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Effects of intensive cognitive-behavioral therapy on cingulate neurochemistry in obsessive–compulsive disorder

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ABSTRACT

The neurophysiological bases of cognitive-behavioral therapy (CBT) for obsessive–compulsive disorder (OCD) are incompletely understood. Previous studies, though sparse, implicate metabolic changes in pregenual anterior cingulate cortex (pACC) and anterior middle cingulate cortex (aMCC) as neural correlates of response to CBT. The goal of this pilot study was to determine the relationship between levels of the neurochemically interlinked metabolites glutamate + glutamine (Glx) and *N*-acetyl-aspartate + *N*-acetyl-aspartyl-glutamate (tNAA) in pACC and aMCC to pretreatment OCD diagnostic status and OCD response to CBT. Proton magnetic resonance spectroscopic imaging (^{1}H MRSI) was acquired from pACC and aMCC in 10 OCD patients at baseline, 8 of whom had a repeat scan after 4 weeks of intensive CBT. pACC was also scanned (baseline only) in 8 age-matched healthy controls. OCD symptoms improved markedly in 8/8 patients after CBT. In right pACC, tNAA was significantly lower in OCD patients than controls at baseline and then increased significantly after CBT. Baseline tNAA also correlated with post-CBT change in OCD symptom severity. In left aMCC, Glx decreased significantly after intensive CBT. These findings add to evidence implicating the pACC and aMCC as loci of the metabolic effects of CBT in OCD, particularly effects on glutamatergic and *N*-acetyl compounds. Moreover, these metabolic responses occurred after just 4 weeks of intensive CBT, compared to 3 months for standard weekly CBT. Baseline levels of tNAA in the pACC may be associated with response to CBT for OCD. Lateralization of metabolite effects of CBT, previously observed in subcortical nuclei and white matter, may also occur in cingulate cortex. Tentative mechanisms for these effects are discussed. Comorbid depressive symptoms in OCD patients may have contributed to metabolite effects, although baseline and post-CBT change in depression ratings varied with choline-compounds and *myo*-inositol rather than Glx or tNAA.

1. Introduction

Cognitive-behavioral therapy (CBT) for obsessive–compulsive disorder (OCD) regularly yields therapeutic responses that rival or exceed those of drug treatments, are achieved more rapidly, and persist after discontinuation of therapy (Foa et al., 2005). Previous [^{18}F]-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) studies of adult OCD patients (Baxter et al., 1987, 1988; Kwon et al., 2003; Nordahl et al., 1989; Perani et al., 1995; Sawle et al., 1991; Saxena et al., 2001; Swedo et al., 1989) identified regional abnormalities in brain metabolism that may respond to CBT. These studies found above-normal pretreatment glucose metabolic rates (GMR) in caudate, thalamus, orbitofrontal cortex and anterior cingulate cortex, which are brain structures that form functional neural circuits thought to be hyperactive in OCD (reviewed in Saxena et al., 2001). Several studies (Baxter et al., 1992; Freyer et al., 2011; Nabeyama et al., 2008; Nakatani et al., 2003; Schwartz et al., 1996; Yamanishi et al., 2009), including ours (Saxena et al., 2009a), found significant changes in glucose metabolism or blood flow in

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these structures after CBT for OCD. Hence, the therapeutic effects of CBT appear to be consistently associated with changes in regional brain energetic metabolism.

Aspects of regional brain energy metabolism are illuminated by proton magnetic resonance spectroscopy (^{1}H MRS), a neuroimaging modality that is safer and better tolerated than PET. Metabolites assayed in living human brain at clinical field strength (0.5–3 T) include the two most abundant CNS amino acids: *N*-acetyl-aspartate (NAA) and glutamate (Glu). Under clinical conditions, NAA is nearly always measured together with spectrally-overlapping *N*-acetyl-aspartyl-glutamate (NAAG) and Glu is frequently measured together with overlapping glutamine (Gln); NAA + NAAG is abbreviated "tNAA" (total NAA) and Glu + Gln is abbreviated "Glx" thereby. ^{1}H MRS has linked GMR to tNAA (O'Neill et al., 2000) and to Glx (Pfund et al., 2000), while ^{13}C MRS has linked GMR to NAA proper (Moreno et al., 2001) and to Glu proper (Sibson et al., 1998). Hence, it is conceivable that elevated GMR in OCD leads to abnormal regional tNAA and/or Glx levels. Likewise, CBT-induced GMR changes may induce or accompany changes in tNAA and/or Glx.

MRS studies of adult (reviewed in O'Neill and Schwartz, 2005; Saxena et al., 2009b; Brennan et al., 2012) and pediatric (reviewed in MacMaster et al., 2008) OCD have, in fact, found abnormal pretreatment levels of tNAA, Glu or Glx, or other MRS metabolites or their ratios to creatine + phosphocreatine (Cr) in cingulate cortex, basal ganglia, thalamus, or their interconnecting white matter (adult: Bartha et al., 1998; Ebert et al., 1997; Jang et al., 2006; Kitamura et al., 2006; Mohamed et al., 2007; Starck et al., 2008; Sumitani et al., 2007; Whiteside et al., 2006; Yücel et al., 2007, 2008; Zurowski et al., 2007; pediatric: Fitzgerald et al., 2000; Mirza et al., 2006; Rosenberg et al., 2000, 2001, 2004; Smith et al., 2003). Some of these findings involved one or more subregions of the cingulate cortex, which we shall designate using the standard nomenclature of Vogt (2009; see also O'Neill et al., 2009). In right pregenual anterior cingulate cortex (pACC), tNAA/Cr was below normal in untreated adult OCD and correlated negatively with OCD symptom severity (Ebert et al., 1997) measured by the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS; Goodman et al., 1989). Again in pretreatment adult OCD, Zurowski et al. (2007) found above-normal Glu in midline (left + right) pACC. In contrast, Glx was below normal in midline pACC in pediatric OCD (Rosenberg et al., 2004), an effect associated with the GRIN2B gene coding for the *N*-methyl-D-aspartate (NMDA) Glu receptor (Arnold et al., 2009). This represents key evidence favoring the glutamatergic hypothesis of pediatric OCD (Rosenberg and Keshavan, 1998). NAA and Glu are linked by the intraneuronal synthesis (NAA + Glu → NAAG; Cangro et al., 1987) and the extracellular decomposition (NAAG → NAA + Glu; Robinson et al., 1987) of NAAG, whereby Glu from the latter reaction is believed to be produced faster than presynaptic vesicular release of free Glu (Rojas et al., 2002). Glu and Gln, the two contributors to the Glx peak, regularly interconvert and are exchanged between neurons and astrocytes (Danbolt, 2001; Hertz and Zielke, 2004; Petroff et al., 2000). Hence, glutamatergic disturbances in OCD may manifest as abnormalities not only in Glx but also in tNAA, as seen in MRS data, including from cingulate cortex.

There have been fewer MRS studies of treatment response in OCD. Jang et al. (2006) found that tNAA/Cr in frontal white matter increased after treatment with serotonin reuptake inhibitors (SRIs). Caudate Glx dropped in response to the SRI paroxetine (Bolton et al., 2001; Moore et al., 1998; Rosenberg et al., 2000) in children with OCD. In one study (Mohamed et al., 2007), OCD patients who were non-responders to SRIs had lower tNAA/Cr in right "basal ganglia" (apparently caudate, globus pallidus, or internal capsule) than responders and healthy controls, as well as higher Cho/Cr in right thalamus than responders. The one published study of CBT for pediatric OCD (Benazon et al., 2003) found no effects on any MRS metabolite, possibly because the study examined only left caudate, leaving out all other brain regions. In adult OCD patients, in contrast, Whiteside et al. (2012) saw tNAA in left caudate increase after CBT and Zurowski et al. (2007) observed declines in midline pACC Glu and in choline-compounds (Cho) in right "ventral striatum" after long-term (3-month) weekly CBT. The same group (Zurowski et al., 2012) acquiring from a voxel containing right orbital frontal cortex and white matter, showed that lower baseline *myo*-inositol (mI) predicted greater drop in Y-BOCS score following 3-month CBT. Thus, MRS studies of OCD treatment, particularly CBT, are scarce, but there is evidence that treatment may alter regional levels of MRS metabolites, including in cingulate cortex.

The present pilot study used the magnetic resonance spectroscopic imaging (MRSI) variant of ^{1}H MRS to further explore tNAA and Glx in cingulate cortex in patients before and after brief intensive CBT. Among other aims, we sought to identify neurometabolite correlates of the significant increase in GMR we observed in right "dorsal anterior cingulate cortex" of OCD patients after intensive CBT (Saxena et al., 2009a); an increase that correlated significantly with pre- to post-treatment decrease in Y-BOCS scores. In Vogt's (2009) more systematic nomenclature, the dorsal anterior cingulate cortex consists of approximately half pACC and half anterior middle cingulate cortex (aMCC). The pACC is associated with anxiety and other negative emotions (Bush et al., 2000; Devinsky et al., 1995; Whalen et al., 1998), while the cingulate motor area within the aMCC is involved in internal selection of voluntary movements (Picard and Strick, 1996). CBT both reduces anxieties and strengthens volitional control and, hence, could elicit metabolite effects in either or both subregions. The MRSI used in this study had higher spatial resolution than earlier single-voxel MRS studies, enabling us to sample pACC and aMCC separately and bilaterally. This allowed us to examine possible lateralized effects of CBT on OCD brain metabolism, such as have been seen in subcortical nuclei (Baxter et al., 1992; Nakatani et al., 2003; Schwartz et al., 1996). Other aims included evaluation of pretreatment abnormalities in tNAA and Glx levels in OCD, and of relationships of these abnormalities to baseline symptom severity and treatment response. Thus, we sought to identify neuroanatomic loci and neurochemical bases of and the effects of CBT in OCD, as well as objective baseline metabolic measures associated with treatment response. We hypothesized such effects would be present in pACC and aMCC.

2. Methods

2.1. Subjects

Ten patients with DSM-IV OCD (all outpatient; 5 male; mean ± std. age 36.2 ± 8.9 years; Table 1) underwent baseline MRSI scans. Eight of these patients (4 male; 37.8 ± 8.9 years) underwent a second scan after 4 weeks of intensive daily CBT. Diagnoses were made by clinical interview and confirmed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). For inclusion into the study, OCD patients needed to have a pretreatment Y-BOCS score ≥ 16, indicating at least moderate OCD symptom severity. All subjects were in good physical health. Subjects with major medical conditions, current or recent substance abuse, or any other concurrent Axis I diagnosis except major depressive disorder and dysthymia were excluded. Depressive symptoms were evaluated using the Hamilton Depression Rating Scale (HamD; Hamilton, 1960). Patients with depressive symptoms were only admitted if the depression was considered "secondary to OCD" (5 patients, Table 1). Secondary meant that OCD and not depression was the primary psychiatric diagnosis, that the patient's OCD was a probable source of the depression, and that onset of OCD symptoms preceded

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