F_{scale} is the scaling factor applied to the metabolite data, S_{met} is the model metabolite signal area per proton, S_{H2O} is the unsuppressed water signal area per proton in the voxel, and $[H_2O]_{voxel}$ is the voxel water concentration in mM. We did not correct for relaxation effects.

We used the following equation to compute the water concentration in the voxel by correcting for estimated different water concentrations of each tissue fraction (Ernst et al., 1993):

$$[H_2O]_{voxel} = ([H_20]_{CSF} \times F_{CSF}) + ([H_20]_{GM} \times F_{GM}) + ([H_20]_{WM} \times F_{WM})$$

where F_{CSF}, F_{GM}, and F_{WM}, were the partial volume fractions of cerebrospinal fluid (CSF), grey matter (GM), and white matter (WM), respectively, and $[H_20]_{CSF}$ = 55,556 mM, $(H_20]_{GM}$ = 43,300 mM, and