

γ -Aminobutyric Acid (GABA) Modulates Functional Connectivity Network Strength in Adolescent Major Depressive Disorder

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Background

Adolescent major depressive disorder (MDD), a neuropsychiatric illness with far-reaching public health consequences, is associated with significant morbidity, and, most critically, with high risk for suicide. To date, sparse evidence has examined the disorder in adolescent populations, which is necessary to minimize the effects of chronicity, prolonged treatment, and aging. A large body of evidence suggests that MDD is associated with both structural and functional abnormalities in specific brain regions, including brain volume changes in the anterior cingulate cortex (ACC) and striatum¹ and alterations in linked fronto-striatal circuits². Additionally, metabolic dysregulation of γ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS, has been hypothesized to contribute to impaired cellular survival in MDD. In this study, we aimed to examine the relationship between striatal functional connectivity (FC) and ACC GABA concentrations in adolescents with MDD and healthy controls. We hypothesized that the ACC GABAergic system modulates fronto-striatal connectivity, and that this modulation is disrupted in adolescents with MDD.

Methods

A. Patient Population Twenty adolescents with MDD and 20 healthy controls, ages 12-19, were enrolled in the study. MDD diagnosis was established using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version. Inclusion criteria for MDD subjects included depressive episode duration \geq 6 weeks and a Children's Depression Rating Scale – Revised score \geq 40. All subjects were psychotropic medication-free for $>$ 3 months and had negative day-of-scan urine toxicology.

B. FC Measurements by fMRI Resting state FC data for six bilateral striatal seeds (three caudate, three putamen) were obtained for all subjects on a 3.0 T scanner by acquiring 197 contiguous echo planar imaging functional volumes (TR = 2s, 39 slices) during rest with eyes open. A high-resolution T_1 -weighted 3D anatomical image was also acquired using a magnetization prepared gradient echo sequence for spatial normalization and localization.

C. In Vivo Brain GABA Measurements by 1 H MRS GABA spectra were acquired from a single 2.5x2.5x3.0 cm³ ACC voxel in 14 MDD subjects and 14 controls. Unobstructed GABA signal detection was achieved by 1 H MRS on a GE 3.0T "EXCITE" MR system and an 8-channel phased-array head coil using the standard J-editing difference method. GABA levels were expressed semiquantitatively as ratios relative to the unsuppressed ACC voxel tissue water. Analysis of covariance based on ranks compared the MDD and control groups while adjusting for age, handedness, sex, and ethnicity.

Results and Discussion

We detected increased fronto-striatal FC for the MDD group relative to controls (Fig. 1). In both the MDD and control groups, we found that FC between the striatal seeds and the anterior prefrontal cortex was inversely correlated with ACC GABA concentrations (Fig. 2). In keeping with our hypothesis, this correlation was much stronger for the control group ($R^2 = 0.78$, Fig. 2B) than for the MDD group ($R^2 = 0.15$, Fig. 2C). The combined MDD and control groups (Fig. 2A) exhibited the same trend with an intermediate correlation strength ($R^2 = 0.28$). As GABA is an inhibitory neurotransmitter, our finding that increased GABA correlates with decreased FC seems reasonable. These results support a role for ACC GABA in modulating striatal FC and that this modulation is disrupted in adolescents with MDD.

Conclusions

Our findings are in line with previously published reports of ACC and striatal metabolic and functional abnormalities in MDD, and are potentially consistent with the ACC GABAergic system modulating fronto-striatal FC. Disruption of this modulation may play a role in the pathophysiology of MDD. These findings suggest that FC and GABA levels could potentially serve as objective imaging biomarkers of MDD and targets for treatment and response monitoring; future studies would investigate interactions between neurotransmitter levels and FC in other brain regions implicated in MDD and related psychiatric disorders.

References

[1] Matsuo K, Rosenberg DR, Easter PC, MacMaster FP, Chen HH, Nicoletti M, Caetano SC, Hatch JP, & Soares JC. *J Child Adol Psychopharm* 18, 121-131 (2008). [2] Mayberg HS. *J Neuropsychiatry Clin Neurosci* 9, 471-481 (1997).

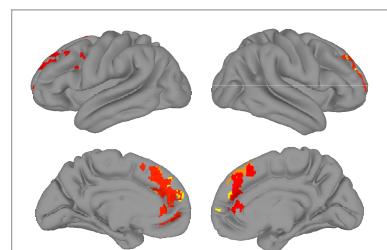


Fig. 1: Prefrontal regions with elevated striatal FC in MDD subjects.

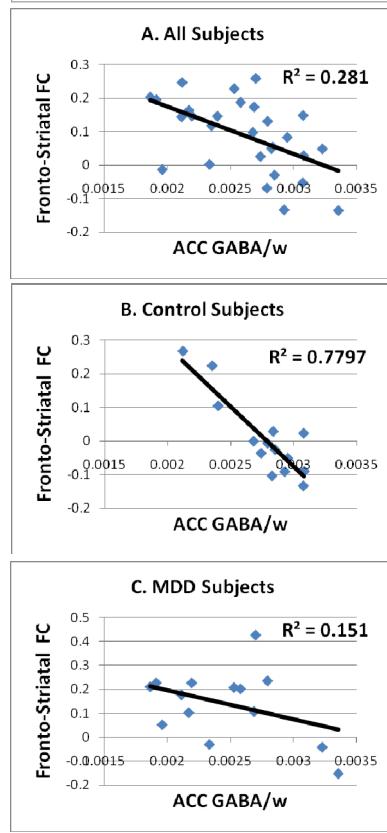


Fig. 2: Correlation of ACC GABA levels and FC between the left ventral caudate seed and the anterior frontal cortex for [A] all subjects, [B] control subjects, and [C] MDD subjects.