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Metabolic mapping of deep brain structures and associations with symptomatology in autism spectrum disorders

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ABSTRACT

Structural neuroimaging studies in autism report atypical volume in deep brain structures which are related to symptomatology. Little is known about metabolic changes in these regions, and how they vary with age and sex, and/or relate to clinical behaviors. Using magnetic resonance spectroscopy we measured N-acetylaspartate, choline, creatine, myoinositol and glutamate in the caudate, putamen, and thalamus of 20 children with autism and 16 typically developing controls (7–18 years). Relative to controls, individuals with autism had elevated glutamate/creatine in the putamen. In addition, both groups showed age-related increases in glutamate in this region. Boys, relative to girls had increased choline/creatine in the thalamus. Lastly, there were correlations between glutamate, choline, and myoinositol in all three regions, and behavioral scores in the ASD group. These findings suggest changes in deep gray matter neurochemistry, which are sensitive to diagnosis, age and sex, and are associated with behavioral differences.

1. Introduction

Atypical structure and function in the caudate, putamen and thalamus have been reported in individuals with autism spectrum disorders (ASD). However to date, little is known about the relation between metabolite concentrations in these regions and ASD symptomatology. These structures link the cortex and basal ganglia in a functional loop (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986). The caudate and putamen, otherwise known as the striatum, are the "input" structures of the basal ganglia and receive projections from the cortex (Alexander & Crutcher, 1990; Alexander et al., 1986). The striatum mediates behaviors such as voluntary motor control (Grillner, Hellgren, Ménard, Saitoh, & Wikström, 2005), learning (Doya, 2000) and cognition (Balleine, Delgado, & Hikosaka, 2007). The thalamus relays sensory and motor information from the basal ganglia and other regions of the brain to the cortex.

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Structural magnetic resonance imaging studies have reported a significant increase in the volume of the caudate in individuals with ASD, relative to typically developing controls (Haznedar et al., 2006; Hollander et al., 2005; Rojas et al., 2006; Sears et al., 1999; Voelbel, Bates, Buckman, Pandina, & Hendren, 2006). Caudate volume in ASD has also been found to increase with age from childhood to adulthood, while caudate volume decreased with age in controls (Langen et al., 2009). Atypical caudate and total putamen volumes were found to correlate positively with repetitive behavior scores on the autism diagnostic interview-revised (ADI-R) (Hollander et al., 2005), and in addition, caudate volume abnormalities were significantly associated with an insistence on sameness also measured by the ADI-R (Langen et al., 2009). Additionally, lower glucose metabolic activity in the caudate, putamen and thalamus has been reported, bilaterally, in individuals with ASD (Haznedar et al., 2006). Despite these findings, our understanding of metabolite concentrations in these regions and how they relate to clinically significant ASD behaviors such as social-communication impairments and repetitive behaviors are largely unknown.

Magnetic resonance spectroscopy (MRS) is a non-invasive imaging technique that can provide metabolite and biochemical information about the brain. Specific metabolite concentrations can indicate neuronal and/or glial density, cell-membrane processes or energy metabolism within brain regions (Cecil & Jones, 2001; Soares & Law, 2009). N-acetylaspartate (NAA) forms the most robust spectral peak because of its abundance in the brain, second in quantity only to glutamate. NAA is often viewed as a marker of neuronal integrity and may be involved in synaptic maintenance, axonal myelination and cellular osmosis (Birken & Oldendorf, 1989; Cecil & Jones, 2001; Miller, 1991; Soares & Law, 2009). Peaks attributed to choline-containing compounds (Cho) are thought to indicate glial density and processes involved in membrane metabolism (Cecil & Jones, 2001; Miller, 1991; Soares & Law, 2009). The creatine + phosphocreatine (Cr) spectrum may also reflect neuronal and/or glial density, as well as energy metabolism (Cecil & Jones, 2001; Miller, 1991; Soares & Law, 2009). The myoinositol (Ins) concentration is thought to be a marker of glial cells, as well as to reflect processes associated with the breakdown of myelin (Berridge, 1984; Cecil & Jones, 2001; Soares & Law, 2009). Lastly, glutamate, glumatine and gamma-aminobutyric acid result in a complex set of peaks, which signal excitatory/inhibitory neuronal function (Berridge, 1984; Mark et al., 2001; Soares & Law, 2009). Glutamate is the main excitatory neurotransmitter and is the most abundant amino acid found in the brain; whereas gamma-aminobutyric acid is derived from glutamate and is the main inhibitory neurotransmitter in the brain (Berridge, 1984; Mark et al., 2001; Soares & Law, 2009).

Changes in brain metabolite concentrations have been used clinically as a way to identify neural insult and understand disease progression in conditions such as tumoural disease (Daly & Cohen, 1989; Hagberg, 1998; Hollingworth et al., 2006; Preul et al., 1996), multiple sclerosis (Davie et al., 1994; De Stefano et al., 1998; Miller, Grossman, Reingold, & McFarland, 1998) and Alzheimer's disease (Barber et al., 1999; Chui et al., 1992). There are increasing efforts to identity reliable biomarkers for ASD that may allow for early screening and treatment (Ipser et al., 2012; Pickett & London, 2005). To date only 3 studies, in children with ASD have examined metabolite concentration in deep gray matter (Friedman et al., 2003; Hardan et al., 2008; Levitt et al., 2003). Cr levels were reported as reduced in the left thalamus (Friedman et al., 2003; Hardan et al., 2008). Concentrations of Cho were found to be lower in the left thalamus (Hardan et al., 2008) and in the body of the left caudate nucleus (Hardan et al., 2008; Levitt et al., 2003), but higher in the head of the right caudate (Levitt et al., 2003). These studies did not examine age- and sex-related changes in metabolite concentrations and the relation between metabolic changes and the three core features of ASD, which are impaired social interaction, communication and stereotyped and repetitive behaviors (APA, 1994). The examination of these associations could provide insight into whether metabolic changes have behavioral significance, and potentially, clinical utility.

Thus, in the present study we used MRS to examine metabolite concentrations in the caudate, putamen and thalamus in individuals with ASD, aged 7–18 years relative to age- and IQ-matched typically developing controls, and examined how concentrations changed with age, sex and related to ASD symptomatology.

2. Materials and methods

2.1. Ethics and consent

This study was approved by institutional Research Ethics Board and conducted in accordance with its guidelines. All participants provided written informed assent and parents provided written informed consent in accordance with Research Ethics Board guidelines.

2.2. Participants

Twenty higher-functioning ASD participants between the ages of 7–18 years were recruited from the Seaver Autism Center at Mount Sinai School of Medicine (mean age = 11.5 ± 3.0; mean FSIQ = 99 ± 18). Sixteen controls were recruited from local newspaper advertisements and through word of mouth, and were group-matched on age and IQ (mean age = 12.5 ± 3.6, mean FSIQ = 101 ± 13) (Please see Table 1 for more details). ASD participants had a clinical diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (APA, 1994) and were not on psychotropic-medications or concomitant medications that would influence results. Diagnoses were confirmed at the time of testing using the Autism Diagnostic Observational Schedule-Generic (ADOS) (Lord, Risi, et al., 2000) and the ADI-R (Lord, Rutter, & Le Couteur, 1994). Any participants who had a primary psychiatric condition (other than ASD in the ASD group), a history of head injury, epilepsy, neuromotor