Assessment of GABA and Glutamate/Glutamine using the J-edited Spin Echo Difference Method at 3 Tesla in Patients with Major Depressive Disorder

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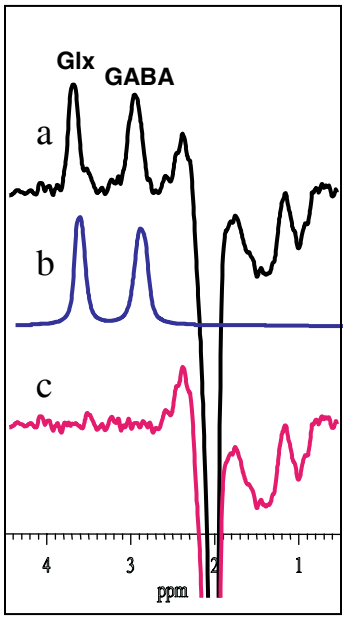
Background: Previous proton magnetic resonance spectroscopy (^{1}H MRS) studies in major depressive disorder (MDD) have shown reductions in occipital lobe GABA concentrations of approximately 30-50% and glutamate elevations of approximately 10% [1,2]. Reductions in occipital GABA were normalized with several forms of antidepressant treatments, including electroconvulsive therapy (ECT) and selective serotonin reuptake inhibitors, but not cognitive behavioral therapy. One study found no differences in prefrontal cortical GABA between remitted MDD patients and controls [3]. To our knowledge, no studies in MDD have examined GABA and glutamate+glutamine ("Glx") in relation to childhood trauma history and anxiety, which has been demonstrated to be salient variables for identifying subgroups of MDD [4]. In this study, we compared occipital cortex GABA and Glx in unmedicated, symptomatic MDD patients and healthy controls.

Methods: We studied 10 patients with MDD (6M, 4F; mean age=36.4, SD=13.2), and 9 non-psychiatrically ill healthy volunteers (3M, 6F; mean age=44.0, SD=13.0), matched age and sex. All subjects were medication-free for at least 1 week prior to scan and had negative urine toxicologies on scan day. The MDD sample was moderately depressed, with day of scan Hamilton Depression Rating Scale scores of 19.3 (SD=5.3), with significant comorbid anxiety (mean Hamilton Anxiety Rating Scale = 20.7, SD= 9.9). Childhood abuse was measured with the Childhood Trauma Questionnaire (CTQ), and as expected showed greater abuse severity in MDD (mean CTQ= 59.0 SD=17.1; control mean= 30.1 SD=17.8; p=0.007). Levels of occipital lobe GABA and Glx were recorded in 13 min from 3x3x2 cm^3 voxels with an 8-channel phased-array coil using the J-editing technique (TE/TR 68/1500ms) on a 3.0 T GE 'LX' MR system, as previously described [6] Mean peak areas for all metabolites of interest were obtained by frequency-domain nonlinear least-squares procedures, and then expressed as ratios relative to the unsuppressed voxel tissue water signal (W). The comparability of the groups in characteristics was tested for continuous variables with analysis of variance (ANOVA) and for dichotomous variables with Fisher exact tests. We examined the associations of MRS metabolites with clinical characteristics using the Pearson product moment correlation coefficient. All statistical tests were 2-tailed, with a level of significance of $P \leq 0.05$.



Results: **Figure 1** illustrates the quality of the occipital GABA and Glx spectra (Fig. 1a), with model fitting (Fig. 1b) and residual difference (Fig. 1c), used in the present analysis. GABA/W was significantly elevated in MDD patients compared to controls [F(1,17)= 4.65, p= 0.045]. There was no effect of age or sex. Glx/W was elevated at the trend level of significance in MDD patients [F(1,17)=3.09, p=0.097]. In MDD subjects, a strong negative correlation was found between Glx/W and day-of-scan anxiety (r=-0.76, p=0.01), with particular robust associations in male patients. No associations for GABA/W were noted with depressive or anxiety symptoms or childhood trauma severity.

Discussion and Conclusion: We recently reported [7] a coefficient of variation of less than 4% for measuring brain GABA and Glx using the method employed in this study. Here, we used the same approach to obtain reliable measures of occipital cortex GABA and Glx in patients with symptomatic MDD. Contrary to previous reports in MDD, we found *elevated* levels of occipital GABA in this sample. As the vast majority of these patients were treatment naive, we cannot attribute this finding to distant effects of psychotropic medication. Differences across studies might reflect the profound level of childhood abuse and comorbid anxiety in our MDD sample, inasmuch as these clinical factors have been previously reported to contribute to variance in neurotransmitter and neuropeptide regulation in mood disorders. Further, differences in magnitude of key genetic polymorphisms regulating glutamate and GABA concentrations, as recently observed in an MRS study analyzing NAA, could be contributory [5]. Confirmation of these findings in larger MDD samples is necessary.

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