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Cingulate and thalamic metabolites in obsessive-compulsive disorder

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ABSTRACT

Focal brain metabolic effects detected by proton magnetic resonance spectroscopy (MRS) in obsessive-compulsive disorder (OCD) represent prospective indices of clinical status and guides to treatment design. Sampling bilateral pregenual anterior cingulate cortex (pACC), anterior middle cingulate cortex (aMCC), and thalamus in 40 adult patients and 16 healthy controls, we examined relationships of the neurometabolites glutamate+glutamine (Glx), creatine+phosphocreatine (Cr), and choline-compounds (Cho) with OCD diagnosis and multiple symptom types. The latter included OC core symptoms (Yale-Brown Obsessive-Compulsive Scale – YBOCS), depressive symptoms (Montgomery-Åsberg Depression Rating Scale – MADRS), and general functioning (Global Assessment Scale – GAS). pACC Glx was 9.7% higher in patients than controls. Within patients, Cr and Cho correlated negatively with YBOCS and MADRS, while Cr correlated positively with the GAS. In aMCC, Cr and Cho correlated negatively with MADRS, while Cr in thalamus correlated positively with GAS. These findings present moderate support for glutamatergic and cingulocentric perspectives on OCD. Based on our prior metabolic model of OCD, we offer one possible interpretation of these group and correlational effects as consequences of a corticothalamic state of elevated glutamatergic receptor activity alongside below-normal glutamatergic transporter activity.

1. Introduction

Regional neurometabolic investigations of obsessive-compulsive disorder (OCD) using proton magnetic resonance spectroscopy (MRS) are clinically relevant to the development of objective diagnostic, symptomatic and prognostic indices, as well as to molecular and anatomic targeting in the design of behavioral, pharmacological, neurostimulatory, and neurosurgical interventions (Brennan et al., 2013).

Intriguing theories of OCD have emerged from such investigations. The best-known theory is the Glutamatergic Hypothesis of OCD (Rosenberg and Keshavan, 1998). It is supported by evidence from MRS, clinical trials, and genetics (reviewed by MacMaster et al. (2008) and Pittenger et al. (2006, 2011)), including some of our work (Feusner et al., 2009; O'Neill et al., 2013a). MRS evidence includes differences between OCD patients and healthy controls in levels of glutamate (Glu) or glutamate+glutamine (Glx), correlations of these levels with OCD symptoms, and changes in the levels after therapy. The Cingulocentric Theory of OCD (Middleton, 2009) is not as well known as the Glutamatergic Hypothesis. The Cingulocentric Theory updates classical cortico-striato-pallido-thalamo-cortical models of OCD. It is supported by OCD-related neuroimaging findings (reviewed in Saxena et al. (2009a)), including our work (O'Neill et al., 2012, 2013a; Saxena et al., 2009b), in the cingulate gyrus. Such findings have been seen in the pregenual anterior cingulate cortex (pACC) and anterior middle cingulate cortex (aMCC) subregions of the cingulate gyrus. The thalamus forms neural circuits with pACC and aMCC and is also a frequent site of imaging findings in OCD (e.g., Mirza et al., 2006; Rosenberg et al., 2001; Saxena et al., 2009b; Smith et al., 2003). Finally, a third perspective on OCD is that it shares certain anatomic and physiological bases with attention deficit-hyperactivity disorder (ADHD), a condition that is, in a sense, its symptomatic opposite (Abramovitch et al., 2012; Carlsson, 2000). Pursuing this notion, we recently extended the Cingulocentric Theory to apply to ADHD (O'Neill et al., 2013b). The present investigation uses MRS to examine these glutamatergic, cingulocentric, and ADHD

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perspectives on OCD.

We measured neurometabolites in pACC, aMCC, and thalamus to determine whether they were affected by OCD diagnosis or OCD symptoms. Positive findings in these regions would represent possible consequences of dysfunction in cingulocentric brain circuits. Motivated by the Glutamatergic Hypothesis, Glu and Glx were our primary metabolite targets. Prior measurements of these in pACC or aMCC in OCD have yielded varying results, including below-normal (Rosenberg et al., 2004), normal (Simpson et al., 2012), or above-normal (Zurowski et al., 2007) levels. To help resolve these disparities, our study methods took several steps to reduce untoward variation in metabolites. We measured absolute metabolite levels rather than ratios to Cr. We chose intermediate-sized acquisition voxels: not so large as to incur extensive partial-voluming and not so small as to induce unduly low signal-to-noise ratios. We acquired MRS bilaterally in the brain to detect any hemispheric asymmetries in metabolites. Finally, we restricted interpatient variability in medication, co-morbidities, and OCD subtype. (To restrict subtype, we recruited only patients with childhood-onset OCD and we excluded individuals with hoarding as their primary symptom). Alongside Glu and Glx, MRS studies of ADHD have demonstrated notable effects involving Cr and Cho (O'Neill et al., 2013b; Perlov et al., 2009). To test for possible neurometabolic similarities between OCD and ADHD we therefore also measured Cr and Cho in pACC, aMCC and thalamus. Effects on Cr (Yücel et al., 2008; Starck et al., 2008) and Cho (Yücel et al., 2007; Starck et al., 2008; Kitamura et al., 2006; Mohamed et al., 2007; Yalçın et al., 2011; Lázaro et al., 2012; Whiteside et al., 2012; Weber et al., 2014) have been observed in OCD, including elevated Cho (Rosenberg et al., 2001; Smith et al., 2003) and Cr (Mirza et al., 2006) in the thalamus. But we were particularly interested in pACC Cr and Cho, since our recent pilot study (O'Neill and Feusner, 2015) showed that pretreatment levels of these metabolites predict long-term response of OCD to cognitive-behavioral therapy, a standard treatment. In summary, the present investigation compared Glu and Glx, Cr, and Cho in pACC, aMCC, and thalamus in OCD patients and healthy controls; within patients we also examined relationships of these metabolites with symptoms of four kinds: core obsessive-compulsive symptoms, depressive symptoms, anxious symptoms, and global functioning.

2. Methods

2.1. Subjects

Forty adults with DSM-IV OCD (Table 1) were recruited from UCLA and other clinics or by advertisement. All provided informed consent, and the UCLA Institutional Review Board approved the study. Diagnoses were established through interview by an author (JDF) experienced with OCD. Primary OCD and comorbid diagnoses were determined using the ADIS-IV Mini. Eligible participants scored ≥ 16 on the Yale-Brown Obsessive Compulsive Scale (YBOCS). All reported pediatric-onset (before age 18) OCD. Exclusions included psychotic disorder, bipolar disorder, lifetime substance dependence, or ADHD. We excluded individuals with hoarding as their primary symptom. Comorbid anxiety disorders were allowed if secondary to OCD. Comorbid major depressive disorder or dysthymic disorder was allowed, but individuals were excluded if the ADIS-IV clinical significance rating was ≥ 6 (severe). Altogether 27 patients had one or more such psychiatric comorbidity and 13 had none. Twelve participants were taking serotonin-reuptake inhibitors (6 fluoxetine, 1 escitalopram, 1 sertraline, 2 paroxetine, 2 fluvoxamine) and 28 were unmedicated; of medicated patients, none had any changes in dose or agent for 12 weeks before enrollment. Of the unmedicated OCD participants, 14 had taken psychiatric medications in the past and 14 were psychiatric medication-naïve. Other exclusions included IQ < 80 on the Wechsler Abbreviated Scales of Intelligence (WASI) and medical conditions that affect cerebral metabolism including diabetes, thyroid disorders, a history of stroke, brain tumors, seizures, and multiple sclerosis.

Table 1.
Clinical characteristics of obsessive-compulsive disorder (OCD) and healthy groups.

Participant characteristics	*OCD (n=40)*	*Control (n=16)*	*P-value comparison*
Mean age ± s.d. (in years)	34.3 ± 11.8	32.1 ± 10.8	0.61[a]
Female sex (%)	20 (50.0)	5 (31.2)	0.25[b]
Education ± s.d. (in years)	15.6 ± 2.3	15.4 ± 2.5	0.55[a]
Handedness ± s.d. (Edinburgh Inventory)	84.7 ± 20.9	82.6 ± 20.7	0.65[a]
Intelligence ± s.d. (WAIS)	108.3 ± 10.4	110.2 ± 8.4	0.37[a]
General functioning ± s.d. (GAS)	54.9† ± 7.5	85.2 ± 7.7	< 0.0005[a]
Anxious symptoms ± s.d. (HamA)	12.6† ± 6.2	1.4 ± 1.1	< 0.0005[a]
Depressive symptoms ± s.d. (MADRS)	15.7† ± 8.9	1.3 ± 1.2	< 0.0005[a]
Obsessive-compulsive symptoms ± s.d. (Y-BOCS)	25.2 ± 4.3		
Obsessive-compulsive symptoms ± s.d.[c] (OCI-R) Total (distress)	1.65 ± 0.64		
Washing ± s.d.	1.82 ± 1.08		
Checking ± s.d.	1.55 ± 0.89		
Doubting ± s.d.	1.97 ± 1.11		
Ordering ± s.d.	1.89 ± 1.10		
Obsessions ± s.d.	1.64 ± 0.77		
Hoarding ± s.d.	1.25 ± 1.06		
Neutralizing ± s.d.	1.44 ± 0.95		
Current serotonin-reuptake inhibitor (%)	12 (30.0)		

Abbreviations: GAS, Global Assessment Scale; HamA, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; WAIS, Wechsler Abbreviated Scale of Intelligence; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; OCI-R, Obsessive-Compulsive Inventory Revised.

[a] Mann-Whitney *U*-test.
[b] χ^2-test.
[c] OCI-R data were missing for 1 participant.

OCD participants were compared to 16 matched healthy controls. We recruited healthy controls *via* flyers and Internet ads. Healthy controls provided signed informed consent. Controls had no history of psychiatric disorder or substance abuse and no current major medical conditions or psychoactive medications.

The primary clinical measure was the YBOCS (patients only). Secondary measures included the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Scale (HamA). General functionality and social and occupational performance were rated by the Global Assessment Scale (GAS; Endicott et al., 1976).

2.2. ^{1}H MRS acquisition

Whole-brain MRI and localized MRS were acquired in 1-h sessions at 3 T on a Siemens Trio with 12-channel phased-array head coil. Structural MRI was acquired with an axial-oblique (genu-splenium parallel) magnetization-prepared rapid gradient-echo (MPRAGE, $1 \times 1 \times 1$ mm^3) pulse-sequence. This MPRAGE and "coronal" and "sagittal" resliced copies were used to prescribe MRS. A neuroradiologist (NS) reviewed MRIs to exclude subjects with clinical abnormalities.

Single-voxel water-suppressed point-resolved spectroscopy (PRESS) MRS (TR/TE = 2000/30 ms, 96 NEX) was acquired bilaterally from three sites. Each PRESS excitation volume ("voxel")