**INTRODUCTION**

There is increasing evidence that oxidative stress plays an important pathophysiological role in severe psychiatric disorders. Glutathione (GSH) is a major intracellular antioxidant and redox regulator that protects cells against oxidative stress. Dysregulation of the GSH system has been hypothesized to reduce glutamatergic activity at the NMDA receptor and attenuate neurotrophin production, processes functionally linked to cognitive and affective symptoms in conditions such as major depressive disorder (MDD). While previous 1H MRS studies in MDD have identified regional brain abnormalities in the amino acid neurotransmitters GABA and glutamate-glutamine (Glx), no study to our knowledge has previously measured in vivo brain GSH in MDD. In this pilot study, we aimed to test the hypothesis that oxidative stress is central to the pathophysiology of MDD and that brain antioxidant capacity as reflected in GSH levels would be decreased compared to an age- and sex-matched sample of non-psychiatrically ill healthy volunteers.

**METHODS**

Seven patients (3 females, mean age=25.6 ± 2.8) met the diagnosis of MDD by DSM-IV-TR criteria and confirmed by SCID interview. Other psychiatric conditions commonly comorbid with MDD (e.g. substance abuse or dependence) were excluded. The MDD group had day-of-scan depressive severity of at least moderate severity. To avoid confounds of psychotropic medication usage on neuroimaging measures, all subjects were psychotropic medication-free for at least 2 weeks prior to scanning. Seven non-psychiatrically ill, medically healthy volunteers (HV; 4 females, mean age= 37.6 ± 9.9) assessed by the SCID-IV-NP, were comparison subjects.

All in vivo brain GSH spectra were recorded from a single 3x3x3-cm³ occipital cortex (OCC) voxel on a GE 3.0 T “EXCITE” MR system using the standard J-edited spin echo difference method and an 8-channel phased-array head coil. Briefly, volume-selective J-editing detection of GSH was accomplished by incorporating into the standard PRESS sequence a pair of frequency-selective “editing” pulses before and after the second 180° rf pulse flanked by spoiler gradients of opposite signs. Each frequency-selective editing pulse was applied at 4.56 ppm (the frequency of the GSH cysteinyl α protons) on alternate scans with TE/TR 68/1500 ms, resulting in alternated inversion of the GSH cysteinyl β doublet at 2.9 ppm by alternatively inhibiting and allowing its J-modulation. Subtracting two subspectra thus acquired in 15 min with 240 interleaved excitations yielded the desired GSH resonance at 2.9 ppm, while the much stronger overlapping tCr resonance -- a singlet that is not J-acquired in 15 min with 240 interleaved excitations yielded the desired GSH resonance at 2.9 ppm, while the much stronger overlapping tCr resonance -- a singlet that is not J-acquired in 15 min with 240 interleaved excitations yielded the desired GSH resonance at 2.9 ppm, while the much stronger overlapping tCr resonance -- a singlet that is not J-acquired in 15 min with 240 interleaved excitations yielded the desired GSH resonance at 2.9 ppm, while the much stronger overlapping tCr resonance -- a singlet that is not J-acquired in 15 min with 240 interleaved excitations yielded the desired GSH resonance at 2.9 ppm, while the much stronger overlapping tCr resonance -- a singlet that is not J-acquired in 15 min with 240 interleaved excitations yielded the desired GSH resonance at 2.9 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