ALTERATIONS OF CEREBRAL WHITE MATTER VOLUME AND METABOLITE CONCENTRATION IN PATIENTS WITH GENERALIZED ANXIETY DISORDER: A VOXEL-BASED MORPHOMETRY AND 1H-MRS

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Synopsis: Generalized anxiety disorder (GAD) is characterized by excessive, pervasive and uncontrollable anxiety in daily life. Recent studies demonstrated that the symptoms of GAD are associated with neural dysfunction related with cognition and emotional regulation. However, it is unclear how the white matter (WM) volume and cerebral metabolites are associated with the typical symptoms of GAD without other comorbid psychiatric disorders.

The purpose of this study was to investigate the abnormalities in WM volumes and cerebral metabolite concentrations in patients with GAD using the voxel-based morphometry (VBM) and localized ^{1}H-MR spectroscopy (^{1}H-MRS).

Subjects and Methods: Thirty subjects comprised 15 patients with GAD (mean age, 35.4±9.6 years) diagnosed by the DSM-IV-TR and 15 age-matched healthy controls (mean age, 38.8±8.9 years). The patients had the average duration of illness for 3.1±3.4 years with anxiety severity (Hamilton Anxiety Rating Scale [HAMA]: 17.8±5.2; Generalized Anxiety Disorder Scale 7 [GAD-7]: 11.7±4.2). All of the patients had a primary diagnosis of GAD and noncomorbid psychiatric disorders.

All experiments were performed on a 3T Magnetom Verio MR scanner. The MR imaging data were processed using the VBM with DARTEL algorithm in SPM8. The ^{1}H-MR spectra were acquired using PRESS sequence (TR/TE= 2000/30 ms, NA= 96, voxel size= 20×20×20 mm^3 and 1024 data points) from a localized voxel in the right dorsolateral prefrontal cortex (DLPFC). The differential metabolic concentration between two groups was analyzed by the Mann-Whitney U test.

Results and Discussion: Patients with GAD showed significant WM volume reduction as compared with healthy controls, especially in the regions of the midbrain (MB), anterior limb of the internal capsule (ALIC) and DLPFC (Brodmann area 46) (FWE corrected p<0.05, Fig. 1). The reverse contrast (controls over GAD) showed no distinct volume difference. The concentration ratio of Cho/NAA in the DLPFC was significantly lower in patients with GAD than in healthy controls: 0.44±0.07 vs. 0.49±0.07 (p=0.024, Table 1). It is noteworthy to reveal the significant changes in both WM volume and Cho level in the DLPFC. In addition, Cho/NAA ratios in patients were negatively correlated with the scores of HAMA (Pearson's coefficient (γ)=-0.68, p=0.006) and GAD-7 (γ=-0.57, p=0.027), respectively (Fig. 2). From the results found in this study, it is assumed that the morphological alterations in the regions of the MB, ALIC and DLPFC are potentially associated with psychopathological symptoms in GAD. Also, the concentration abnormality in Cho, which is a biomarker of cell membrane metabolism/turnover and cholinergic neurotransmission, may be related to anxiety symptoms of GAD.

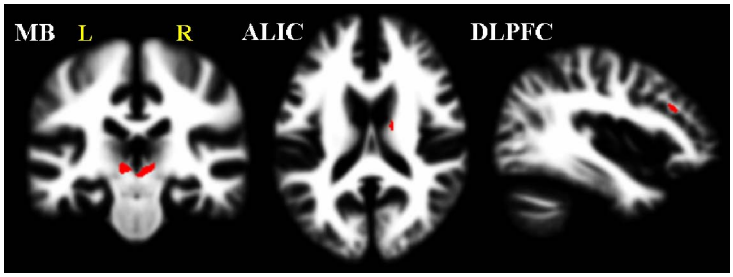

Figure 1. Key brain centers demonstrating distinct volume reduction of white matters in patients with GAD compared to healthy controls, which were resulted from two-sample t-test (FWE, p<0.05).

Conclusion: This study demonstrated variations of the WM volumes and metabolites concentration in patients with GAD. The findings on the specific morphology and metabolite change will be useful to understand the neuroanaomical mechanisms associated with the symptoms of GAD.

References: 1) Strawn *et al.* Depress Anxiety 2013;30:842–8. 2) Mathew *et al.* Am J Psychiatry 2004;161:1119-21.

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Table 1. Comparison of the brain metabolic concentration between patients with GAD and healthy controls in the dorsalateral prefrontal cortex (DLPFC)

Metabolites	GAD (n=15)	Control (n=15)	p- value*
Lip/NAA	0.30±0.08 (26.7 %)	0.34±0.08 (23.5 %)	0.101
Lac/NAA	0.11±0.03 (27.3 %)	0.12±0.03 (25.0 %)	0.268
Cr/NAA	0.60± 0.07 (11.7 %)	0.61±0.06 (9.80 %)	0.406
β·γ-Glx/NAA	0.52±0.11 (21.2 %)	0.61±0.15 (24.6 %)	0.059
Cho/NAA	0.44±0.07 (15.9 %)	0.49±0.07 (14.3 %)	0.024
mI/NAA	0.34±0.09 (26.5 %)	0.31±0.12 (38.7 %)	0.430
α-Glx/NAA	0.25±0.05 (20.0 %)	0.25±0.08 (32.0 %)	0.647

Data are presented as mean±SD (% CV).

Lip, lipid; Cr, creatine; Lac, lactate; β·γ-Glx, β·γ-glutamate/glutamine; Cho, choline; mI, myo-inositol; α-Glx, α-glutamate/glutamine; NAA, *N*-acetyl aspartate.

*Mann-Whitney U test

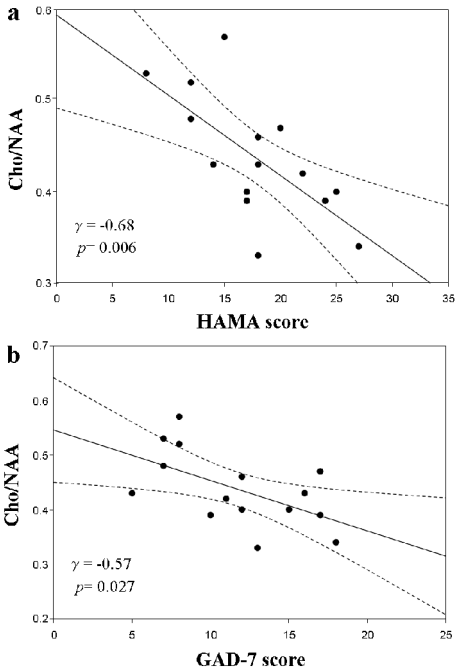

Figure 2. The correlations of Cho/NAA ratios in the dorsolateral prefrontal cortex with HAMA scores (a) and GAD-7 scores (b) in patients with GAD, in which the band with dotted lines shows 95% confidence interval.