^{1}H MRS Measurement of Brain Glutathione Supports Increased Oxidative Stress in Major Depressive Disorder

S. J. Mathew[1], X. Mao[2], S. Pillemer[1], J. W. Murrough[1], and D. C. Shungu[2]
[1]Psychiatry, Mount Sinai School of Medicine, New York, NY, United States, [2]Radiology, Weill Cornell Medical College, New York, NY, United States

INTRODUCTION

There is increasing evidence that oxidative stress plays an important pathophysiological role in severe psychiatric disorders[1]. 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 ^{1}H 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.

In vivo Brain GSH Measurements by ^{1}H MRS

All *in vivo* brain GSH spectra were recorded from a single 3x3x3-cm^3 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^o 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-modulated -- was eliminated. The result of implementing this GSH editing method is shown in **Fig. 1**. GSH peak areas were derived by frequency-domain spectral fitting (**Fig. 1d**) and expressed as ratios relative to the area of a simultaneously acquired unsuppressed voxel tissue water (W).

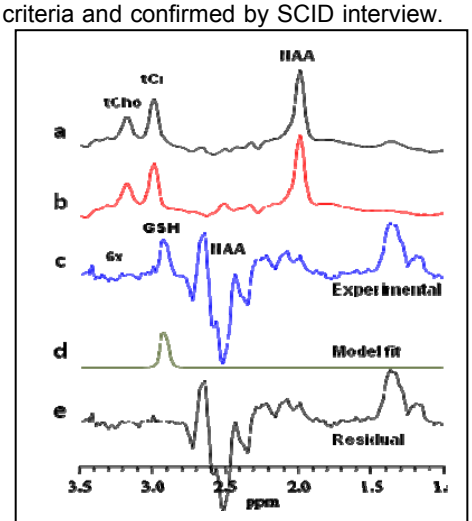

Fig. 1: *In vivo* GSH detection by ^{1}H MRS: (a) and (b) subspectra with the editing pulse on and off; (c) edited brain GSH; (d) model-fitting of (c); (e) residual of difference between (c) and (d).

RESULTS

Mean GSH/W in the occipital cortex (**Fig. 2**) was 31% lower in the MDD group compared to healthy volunteers (P<0.01; Cohen d=1.5). Notably, all 7 MDD patients had occipital GSH/W below the group mean of the HV group, compared to 2 of 7 in the HV group (Fisher Exact Test p< 0.05). There was a significant difference between groups in mean age (p=0.02), and a negative correlation between GSH/W and age (r= -0.622, p=0.01). However, GSH/W in the MDD group remained significantly lower than in the HV group after adjusting for the group age difference (p<.05).

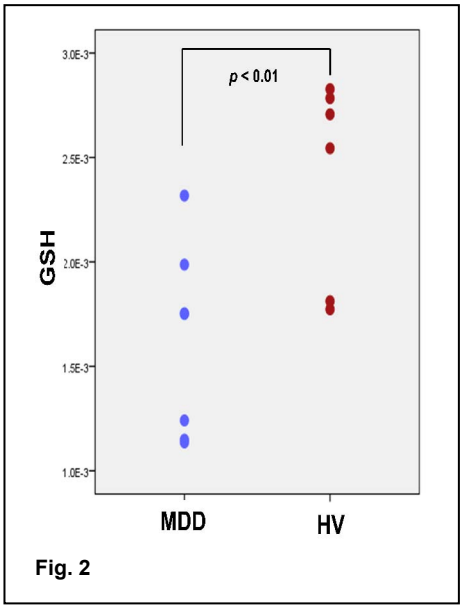

Fig. 2

DISCUSSION AND CONCLUSION

This is the first study to our knowledge to report *in vivo* cortical GSH in patients with MDD. Our preliminary finding of decreased cortical GSH in MDD is consistent with pathophysiological models postulating a role for oxidative stress and oxidative metabolic pathways in mood disorders.[1] The potential therapeutic relevance of these findings was recently suggested by a clinical trial showing that the GSH precursor N-acetyl cysteine (NAC) has benefit in serious mood disorders such as bipolar disorder.[2] These promising preliminary results suggest further investigations in larger samples to (a) confirm the present finding of a significant decrease of OCC GSH in MDD, (b) assess antioxidant capacity in additional brain regions implicated in mood regulation, (c) conduct careful scrutiny of clinical characteristics such as disease chronicity, which might impact expression of GSH,[3] and lifestyle factors that impact oxidative stress such as physical exercise, diet, and smoking history. Follow-up studies examining and comparing peripheral markers of oxidative stress with temporally concordant ^{1}H MRS measures of brain GSH would offer the opportunity to establish whether increased oxidative stress in MDD is the result of decreased antioxidant capacity (GSH), increased production and accumulation of reactive oxygen species or pro-oxidants that overwhelm the cell's antioxidant capacity, or both, which might help in the development of effective targeted dietary or pharmacological treatments.

REFERENCES

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