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Brain magnetic resonance spectroscopy in obsessive–compulsive disorder: The importance of considering subclinical symptoms of anxiety and depression

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ABSTRACT

Brain metabolite concentrations have recently been assessed in different cerebral regions presumably targeted in patients with obsessive–compulsive disorder (OCD) using magnetic resonance spectroscopy (MRS). However, results have been divergent. Possible confounding variables, such as the cerebral localisation of investigated regions and metabolites considered, as well as subclinical symptoms of anxiety and depression, could have affected these MRS profiles. The main goal of this study was to assess MRS metabolite differences between 13 individuals with OCD and 12 matched healthy controls in seven brain regions potentially involved in OCD. The secondary objective was to assess the relationships between levels of anxiety and depression and brain metabolite concentrations. No difference was found for *N*-acetylaspartate, glutamate–glutamine, *myo*-inositol (*m*I) and choline relative to creatine (Cr) concentration in either the left or right orbitofrontal area, left or right median temporal lobe, left or right thalamus or the anterior cingulate cortex. A significant negative correlation between the *m*I/Cr in the left orbitofrontal area and the severity of OCD symptomatology was observed while subclinical anxiety and depression were closely related to brain metabolite ratios. Thus, these subclinical symptoms, commonly associated with OCD, should be considered in assessing brain metabolite concentrations and may be central to the comprehension of this disorder.

1. Introduction

Current views of obsessive–compulsive disorder (OCD) suggest that neurobiological anomalies play a crucial role in its etiology and course. More specifically, the cortico-striato-thalamo-cortical circuit has repeatedly been found abnormal in OCD (Saxena et al., 2001; Kwon et al., 2003; Saxena, 2003). Single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have certainly helped identify the anomalies in several structures such as the orbitofrontal area (OFA), the anterior cingulate cortex (ACC), the caudate nucleus and the thalamus (Baxter et al., 1987; Rauch et al., 1994; Breiter et al., 1996; Rauch et al., 1997; Saxena and Rauch, 2000; Saxena et al., 2001; Kwon et al., 2003; Chamberlain et al., 2008). The contribution of fronto-striatal structures in the pathophysiology of OCD is also supported by neuropsychological studies, which have commonly reported executive dysfunctions that are highly dependent upon frontal integrity, notably the OFA (Menzies et al., 2007), and basic attentional problems associated to a dysfunctional ACC (de Geus et al., 2007). Moreover, reduction of the symptomatology of OCD following a course of pharmacological and/or behavioural therapy have been associated with a normalization of hyperactive cerebral metabolism, particularly in the OFA and caudate nucleus (Benkelfat et al., 1990; Rubin et al., 1995; Hansen et al., 2002). Similarly, reports of symptomatic improvement following a neurosurgical disruption of prefrontal-striatal circuits (Jenike, 1998) provide additional evidence of a fronto-striatal substrate pathology.

More recently, metabolite concentrations in these cerebral regions have been assessed in patients with OCD using magnetic resonance spectroscopy (MRS), yielding various and seemingly contradictory results. For instance, both reduced (Jang et al., 2006; Yücel et al., 2007) and increased (Whiteside et al., 2006) concentrations of *N*-acetylaspartate (NAA; a neuronal marker) have been reported in OCD diagnosed patients in comparison with healthy participants. However, brain metabolite concentrations seem to be regionally specific. Thus, lower NAA concentration has been observed in both the left (Bartha et al., 1998) and right (Ebert et al., 1997) striata, the left and right thalami in paediatric OCD (Fitzgerald et al., 2000), the ACC (Ebert et al., 1997; Jang et al., 2006; Yücel et al., 2007) as well as in the dorsolateral prefrontal cortex (DPFC) and the dorsolateral prefrontal white matter of adults with OCD, although the dorsolateral region was not precisely delineated in this case (Jang et al., 2006). Instead, lower NAA concentration in the dorsolateral prefrontal regions, higher levels of NAA have been reported in the right orbitofrontal white matter of adults (Whiteside et al., 2006) and in the right dorsolateral PFC of paediatric

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OCD (Russell et al., 2003). Thus, the targeted cerebral region is important, with the most consistent finding being lower NAA concentrations within right and/or left DPFC and subcortical structures (such as the thalami and the striata), while the OFA appears to be associated with higher levels of NAA. Other factors, especially the age of participants (adults vs. children), may account for some of the inconsistent findings in the DPFC.

Another metabolite of interest is glutamate–glutamine (Glx; a marker for excitatory neurotransmitters), of which abnormal concentrations are also regionally specific. While decreases of Glx ratios have been observed in the ACC of children and adults with OCD (Rosenberg et al., 2004; Yücel et al., 2008), increases were reported in the orbitofrontal white matter (Whiteside et al., 2006) and the head of the caudate nucleus (Rosenberg et al., 2000). Importantly, both NAA (Jang et al., 2006) and Glx (Rosenberg et al., 2000; Bolton et al., 2001) alterations normalized after the administration of selective serotonin reuptake inhibitors (SSRI). The severity of OCD symptomatology may represent another important factor, as it seems to influence biochemical alterations associated with OCD. Although very few data are available to date, OCD symptom severity seems to be inversely proportional to NAA concentrations in the orbitofrontal region (Whiteside et al., 2006) as well as to occipital cortex Glx concentrations (Starck et al., 2008), and positively correlated to Glx ratios (Whiteside et al., 2006; Starck et al., 2008; Yücel et al., 2008) and a number of caudate MRS metabolites, i.e. creatine, glutamate, glutamate–glutamine and choline compounds (Starck et al., 2008). This potential link between brain metabolite concentrations and OCD symptom severity deserves further attention.

Abnormal concentrations of two other brain metabolites, choline (Cho; a marker of cell membrane turnover) and *myo*-inositol (*m*I; a glial marker) are associated with OCD. While higher concentrations of Cho were found in the left and right medial thalamic nuclei of OCD paediatric patients (Rosenberg et al., 2001; Smith et al., 2003), no difference was reported among adults in the ACC (Starck et al., 2008; Yücel et al., 2008). Again, patient age may have affected these findings (one study also reported a gender effect among 20 participants; Yücel et al., 2008). As for *m*I, higher concentrations were found in the ACC (Yücel et al., 2008) and lower concentrations in the head of the caudate nucleus bilaterally (Whiteside et al., 2006) of adults with OCD compared with concentrations in controls. Interestingly, *m*I concentrations were significantly correlated with trait anxiety (negatively) and depression (positively) in the latter study. Thus, stable symptoms of anxiety or depression, two conditions occurring frequently in OCD (Steketee et al., 1999), should also be considered when assessing brain metabolite concentrations. Major and prolonged depression (Bremner et al., 2000), and also anxiety disorders such as panic and post-traumatic stress disorders (Gurvits et al., 1997; Wignall et al., 2004; Winter and Irle, 2004; Kitayama et al., 2005; Bremner, 2006) also appear to involve morphological and functional changes in the brain, notably in similar cerebral regions of OCD, but also a decreased hippocampal volume. The hippocampus, a structure located in the median temporal lobe (MTL), plays an essential role in learning and memory, contextual fear conditioning and neuroendocrine regulation (Sapolsky, 2000; Charney, 2003; Kent and Rauch, 2003). It remains feasible that certain differences observed in the brain chemistry between OCD patients and healthy controls might in fact be related to different levels of subclinical symptoms of anxiety or depression.

Taken together, various brain regions, specific metabolites, OCD severity, and concomitant anxiety and depression symptoms should be considered when assessing brain metabolite ratios in OCD patients (as well as the mean age of participants). The first goal of this study was to assess four brain metabolites in seven cerebral regions associated to the pathophysiology of OCD and potential concomitant depression and anxiety symptoms among adult patients. Due to methodological considerations, notably the total MRS examination time, we have chosen to examine the OFA, ACC and thalamus since these regions have repeatedly been found to be involved in OCD in several functional imaging approaches, including MRS. The MTL including the hippocampus was also examined considering the role it plays in the "fear neurocircuitry" associated with anxiety disorder and its decreased volume in depression.

The secondary objective of this investigation was to assess the relationships between the severity of OCD, the concomitant levels of anxiety and depression, and brain metabolite concentrations. To our knowledge, this is the first MRS study which examines NAA, Glx, Cho and *m*I concentrations in seven brain regions of OCD patients.

2. Method

2.1. Subjects

Thirteen patients with OCD (4 males and 9 females) and 12 healthy controls (4 males and 8 females) participated in the protocol. OCD patients were recruited in outpatient clinics of the Centre Hospitalier Robert-Giffard or the Hôpital de l'Enfant-Jésus du Centre Hospitalier Affilié Universitaire de Québec, both located in Quebec City, Canada. The diagnosis of OCD was confirmed independently by two psychiatrists using the DSM-IV criteria. The mean Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score was 26.54 (standard deviation (S.D.) = 7.76), representing moderate-to-severe disease severity (obsessions: mean = 12.92, S.D. = 3.55; compulsions: mean = 13.62, S.D. = 4.45, see Table 1). Of the OCD participants, 6/13 had severe and refractory symptoms and were on a waiting list for a capsulotomy (neurosurgery) for the treatment of their OCD symptoms. These participants were chosen because we wished to recruit participants with moderate-to-severe symptoms. Seven patients had checking behaviour as predominant symptoms, two had washing rituals and three had mixed symptoms with repetition rituals; counting, exactness and ordering. Patients with an active comorbid axis I disorder (for at least 6 months prior to the study), history of brain injury, any neurological condition, psychosis, primary personality disorder, mental retardation and a history of alcohol or substance abuse were excluded. Most of the OCD patients ($n = 11$, 84.62%) were on medication (mean duration = 12.77 years, S.D., = 8.21) at the time of the study: citalopram ($n = 4$; mean dose = 80 mg), clomipramine ($n = 2$; mean dose = 25 mg), fluoxetine ($n = 2$; mean dose = 46.7 mg), paroxetine ($n = 1$; mean dose = 60 mg), sertraline ($n = 1$; mean dose = 140 mg), and venlafaxine ($n = 1$; mean dose = 150 mg). Additional medications included zopiclone ($n = 1$; mean dose = 10 mg), lorazepam ($n = 2$; mean dose = 2 mg) and clonazepam ($n = 2$; mean dose = 1 mg). Following the Expert Consensus

Table 1
Demographic and clinical characteristics of obsessive–compulsive disorder (OCD) and healthy control samples.

Variable	OCD ($n = 13$)	Controls ($n = 12$)	Statistic	*P*
Gender			$\chi^2 = 0.19$	0.89
Men	4 (30.8)	4 (33.33)		
Women	9 (69.2)	8 (66.67)		
Age, years	40.54 (10.18)	40.17 (12.66)	$t = 0.08$	0.94
Education, years	12.69 (3.07)	14.00 (1.95)	$t = 1.26$	0.22
Estimation of IQ	96.42 (16.45)	105.50 (10.76)	$t = 1.60$	0.12
BDI-II	25.00 (13.94)	5.5 (4.46)	$t = 4.79$	<0.0001
BAI	15.31 (7.42)	2.25 (2.18)	$t = 6.07$	<0.0001
Y-BOCS				
Total	26.54 (7.76)	–	–	–
Obsessions	12.92 (3.55)	–	–	–
Compulsions	13.62 (4.45)	–	–	–
Age of onset	27.77 (7.42)	–	–	–

Data are means (and standard deviations) except for gender data, which are number of men and women (and percentages of samples).
BDI-II = Beck Depression Inventory II; BAI = Beck Anxiety Inventory; Y-BOCS = Yale–Brown Obsessive–Compulsive Scale.