Subcortical Glutamate Increase Suggestive of Glial Toxicity in Depressed patients with High Inflammation

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Target Audience: This work will be of interest to scientists involved in the study of neurological and behavioral disorders associated with basal ganglia.

Purpose: Previous work using a variety of inflammatory stimuli and multiple functional imaging modalities have consistently indicated that cytokine and related inflammatory molecules selectively target subcortical brain regions including basal ganglia (BG) regions and dorsal anterior cingulate cortex (dACC), resulting in behavioral symptoms including depression, anhedonia and fatigue. Data from several sources indicate that cytokines might induce increased glutamate concentrations by decreasing its clearance by glial elements. Using magnetic resonance spectroscopy (MRS) we had reported that four weeks of exposure to the innate immune cytokine interferon (IFN)-alpha was associated with significant increases in normalized glutamate concentrations (to creatine, Glu/Cr) in dACC and left BG regions, which in turn were correlated with increases in depression and fatigue and reduction in activity levels and motivation.[1, 2] However, it is unclear if similar Glu/Cr changes are observable among patients with major depression with high inflammation. In this study, we used a short TE (=30 ms), magnetic resonance spectroscopic imaging as we intended to obtain spectra simultaneously from both left and right BG. This afforded a distinct advantage over the single voxel procedure as the regions were imaged sequentially.

Methods: Twenty-four patients with a diagnosis of major depressive Disorder (MDD as determined by SCID) and who were free of psychotropic medications or unstable medical conditions participated in the study. Nine patients "high" inflammation (MDE_H) based on the concentrations of C-reactive protein (CRP>3mg/dl) and fifteen patients with "low" inflammation (MDE_L, CRP<3mg/dl) underwent MRS scanning, blood draws and psychiatric assessments (consisting of measures of anxiety, depression and fatigue). During scanning T_1-weighted images were obtained on a 3.0 Tesla Siemens Magnetom TRIO scanner (Siemens Medical Solutions, Malvern, PA) with an MPRAGE sequence (TR = 2300 ms, TE = 3.02 ms, TI = 1100 ms, Flip Angle = 8°, voxel size = 1 × 1 × 1 mm^3). Spectroscopic data were acquired by 2D PRESS-based MRSI sequence (TR = 1590 ms, TE = 30 ms, sampling size = 1024, matrix=16 × 16, voxel size= 11. 3 × 11.3×15 mm^3). All MRSI data were analyzed with LCModel, using a 18-metabolite basis file and the water signal as the internal reference. Metabolite levels extracted from a 1 x 1x 4 mm^3 subregion located within the left and right BG regions (delineated by red line in the Figure 1. B). "Average" metabolite levels were computed using the metabolite levels from left and right and was also used in the analysis. The MDE_H and MDE_L group means were compared using two-sample t-test and significance levels were thresholded at p<0.05.

Results: The study groups did not differ in any of the background variables. The results are presented in Table 1. Marginally significant elevations of Cho/Cr were seen in the left hemisphere. In the left subcortical voxel, significant elevation in Cho/Cr was seen in MDD_H group with a trend towards significance P=0.09 with regards to Ins/Cr. Right subcortical region, Ins/Cr and Glu/Cr were significantly increased in the MDE_H group. On averaging the values of the Glu/Cr and Ins/Cr were significantly increased in the MDE_H group.

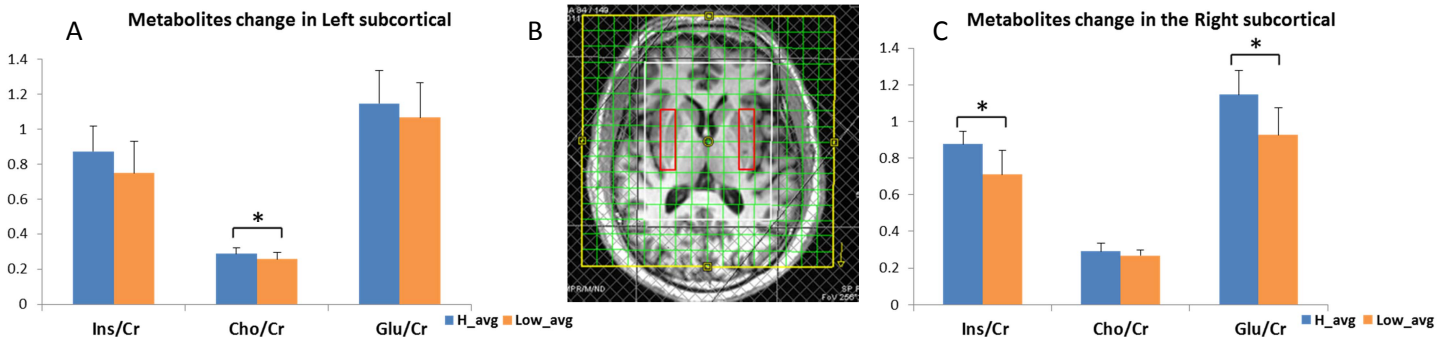

Figure 1: The figure shows the localization of right and left subcortical area around basal ganglia (B) and the corresponding metabolite levels acquiring by chemical shift imaging (Left: A; Right: C). The red area in T1-wighted structural image were chosen for representing right and left subcortical. In Left subcortical, Ins/Cr and Cho/Cr were higher in high inflammation group. In Right subcortical, Ins/Cr and glu/Cr were higher in high inflammation group. *: P<0.05

Table 1. Metabolite levels in Left, Right and Average

	LEFT			RIGHT			AVERAGE		
	H_INF	L_INF	P-value	H_INF	L_INF	P-value	H_INF	L_INF	P-value
Ins/Cr	0.88±0.14	0.75±0.18	0.091	0.88±0.07	0.71±0.13	0.002	0.88±0.10	0.73±0.15	0.015
Cho/Cr	0.29±0.04	0.26±0.04	0.056	0.29±0.05	0.27±0.03	0.151	0.29±0.04	0.26±0.03	0.072
Glu/Cr	1.15±0.19	1.07±0.20	0.339	1.15±0.13	0.93±0.15	0.001	1.15±0.07	1.00±0.12	0.003

Discussion and Conclusion Our results indicate that increased systemic inflammation as measured by CRP values >3 mg/L were associated with increased Glu/Cr and Ins/Cr in the right subcortical region and on averaging metabolites across both sides. The high levels of Glu/Cr in the subcortical regions are along the same lines as our previous findings and those of others. In fact, increased Glu/Cr is one of the most consistent neuroimaging findings seen among patients with bipolar depression.[3] The precise etiology of these changes are not known but are believed to be due to decreased clearance of glutamate by glial elements impaired by the toxic effects of inflammatory molecules Such as inflammatory cytokines. Myoinositol (Ins) is a marker of astroglial toxicity, and high levels of Ins/Cr provide an insight into the glial toxicity set in motion by the inflammatory process.[4] We had earlier reported that chronic administration of interferon-alpha (a pro-inflammatory cytokine) can precipitate astrocytic dysfunction resulting in a decrease in glutamate clearance by astrocytes. Similar results have also been reported in post mortem studies and MRS studies among patients with late life depressive disorders.[5, 6].

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