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The effect of behavior therapy on caudate *N*-acetyl-*l*-aspartic acid in adults with obsessive–compulsive disorder

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ABSTRACT

Previous studies suggest that baseline differences in neuronal markers between patients with obsessive–compulsive disorder (OCD) and healthy controls no longer exist following successful pharmacotherapy. The current study used proton magnetic resonance spectroscopy (MRS) to investigate differences in absolute concentrations of neurochemicals (i.e., *N*-acetyl-*l*-aspartic; NAA) in the head of the caudate nucleus (HOC) and orbital frontal white matter (OFWM) between 15 adults with OCD and a sex- and age-matched control group, as well as the effects of behavior therapy on these chemicals. Behavior therapy was associated with a significant increase in left HOC NAA. When the analyses were restricted to only pairings with complete data (OCD patient, control, post-treatment), the levels of left HOC NAA were significantly lower in patients compared to controls, and increased significantly with treatment. Exploratory analyses suggested that levels of NAA and Cr (creatine) in the right OFWM may be significantly lower in the OCD group than the control group. The results raise the possibility that successful behavioral treatment may be associated with increases in markers of neuronal viability, although other associations found in the literature were not replicated.

1. Introduction

Neuroimaging studies in obsessive-compulsive disorder (OCD) have the potential to increase our understanding of how observable symptoms (i.e., obsessions and compulsions) are implemented in neurobiological processes, which could lead to improvements in treatment and matching treatment to patient needs (Rauch, 2000). With respect to neurobiology, brain regions involved in processing threat cues and routine complex motor programming have been implicated in OCD. For instance, the orbitofrontal cortex (OFC) and the caudate nucleus are thought to be involved in the mediation of emotional responses to stimuli associated with biologically based threats, a process that appears to be disrupted in OCD (Saxena et al., 2001). The most consistent differences between patients with OCD and healthy controls identified with functional neuroimaging have been in the more focal orbital gyrus and head of the caudate (HOC) nucleus (Saxena et al., 2001; Whiteside et al., 2004). In addition, some studies have found that medication and behavioral therapy affect activity in these same areas (Benkelfat et al., 1990; Baxter et al., 1992; Swedo et al., 1992; Schwartz et al., 1996; Nakatani et al., 2003; Nakao et al., 2005; Nabeyama et al., 2008).

Compared with other imaging techniques, magnetic resonance spectroscopy (MRS) is a less invasive methodology for measuring neuronal processes associated with OCD and may be a more sensitive measure of subtle treatment effects on these processes (Cendes et al., 1994). MRS has been used primarily to measure brain tissue concentrations of metabolites such as *N*-acetyl-*l*-aspartic (NAA; a marker of neuronal viability), combined glutamate and glutamine (Glx; glutamate is the most abundant excitatory neurotransmitter, with synaptic glutamate rapidly converted into glutamine as part of neuron-astrocyte glutamate–glutamine cycling), choline (cho; a marker of cell membrane turnover), myo-inositol (mI; involved in phospholipid metabolism), and creatine (Cr; a marker of cellular energetics, commonly used as a reference level).

Investigations with MRS have yielded promising, but inconsistent results. The involvement of the caudate is supported by research suggesting that compared to healthy controls, adults with OCD have unilaterally decreased NAA [relative to creatine + phosphocreatine in the *right* (Ebert et al., 1997) and to water volume in the *left* (Bartha et al., 1998)] striatum and bilaterally decreased mI/Cr in the HOC (Whiteside et al., 2006). Moreover, elevated Glx in the left caudate in pediatric OCD patients has been found to decrease with paroxetine treatment (Rosenberg et al., 2000). However, baseline differences in these neurochemicals have not been replicated as individual studies have only found differences in NAA, mI/Cr *or* Glx. In addition, absolute concentrations of Glx in the caudate have not changed with successful

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behavior therapy (BT; Benazon et al., 2003). To date, no studies have used MRS to examine the orbitofrontal cortex (OFC) or the effect of treatment (medication or BT) on any brain regions in adult patients with OCD.

To further complicate the situation, the manner in which neurochemical levels are quantified can affect the results of a study. For instance, differences in thalamic NAA/(creatine/phosphocreatine + choline) and NAA/cho levels, which were originally ascribed to NAA (Fitzgerald et al., 2000), were subsequently attributed to choline after the absolute concentrations were assessed (Rosenberg et al., 2001). Thus, the results of our previous study (Whiteside et al., 2006) that found increased levels of Glx/Cr and NAA/Cr in the right orbital frontal white matter OFWM, and decreased levels of mI/Cr in the HOC bilaterally in patients with OCD compared to controls may reflect differences in Cr rather than the hypothesized Glx, NAA, and mI. More broadly, differences in quantification make it difficult to evaluate the consistency of findings across the literature.

As such, the present study had two objectives. First, to address confounds associated with measuring relative neurochemical values, differences in neuronal functioning as measured by MRS in the orbital frontal white matter (OFWM) and HOC between adults with and without OCD (Whiteside et al., 2006), results were reanalyzed using tissue-volume corrected absolute concentrations. Second, for the first time MRS was used to explore the effects of BT for OCD on neurochemical levels in adult patients. Based on the previous literature we predicted that compared to healthy controls, OCD patients would evidence higher Glx and lower NAA in the left HOC (Bartha et al., 1998; Rosenberg et al., 2000). In addition, we hypothesized that left HOC Glx would decrease and NAA would increase with BT. Secondary analyses examined baseline differences and treatment effects in the remaining neurochemicals in the HOC and OFWM, as well as correlations between neurochemical values and measures of OCD, anxiety, and depressive symptom severity.

2. Methods

2.1. Participants

This study utilized the sample of 30 Caucasian adults (age range = 31–62) described in our previous study (Whiteside et al., 2006), who provided written informed consent to participate in all study procedures. The clinical group consisted of 15 patients with OCD who presented for treatment at an outpatient anxiety disorders clinic. Fifteen age- and sex-matched healthy controls were recruited through print advertising. All participants were provided a stipend of $50 as compensation for their time.

All participants received a diagnostic interview by a trained doctoral level psychologist using the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID-IV; First et al., 1996). The OCD group was also administered the Yale–Brown Obsessive Compulsive Scale (YBOCS) to assess the severity of obsessions and compulsions. Eligibility criteria for the study included meeting SCID-IV criteria for OCD and a score of 18 or higher on the Y-BOCS. Participants were excluded if they had a current or previous diagnosis of bipolar disorder, schizophrenia, mental retardation, or substance abuse, or a current diagnosis of major depression. Individuals were also excluded if they had major medical or neurological problems, evidenced an acute risk for suicide or danger to others, or had a history of a failed trial of BT for OCD. A total of 18 patients with OCD and 17 potential controls were screened.

As the Expert Consensus Guidelines for the treatment of OCD (Frances et al., 1997) consider 8 to 13 weeks to be an adequate medication trial, the eight OCD patients who were receiving treatment with psychotropic medication were required to have been on a stable dose of their medication for at least 3 months. Furthermore, these patients were required to maintain this dose throughout the duration of the study. Adherence to this criterion was assessed on a regular basis by the BT therapist. Medications used by patients in the study included trazodone, mirtazapine, citalopram, clomipramine, clonazepam, fluoxetine, paroxetine, methylphenidate, bupropion, and fluvoxamine. Individuals in the healthy control group had no current, or history of, psychiatric diagnoses or treatment for a psychiatric diagnosis. None were taking psychotropic medication. Table 1 presents demographic and clinical information for both groups.

2.2. Procedures and design

The study and consent procedures were approved by the institutional review board. Following a review of the study procedures and provision of consent, potential participants received the diagnostic interview. Participants who met the inclusion criteria provided a urine sample to screen for recreational drug use and, once it was established that they were drug free, they received the MRS scan. Following the initial assessment and scan, patients with OCD received up to 16 sessions of BT followed by a second clinical assessment and MRS scan. Data were available for healthy controls (Control), OCD patients before treatment (OCD pre-test), and OCD patients following treatment (OCD post-test).

2.3. Clinical assessment

All participants completed the diagnostic interview and a battery of self-report symptom measures. Pre- and post-treatment data were obtained from OCD patients on all variables except the diagnostic interview.

2.3.1. Diagnostic interview

A clinician administered parts I and II of the Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1996) to make Axis I and II diagnoses according to DSM-IV criteria. In addition, the Yale–Brown Obsessive Compulsive Scale (YBOCS; Goodman et al., 1989a, 1989b), a reliable and valid 10-item interview that assesses OCD symptoms on a scale from 0 to 40, was the primary outcome measure of OCD symptoms. It is known to have an internal consistency of 0.91, sensitivity to treatment effects, and good convergent validity with other OCD measures (Taylor, 1995). The 17-item interview-based Hamilton Depression Scale (HAM-D; Hamilton, 1960) was used to assess the severity of depressive symptoms.

Table 1
Participant demographic and clinical information.

	Control ($N=15$)	OCD pre-test ($N=15$)	OCD post-test ($N=11$)	Treatment effect (t-test)
Mean age (S.D.)	41.40 (7.9)	41.20 (7.1)	40.36 (8.1)	–
No. males	9 (60%)	9 (53.8%)	7 (63.6%)	–
Education (years)	16.14 (4.0)	16.71 (3.2)	17.18 (3.4)	–
Mean age of onset (S.D.)	–	17.56 (7.6)	16.38 (7.2)	–
Sx duration (years)	–	24.22 (10.1)	24.88 (10.5)	–
YBOCS total	–	24.13 (3.2)	7.64 (5.3)	9.68[a]
Obsessions	–	11.73 (1.5)	4.09 (3.1)	8.03[a]
Compulsions	–	12.40 (2.5)	3.45 (2.4)	8.80[a]
OCI-R	2.79 (4.7)	27.50 (10.3)	8.82 (5.2)	4.94[a,b]
STAI-T	23.93 (5.1)	37.73 (8.7)	31.46 (7.6)	3.07[a,b]
Ham-D	–	8.80 (4.4)	1.91 (1.9)	5.56[a]
BDI	1.57 (2.4)	13.07 (7.7)	5.09 (5.2)	2.46[a,b]
SUDS in scanner	7.27 (6.9)	31.36 (14.3)	22.96 (12.5)	3.33[b]

Pre-tx = OCD group prior to treatment. Post-tx = OCD group after treatment.
Test statistic is a t-value for all comparisons except for the number of males, which was examined with a Chi-square.
[a] Pre-tx group differs from post-tx group, $p<0.05$.
[b] Control group differs from pre-tx group, $p<0.05$.