MRS measurement of GABA and glutamate-glutamine in frontal cortex in obsessive-compulsive disorder

L. S. Kegeles[1,2], H. B. Simpson[1], X. Mao[3], R. Staub[1], and D. C. Shungu[3]
[1]Psychiatry, Columbia University, New York, NY, United States, [2]Radiology, Columbia University, New York, NY, United States, [3]Radiology, Weill Cornell Medical Center, New York, NY, United States

Background: Functional brain imaging studies suggest that obsessive-compulsive disorder (OCD) results from a malfunctioning brain circuit that includes the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), striatum, and thalamus. Because only serotonin reuptake inhibitors (SRIs) are effective for many (but not all) patients with OCD, abnormalities in the brain serotonin (5-HT) system have long been hypothesized to underlie OCD. However, recent animal and human studies have also implicated the glutamatergic system in OCD. In particular, human genetic studies demonstrated associations between the glutamate transporter SLC1A1 and OCD, animal studies found that disrupting glutamatergic signaling at cortico-striatal synapses leads to OCD-like behaviors, and case studies and open label trials demonstrate efficacy of glutamatergic agents in reducing OCD symptoms. This has led to the hypothesis that OCD symptoms result either directly or indirectly from increased glutamatergic signaling in cortico-striatal pathways. To date, there are only a few magnetic resonance spectroscopy (MRS) studies in OCD that have measured glutamatergic compounds. Most have been limited by small samples (e.g., <15), OCD patients on medications at the time of imaging, or MRS methods that cannot distinguish glutamatergic compounds (glutamate and glutamine=Glx) from GABA. To test whether there are glutamate or GABA abnormalities in frontal cortical regions in OCD, we used spectroscopic editing to measure glutamate-glutamine (Glx) and GABA levels in unmedicated OCD patients compared to healthy controls. We examined two frontal regions: the ACC, a region implicated in OCD, and the dorsolateral prefrontal cortex (DLPFC), a region not typically implicated in OCD but anatomically connected to the OFC.

Methods: Forty-two subjects were recruited and signed consent. Forty completed the MRS and clinical evaluations: 21 patients with OCD (ages 30 ± 10 years, 9 F, 12 M), and 19 matched healthy control subjects (ages 30 ± 10 years, 9 F, 10 M). All 21 OCD patients were free of medications at the time of imaging; 14 were treatment naïve. The others had been free of medications for on average 50 weeks (standard deviation (SD)=50, range=10-156 weeks). In all cases, OCD was the primary diagnosis with no current Axis I comorbidity; the severity of OCD was at least moderate (mean Yale-Brown Obsessive Compulsive Scale score=26 (SD=4), range 20-36). MRS data were acquired from an 18.8 cc ACC voxel and a 9.6 cc DLPFC voxel. All spectra were recorded on a 3T GE 'EXCITE' MR system using an 8-channel phased-array head coil. The J-edited spin echo difference technique followed by a frequency-domain nonlinear least-squares spectral fitting procedure were used to determine the two main outcome measures GABA and Glx, which were normalized to the internal water signal recorded simultaneously. Test-retest reliability using these methods was previously shown to be high (percent coefficient of variation or %CV was 5.2%, and intraclass correlation coefficient or ICC was 0.84 for GABA/W). Group differences were assessed for significance by 2-tailed Student's t test.

Results: Neither outcome measure differed between patients and control subjects in either the DLPFC or the ACC. Glx/W was 3.3 ± .95 in the patients and 3.3 ± .59 in controls in the DLPFC ($p = 0.9$); Glx/W was 1.5 ± .44 in patients and 1.6 ± .25 in controls in ACC ($p = 0.6$, all values times 10^{-3}). Similarly, GABA/W values were 5.3 ± 1.1 in the patients and 5.0 ± .97 in controls in DLPFC ($p = 0.3$); GABA/W was 2.1 ± .59 in patients and 2.4 ± .54 ($p = .11$) in the controls in ACC. None of the outcome measures (DLPFC Glx/W, GABA/W; ACC Glx/W, GABA/W) was associated with OCD severity.

Discussion: These data indicate the absence of abnormalities in glutamate or GABA transmission in OCD in the brain regions examined. If these transmitters do play a role in the malfunctioning circuitry of OCD, abnormal levels may be found in other sites in the circuit, such as striatum or OFC. Further studies are needed to fully characterize the neurochemistry of the hypothesized abnormal circuitry in OCD, to determine whether specific subtypes of OCD are associated with distinct neurochemical abnormalities, and to examine whether neurochemical findings at baseline predict who will or will not respond to pharmacotherapy.