Psychiatry Research: Neuroimaging 222 (2014) 67–74

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Proton magnetic resonance spectroscopy of prefrontal white matter in psychotropic naïve children and adolescents with obsessive–compulsive disorder

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ARTICLE INFO

Article history:
Received 12 December 2012
Received in revised form
13 December 2013
Accepted 7 February 2014
Available online 17 February 2014

Keywords:
^{1}H-MRS
OCD
Pediatric
White matter
Psychotropic-naïve
Brain

ABSTRACT

Obsessive–compulsive disorder (OCD) has a typical onset during childhood or adolescence. Although recent in-vivo proton magnetic resonance spectroscopy (^{1}H-MRS) studies report gray matter metabolite abnormalities in children and adolescents with OCD, there are no existing ^{1}H-MRS studies that measure white matter (WM) metabolite levels in this population. In the present study, we measured metabolite levels in the left and right prefrontal WM (LPFWM and RPFWM, respectively) of psychotropic-naïve children and adolescents with OCD (LPFWM: $N=15$, mean age 13.3 ± 2.4 years; right RPFWM: $N=14$, mean age 13.0 ± 2.3 years) and healthy controls (LPFWM: $N=17$, mean age 11.8 ± 2.7 years; RPFWM: $N=18$, mean age 12.2 ± 2.8 years). Spectra were acquired using a 3T single voxel PRESS sequence ($1.5 \times 2.0 \times 2.0$ cm^3). When age and sex effects were controlled, OCD patients had higher levels of RPFWM choline and *N*-acetyl-aspartate (NAA). In addition, RPFWM levels of NAA, creatine and myo-inositol were positively and significantly correlated with severity of OCD symptoms. In summary, this is the first published study of WM metabolite levels in children and adolescents with OCD. Our preliminary findings lend further support to the previous findings of WM abnormalities in OCD.

1. Introduction

Obsessive–compulsive disorder (OCD) is a common and severe neuropsychiatric disorder, with a lifetime prevalence of 1–2.5% (Bebbington, 1998; Horwath and Weissman, 2000; Ruscio et al., 2010). The onset of OCD is usually during youth (i.e., childhood and adolescence) (Angst et al., 2004), resulting in functional impairment in home, school and social settings (Valderhaug and Ivarsson, 2005).

Structural and functional neuroimaging studies of youth and adults with OCD suggest an impairment of the cortico-striatal-thalamic-cortical (CSTC) circuits (Saxena et al., 1998, 2001; Graybiel and Rauch, 2000), which include cortical and sub-cortical gray matter structures, connected through glutamatergic downstream cortico-striatal and upstream thalamo-cortical white matter (WM) projections (Carlsson, 2001; Greenamyre, 2001).

A recent meta-analysis (Menzies et al., 2008) supported the association of CSTC circuitries with OCD and also implicated several other brain regions, including the limbic and paralimbic structures, connected to the CSTC circuitries by way of the anterior

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http://dx.doi.org/10.1016/j.pscychresns.2014.02.004
0925-4927

cingulate gyrus (Menzies et al., 2008; Middleton, 2009), as well as the parietal cortex and dorso-lateral prefrontal cortex (DLPFC) (Menzies et al., 2008). In line with these findings, neuropsychological findings in OCD include impairments in memory and executive functioning, along with deficits in emotion and reward systems (Sachdev and Malhi, 2005; Olley et al., 2007; Jayarajan et al., 2012).

Although numerous OCD imaging studies have shown structural, functional and metabolic abnormalities in gray matter structures (Huyser et al., 2009), a recent article suggested that relatively few studies have focused on white matter (WM) tracts in this disorder (Silk et al., 2013). The relevance of studying WM in OCD was first highlighted by Moniz (Wilkins, 1964), who reported that prefrontal leucotomy improved OCD-like symptoms. Indeed, leucotomy is considered a treatment option for severe, treatment-resistant OCD cases (D'Astous et al., 2013).

The paucity of WM studies in OCD is important in the context of recent suggestions that psychiatric illnesses are currently thought of as network dysfunctions, naturally implicating WM connectivity (Filley, 2011). For example, WM regions connect prefrontal regions with the subcortex in the following three important CSTC circuits (Aoki et al., 2012): the DLPFC circuit, which organizes information to facilitate a response; the medial prefrontal cortex (mPFC) circuit, which is involved in motivation-related behavior; and the OFC circuit, which integrates limbic and emotional information into behavioral responses (Bonelli and Cummings, 2007).

Initial evidence for frontal WM abnormalities in OCD can be found in diffusion tensor imaging (DTI) studies. DTI is a magnetic resonance imaging (MRI) method that provides a measure of the degree of anisotropy of water diffusion and can elucidate WM tissue architecture. To date, there have been only three published DTI studies in children or adolescents with OCD (Zarei et al., 2011; Jayarajan et al., 2012; Silk et al., 2013). In terms of frontal white matter DTI differences, Silk et al. (2013) reported greater axial diffusivity in the genu of the corpus callosum (CC), Zarei et al. (2011) reported higher FA values in the genu of the CC, the minor forceps, and the cingulum, while Jayarajan et al. (2012) found no FA differences, but did report increased axial and radial diffusivity in the genu of the CC.

An important limitation of DTI studies is that the method is not directly informative on the metabolic processes that may underlie observed tissue abnormalities. To date, the only non-invasive method of measuring in vivo neurochemical differences is magnetic resonance spectroscopy (MRS) (Stanley et al., 2000; Stanley, 2002). ^{1}H-MRS studies in OCD have targeted several CSTC-related structures, primarily focusing on the following four metabolites that have consistent measurement reliabilities (Posse et al., 2007): *N*-acetyl-aspartate (NAA); glycero-phosphocholine plus phosphocholine (Cho); phosphocreatine plus creatine (Cr), and myo-inositol (mI). These metabolites are considered markers of multiple facets of neural tissues, such as high-energy phosphate metabolism (Cr), membrane phospholipid metabolism (Cho), neuronal and axonal integrity/density (NAA) and glial cell density (mI) (Stanley et al., 2000, 2006; Stanley, 2002). In addition, ^{1}H-MRS studies of OCD patients often hae reported levels of the excitatory neurotransmitter glutamate (Glu) or the complex glutamatergic signal (Glx), that is, a combination of Glu and glutamine signals (Soares and Law, 2009).

Although a recent critical review of ^{1}H-MRS studies in OCD (Brennan et al., 2013) suggested that future ^{1}H-MRS studies should target WM abnormalities in OCD, only five existing ^{1}H-MRS studies in adults with OCD (Whiteside et al., 2006, 2012; Jang et al., 2006; Kitamura et al., 2006; Sumitani et al., 2007) have measured brain metabolite levels in CSTC WM regions (see Table 1, which summarizes positive ^{1}H-MRS WM findings in OCD). To date, however, there are no published ^{1}H-MRS studies of WM in children and adolescents with OCD

All five existing ^{1}H-MRS WM studies in adult OCD looked at frontal white matter, a key CSTC region that connects frontal with subcortical CSTC circuits (Table 1) (Whiteside et al., 2006, 2012; Jang et al., 2006; Kitamura et al., 2006; Sumitani et al., 2007). Investigators in one study (Whiteside et al., 2006) originally reported their metabolite results as ratios of Cr, which was later reinterpreted using 'absolute values' in a 2012 article (Whiteside et al., 2012). Jang et al. (2006) found reduced levels of NAA/Cr bilaterally in frontal WM. Whiteside et al. (2012) also reported decreased NAA and Cr levels, but only in the right orbito-frontal WM. Kitamura et al. (2006) looked at the left parietal WM and left frontal WM, finding that Cho/Cr ratios were higher in left parietal WM, with no differences observed in the left frontal WM. Sumitani et al. (2007) looked at NAA exclusively in the left frontal white matter, and did not find any differences.

In summary, there is preliminary evidence of reduced NAA WM differences in adults with OCD, but no ^{1}H-MRS WM studies in children and adolescents have been performed. In line with adult findings, the primary hypothesis of the present study was that statistically significant reduced NAA WM levels would be found between psychotropic-naïve children and adolescents with OCD and healthy controls. The secondary hypothesis of the study was that a significant association between NAA levels and severity of OCD symptoms would be found. To study these hypotheses, the present short-TE single-voxel in vivo ^{1}H-MRS study compared absolute metabolite levels in the left and right prefrontal WM (LPFWM and RPFWM, respectively) between psychotropic-naive children and adolescents with OCD and healthy controls. In addition to NAA levels, we also measured WM levels of Cr, mI, Cho and glutamate (Glu).

Table 1
Positive findings of ^{1}H-MRS studies of white matter regions in adults with OCD.

Author	Date	*N* (OCD, controls)	Age	Mean age	Med	ROI	Met	OCD vs. controls
Whiteside et al.	2006	15	A	41.2	M	Right	Glx/Cr	↑
		15		41.4		OFWM	NAA/Cr	↑
Jang et al.	2006	13	A	27.8	N	OFWM	NAA/Cr	↓
		13		26.9				
Kitamura et al.	2006	12	A	22.7	M	Parietal	Cho/Cr	↑
		32		24.5		WM		
Whiteside et al.	2012	15	A	41.2	M	Right	NAA	↓
		15		41.4		OFWM	Cr	↓

Note. Only the positive findings from adult OCD MRS studies on white matter are presented here, leaving out negative findings.
Med=medicated or not; A=adults; M=medicated patients; ROI=region of interest; Met=metabolite; OCD vs. Controls=evidence of significant differences between patients with OCD and controls; N=medication naïve patients; ↓decreased values ↑increased values.