



## Proton magnetic resonance spectroscopy and thought disorder in childhood schizophrenia

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### ABSTRACT

**Objective:** Although magnetic resonance spectroscopy has identified metabolic abnormalities in adult and childhood schizophrenia, no prior studies have investigated the relationship between neurometabolites and thought disorder. This study examined this association in language-related brain regions using proton magnetic resonance spectroscopic imaging ( $^1\text{H}$  MRSI).

**Method:** MRSI was acquired bilaterally from 28 youth with childhood-onset schizophrenia and 34 healthy control subjects in inferior frontal, middle frontal, and superior temporal gyri at 1.5 T and short echo time (TR/TE = 1500/30 ms). CSF-corrected “total NAA” (tNAA; N-acetyl-aspartate + N-acetyl-aspartyl-glutamate), glutamate + glutamine (Glx), creatine + phosphocreatine (Cr + PCr), choline compounds (Cho), and myo-inositol (ml) were assayed in manually drawn regions-of-interest partitioned into gray matter, white matter, and CSF and then coregistered with MRSI. Speech samples of all subjects were coded for thought disorder.

**Results:** In the schizophrenia group, the severity of formal thought disorder correlated significantly with tNAA in the left inferior frontal and superior temporal gyri and with Cr + PCr in left superior temporal gyrus.

**Conclusions:** Neurometabolite concentrations in language-related brain regions are associated with thought disorder in childhood-onset schizophrenia.

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### 1. Introduction

Proton magnetic resonance spectroscopy ( $^1\text{H}$  MRS) is a non-invasive, *in vivo* neuroimaging technique that interrogates specific aspects of neurochemistry. As such, MRS offers possibilities to better understand underlying abnormalities and to develop therapeutics for brain-related illnesses like schizophrenia. Most MRS studies on schizophrenia (reviewed in Steen et al., 2005) have focused on the largest  $^1\text{H}$  MRS peak thought to indicate neuronal integrity (Urenjak et al., 1993; Demougeot et al., 2001). About three-quarters of this resonance's intensity is generated by the amino acid N-acetyl-aspartate (NAA); the remaining quarter is due to its derivative N-acetyl-aspartyl-glutamate (NAAG) (Pouwels and Frahm, 1997; Edden et al., 2007). In this paper, we refer to the combined peak “total NAA” (tNAA). Other metabolites of interest in  $^1\text{H}$  MRS include glutamate plus glutamine (Glx), creatine plus phosphocreatine (Cr + PCr), choline compounds (Cho), and myo-inositol (ml).

Several MRS studies have found that absolute tNAA levels and the ratios, tNAA/Cr + PCr and tNAA/Cho, are below-normal in the hippo-

campus (Maier et al., 1995; Bertolino et al., 1996; Deicken et al., 1998, 1999), anterior cingulate cortex (Yamasue et al., 2002; Yasukawa et al., 2005; Jessen et al., 2006), and dorsolateral prefrontal cortex (Bertolino et al., 1996; Callicott et al., 2000; Molina et al., 2007; Zabala et al., 2007) of adult schizophrenia patients. Similar to these findings in adults, MRS studies in childhood schizophrenia demonstrated lower tNAA/Cr + PCr in the hippocampus and dorsolateral prefrontal cortex bilaterally compared to healthy control children (Bertolino et al., 1998) and significantly lower tNAA in left dorsolateral prefrontal cortex compared both to children experiencing first episodes of psychosis and to healthy controls (Zabala et al., 2007). Another study illustrated above-normal Cr + PCr and Cho in the anterior middle cingulate cortex, non-cingulate frontal cortex, and caudate head (O'Neill et al., 2004). Above-normal Glx was also found in the right medial frontal lobe in children at high genetic risk for schizophrenia (Tibbo et al., 2004).

Formal thought disorder, a symptom of childhood schizophrenia, includes illogical reasoning and loosening of associations (Caplan et al., 2000). Prior volumetric, functional magnetic resonance imaging (fMRI), and  $\text{H}_2^{15}\text{O}$ -PET studies demonstrated involvement of the superior temporal (Shenton et al., 1992; McGuire et al., 1998; Holinger et al., 1999; Kircher et al., 2003), middle frontal (Kircher et al., 2003), and inferior frontal gyri (McGuire et al., 1998; Assaf et al., 2006; Cerullo et al., 2007) in the thought disorder of adults with schizophrenia. A recent fMRI study showed that the severity of thought disorder in childhood schizophrenia was associated with

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reduced cortical activity in the left inferior frontal gyrus and superior temporal gyrus during semantic and syntactic tasks, in the dorsolateral prefrontal cortex and dorsal medial prefrontal cortex during the semantic task, and in the insula during the syntactic task (Borofsky et al., 2010). Combined, these studies suggest that cortical regions that process language-related information may play a role in the thought disorder of schizophrenia.

Thus, the exploratory proton magnetic resonance spectroscopy investigation described here not only interrogated possible metabolite differences in patients compared to healthy controls, but also examined the relationship between metabolite concentrations and severity of thought disorder in childhood onset schizophrenia. We employed the magnetic resonance spectroscopic imaging (MRSI) variety of MRS to simultaneously examine multiple small ( $\sim 1 \text{ cm}^3$ ) volume elements ("voxels") each containing a high percentage of the targeted region-of-interest (ROI) (Bertolino et al., 1999; Maudsley, 2002). Moreover, we acquired MRSI at short-TE (30 ms), which allows for superior detection of Glx and ml and also yields larger signal intensities for tNAA, Cr + PCr, and Cho. We anticipated significantly different regional metabolite levels in the superior temporal (Shenton et al., 1992; McGuire et al., 1998; Holinger et al., 1999; Kircher et al., 2003), middle frontal (Kircher et al., 2003), and inferior frontal (McGuire et al., 1998; Assaf et al., 2006; Cerullo et al., 2007) gyri in patients with schizophrenia compared to the healthy control subjects and that, within the schizophrenia group, neurometabolite levels in these brain regions would vary in relation to the severity of thought disorder.

## 2. Methods

### 2.1. Subjects

The study included 28 children with schizophrenia (15 boys, 13 girls), aged 8.4–17.8 years (mean age  $\pm$  SD:  $14.1 \pm 3.0$ ), recruited from community child psychiatry clinics. The 28 subjects were screened from a total population of 207. Two additional subjects met all inclusion and no exclusion criteria, but could not participate in the study because they were severely ill and unable to get to or lie in the scanner. A schizophrenia diagnosis was based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), administered separately to each child and parent as described previously (Caplan et al., 2000). At the time of testing, the average duration of illness was (mean  $\pm$  SD)  $3.4 \pm 3.1$  years. To be included in the study, these children met DSM-IV criteria for schizophrenia with onset of symptoms by age 13. Exclusionary criteria included: (a) IQ < 70, (b) bilingualism, (c) braces, (d) an underlying neurological disorder, (e) a metabolic disorder, (f) a hearing disorder, (g) left handedness, and (h) psychosis associated with an organic disorder or substance abuse. At the time of the study, 23 patients were being treated with medications: 11 with neuroleptics alone, 10 with neuroleptics plus non-neuroleptics, and 2 with non-neuroleptics alone. None of the healthy control subjects were medicated. Neuroleptic dose was expressed as chlorpromazine equivalents (CPZ) (mean  $\pm$  SD for schizophrenia group:  $162.3 \pm 171.3$ ).

We also included 34 healthy control subjects (15 boys, 19 girls), aged 6.4–17.2 years (mean age  $\pm$  SD:  $11.5 \pm 2.9$ ), who were recruited from four public and two private schools in the Los Angeles community. Both healthy control and schizophrenia subjects completed face-to-face evaluations and were screened for psychiatric, neurological, language, and hearing disorders through a structured telephone interview with a parent. We excluded any children manifesting symptoms of these disorders in the past or after enrolling in the study.

### 2.2. Procedures

This study was conducted in accordance with the policies of the Human Subjects Protection Committees of the University of California,

Los Angeles. Informed assent and consent were obtained from all subjects and parents, respectively.

#### 2.2.1. Neuroimaging

Structural MRI and  $^1\text{H}$  MRSI were acquired together at 1.5 T with a Siemens Sonata scanner using a standard quadrature head coil. Study subjects were not sedated at the time of scanning. In addition to localizer scout scans, structural MRI consisted of a pair of sagittal spoiled gradient recalled (SPGR) sequences yielding high-resolution T1-weighted whole-brain volumes. Two acquisitions were performed separately and subsequently co-registered to each other and averaged to diminish the contribution of any subject movement during scanning. MRSI was acquired with PRESS (TR/TE = 1500/30 ms, NEX = 4, slab thickness = 9 mm, in-plane resolution =  $11 \times 11 \text{ mm}^2$ ) from three slabs. Figs. 1–2 indicate slab positioning and anatomical parameters used to make sure that all slabs were localized approximately in the same brain regions across subjects. The first two slabs (Fig. 1) were sagittal-oblique (roughly parallel to the ipsilateral temple) in orientation and sampled the left and right peri-Sylvian region including inferior frontal, superior temporal, and other nearby cortex. The third slab (Fig. 2) was coronal-oblique and sampled bilateral middle frontal ("dorsolateral prefrontal") cortex, mesial prefrontal cortex (pregenual anterior, anterior middle paracingulate cortex, or superior frontal cortex depending on individual subject anatomy) and prefrontal white matter (mainly corona radiata) lying in between. We excluded any subjects with clinically relevant structural abnormalities.

Using software and protocols developed at the UCLA Laboratory of Neuroimaging (Blanton et al., 2004; Taylor et al., 2005), regions-of-interest (ROIs) consisting of cortex, superjacent sulcal CSF, and subjacent white matter were sketched manually for bilateral inferior frontal gyri (IFG), superior temporal gyri (STG), and middle frontal gyri (MFG) using the sagittal T1-weighted MRI volume of each subject in multiplanar view (Fig. 3). Independently, the entire brain was segregated into gray matter, white matter, and CSF subvolumes (Shattuck et al., 2001). By overlapping the ROIs with the whole-brain gray matter, white matter, and CSF subvolumes, we divided each ROI into three separate "tissue-segmented ROIs." All personnel involved in region measurement received extensive specialized training in neuroanatomy. Intra- and interrater reliability were maintained at an intraclass correlation coefficient of at least 0.90 for each ROI.

MRSI data were post-processed with the LCMoDel package (Provencher, 2001), yielding metabolite values for major resonances of tNAA (2.01 ppm), Glx (2.1–2.5 ppm), Cr + PCr (3.01 ppm), Cho (3.24 ppm), and ml (3.54 ppm). Numerous minor metabolites, particularly lipids and macromolecules, were included in the fit. Our self-designed MRSI Voxel Picker (MVP) program (Fig. 4) (O'Neill et al., 2006) was used for co-processing of MRI and MRSI data. For each MRSI slab, MVP reconstructed the subject's whole-brain T1-weighted gray matter, white matter, and CSF volumes, as well as the tissue-segmented ROIs, which were manually delineated as described above, into the space of the chosen MRSI slab. MVP then returned the tissue content (both on whole-brain and ROI bases) and CSF-corrected metabolite levels for each voxel in the slab and given ROI. Using automated quality control features (aided by manual inspection), the operator selected and averaged together all voxels within the ROI meeting fixed tissue-content and spectral quality criteria. For each ROI, values were averaged together for voxels containing at least 75% by volume gray matter plus white matter, a signal-to-noise ratio of three or greater, and a full width at half maximum (FWHM) less than or equal to 0.1 ppm. Only metabolite peaks satisfying the LCMoDel criterion of less than or equal to 20% standard deviation were included in the average. MVP implemented these quality-control criteria automatically. Additionally, with the help of a guided user interface, all voxels that passed these criteria were manually inspected by raters blind to age, gender, and diagnosis. Voxels that showed significant

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