# Assessment of GABA and Glutamate/Glutamine at 3.0 T in Chronic Fatigue Syndrome, Major Depressive Disorder and Healthy Volunteers

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**Purpose:** Chronic fatigue syndrome (CFS) is a controversial diagnosis due to the lack of biomarkers for the illness, and its symptom overlap with neuropsychiatric, infectious, and rheumatologic disorders. The CDC case definition requires at least 6 months of new-onset fatigue with four or more symptoms, including impaired memory or concentration, muscle pain, new headaches, unrefreshing sleep, and post-exertional malaise. Many of these symptoms are also found in patients with major depressive disorder (MDD), a much more prevalent illness, resulting in frequent misdiagnosis of CFS. Significant alterations in γ-aminobutyric acid (GABA) and glutamate levels have been previously reported in symptomatic and remitted major depressive disorder (MDD) using proton magnetic resonance spectroscopy (1H MRS) in occipital cortex (OCC) and prefrontal cortical regions [1-4]. To our knowledge, no previous studies have investigated *in vivo* amino acid neurotransmitter function in CFS patients. OCC and anterior cingulate cortex (ACC) were selected as ROIs based on previous studies in depression and feasibility of obtaining high-quality spectroscopic data in these regions. In this pilot study, we compared cortical levels of GABA and glutamate + glutamine (Glx) levels in CFS patients and a cohort of unmedicated patients with MDD and healthy volunteers.

**Methods**: Nineteen CFS patients (mean age = $47.9 \pm 8.8$; 16 F) were compared to 31 MDD patients (mean age $42.9 \pm 12.5$; 14 F) and 23 healthy volunteers (mean age = $37.7 \pm 13.6$; 12 F). All subjects were medication-free for at least 1 wk prior to scan and had negative urine toxicologies on scan day. Four patients in the CFS group met criteria for current MDD, and 6 met criteria for a previous major depressive episode (no MDD patients met criteria for CFS). Symptom severity on day-of-scan was assessed with the Fatigue Severity Scale and the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). Levels of occipital lobe and anterior cingulate cortex (ACC) GABA and Glx were recorded in 13 min from $3 \times 3 \times 2$ $cm^3$ voxels with an 8-channel phased-array coil using the J-editing technique (TE/TR 68/1500 ms) on a 3.0 T GE 'LX' MR system, as previously described [5]. 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). 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 $P \le 0.05$.

**Results**: **Figure 1** illustrates the quality of the occipital GABA and Glx spectra (Fig. 1a), with model fitting (Fig. 1b) and residual difference (Fig. 1d), used in the present analysis. There was no significant main effect of diagnostic group [F=2.57, d.f.=2,70, *p*=0.08]. Consistent with previous reports, the MDD group had significantly lower OCC GABA/W levels compared to healthy volunteers (*p* = 0.027). There were no significant group differences in ACC GABA/W or Glx/W in either ROI. Exploratory analyses did not reveal significant differences in regional GABA or Glx between CFS patients with and without lifetime comorbid depression. Across all participants, fatigue severity was negatively correlated with GABA/W levels in OCC (R=-0.24, *p* = 0.038), and within the MDD group, was negatively correlated with GABA/W in ACC (R=-0.391, p=0.048 ). There were no significant associations between amino acid neurotransmitter levels and current mood symptoms in either patient group.
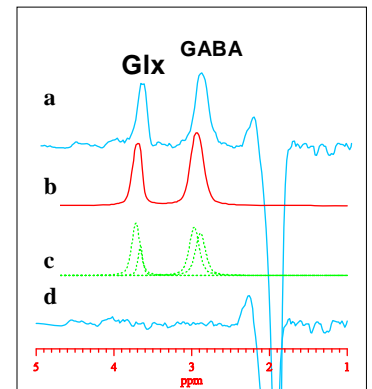


**Conclusions**: The present study does not provide evidence for significant abnormalities in regional amino acid neurotransmitter function in CFS, while confirming previously observed reductions in occipital GABA in MDD. Further investigation of larger samples of CFS patients with and without mood disorder comorbidity, as well as studies of remitted CFS patients, are necessary to uncover state and trait-related neurochemical abnormalities that may distinguish this condition from phenotypically similar disorders.

**References**

[1] Sanacora G, et al. (2004). *Arch Gen Psychiatry* 61(7):705-13.  [2]  Bhagwagar Z, et al. (2007). *Biol Psychiatry* 61:806–812.  [3] Bhagwagar Z, et al. (2008). *Int J Neuropsychopharm* 11:255-260. [4] Hasler G, et al. (2007). *Arch Gen Psychiatry* 64:193-200. [5] Shungu DC, et al., Proc. Intl. Soc. Mag. Reson. Med. 14:488 (2006).

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