

Glutamate, GABA and NAAG in Medicated Patients with Obsessive-Compulsive Disorder

Mona A. Mohamed¹, Nicolaas A Puts¹, James Robert Brasic², Manuel O Uy³, Jarunee Intrapiromkul¹, Gerald Nestadt⁴, Richard AE Edden¹, and Peter Barker¹
¹The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Medical Institutions, Baltimore, MD, United States, ²Radiology, Johns Hopkins Medical Institutions, Baltimore, MD, United States, ³Applied Physics Laboratory, JHU, Laurel, MD, United States, ⁴Psychiatry, Johns Hopkins Medical Institutions, Baltimore, MD, United States

Target audience: Scientists with an interest in the GABAergic and Glutamatergic brain pathways in psychiatric diseases, particularly in Obsessive Compulsive Disorder (OCD).

Purpose: Cortical excitability reflects a balance between excitation (glutamatergic) and inhibition (GABAergic). The purpose of this study was to use magnetic resonance spectroscopy (MRS) to determine if the inhibitory GABAergic and the excitatory glutamatergic systems are abnormal in obsessive-compulsive disorder (OCD), and are different in patients who do or do not respond to treatment with selective serotonin reuptake inhibitors (SSRIs).

Methods: Forty OCD patients (18 females and 22 males, age range 21 to 67 years) and 20 age and gender matched controls were included in this study. Nineteen patients were SSRI responders, 17 were SSRI non responders, and 4 were treatment naïve. All patients fulfilled Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for OCD, and had a Yale-Brown Obsessive Compulsive (YBOCS) score of greater than 20 prior to treatment for responders or greater than 20 for non-responders at the time of inclusion. Responders were defined as patients who had a 35% or greater reduction in their YBOCS score after a 10 week trial of any appropriate SSRI. All studies were performed on a Philips Achieva 3T system using a 32-channel head coil. Subjects underwent single voxel MRS (4.0 x 3.0x 2.5 cm voxel, TR/TE=2000/35 ms) acquired from the anterior cingulate cortex (ACC) and the basal ganglia/thalamus (BG/TH) with and without water suppression. MEGA-PRESS experiments were performed for N-acetyl aspartate (NAA) and NAA-glutamate (NAAG) (TE = 140, TR= 2s; 256 transients, 8 min 32 sec. 35 msec sinc-Gauss editing pulses with "on/off" frequencies of 4.61/4.15 ppm and 4.38/4.84 ppm selected NAAG and NAA respectively. For γ -amino butyric acid (GABA), 14 ms Gaussian editing pulses were used with on/off frequencies of 1.9/7.6 ppm. Experimental parameters were TE=68 ms; TR= 2s; 256 transients; scan time of 8 min 32 sec (Figure 1). Metabolites

concentrations were determined using the GANNET program (gabamrs.blogspot.com) for GABA, NAA and NAAG and LCModel for glutamate (Glu), glutamine (Gln), NAA, creatine (Cr), myoinositol (ml), Gln and choline (Cho) [both glycerophosphocholine (GPC) and phosphocholine (PC)] concentrations and ratios. One-way ANOVA and t tests with correction for multiple comparisons were performed between controls, SSRI responders and non-responders controlling for age and gender.

Results: ACC NAA and NAA+NAAG concentrations were higher in younger subjects as compared to older ($P < 0.006$, $P < 0.003$ respectively) with no gender differences. BG/TH GPC and GPC+PC was higher in males compared to females ($P < 0.01$, $P < 0.02$ respectively) and showed a trend increase in their concentrations in older subjects ($P < 0.06$, $P < 0.02$ respectively). OCD patients showed lower BG/TH Glu+Gln(Glx)/Cr compared to controls ($P < 0.03$), however the significance was lost when age and gender were co-varied for. There were no significant differences in Glu, ml, Cho, NAA, NAAG, GABA/Cr between the 3 groups.

Discussion: In this study, there were no significant differences between medicated OCD patients and controls; also no differences were found between SSRI responders and non-responders. This is in contrast to a previous 1.5T MRS study which showed a significant decrease in orbitofrontal white matter Glx and which correlated with OCD symptom severity¹. Other studies have found higher CSF Glu levels in drug-naïve OCD². Furthermore, a recent 3T MRS study found that un-medicated OCD patients did not have any Glx abnormalities in the medial prefrontal cortex; however, they may have decreased GABA levels³.

Conclusion: The current study did not find any significant differences in compounds related to the glutamatergic or GABAergic systems (Glu, NAAG, GABA) in the ACC and BG/TH between OCD patients and controls when co-varying for age and gender. The role of MRS in OCD remains to be determined.

References: (1) Whiteside, S.P., et al., *Psychiatry Res*, 2006. **146**(2): p. 137-47, (2) Chakrabarty, K., et al., *Neuropsychopharmacology*, 2005. **30**(9): p. 1735-40, (3) Simpson HB, et al. *Neuropsychopharmacology*. 2012 Nov; **37**(12):2684-92.

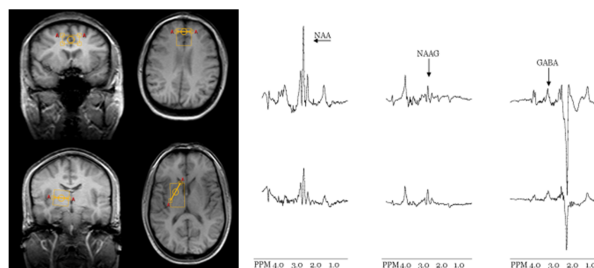


Figure 1 A 35 y.o. male OCD patient who is SSRI responder. Top row shows the ACC voxel location and the corresponding MEGA-PRESS edited spectra with NAA, NAAG and GABA. Lower row BG/TH location and corresponding MEGA-PRESS edited spectra.