Excitatory amino acid transporters 1 (EAAT1) affects corticolimbic circuitry during implicit processing of negative stimuli in bipolar disorder

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INTRODUCTION

Glutamatergic overactivity has been reported as a potential pathophysiological mechanism and antidepressant target in bipolar disorder (BD). Patients showed elevated levels of glutamate (Glu) in frontal and limbic regions compared to controls, exerting an excitotoxic damage on corticolimbic circuitry [1]. The family of the excitatory amino acid transporters (EAATs) affects the glutamatergic neurotransmission and its reuptake in the synapse, and help in limiting Glu neural excitotoxicity. The rs2731880 polymorphism is a SNP (C/T) located in EAAT1 gene promoter region: previous studies pointed out that homozygote carriers of T allele were associated with lower expression of EAAT1, more Glu in synaptic space, and impaired cognitive functions compared to C carriers [2]. The dysregulation of corticolimbic circuitry has been proposed as biomarker for BD. This study is aimed at exploring the effect of rs2731880 on functional corticolimbic connectivity during emotional processing in bipolar depressed patients.

METHODS

We used fMRI and a Functional Connectivity analysis (CONN toolbox) to study the effect of rs2731880 on the response to emotional faces [3] in 68 BD patients (43 C carriers, 25 TT). Seed-based analyses were performed by comparing the temporal bivariate correlation between the BOLD signals from bilateral Amygdala (Amy) to all other voxels in the brain between genotypes and, as within effect, the difference between the processing of emotional faces and the control condition of the task. Medication load was entered as nuisance covariate. Z-score standardizing was introduced to validate the multiple comparisons (analyses were thresholded at cluster-size pFDR<0.05), and the significance tests were based on the Z-scores.

RESULTS

A significant interaction between rs2731880 and the within effect of the task was found for the connectivity between right Amy and right subgenual Anterior Cingulate Cortex (sgACC) (T = 4.70). TT patients showed a significant reduced connectivity between right Amy and right sgACC, although in C carriers this connection was absent. In homozygote carriers of T allele the coupling was significantly affected by emotional processing and different among tasks conditions (p<.05) (Figure 1).

CONCLUSIONS

Our study reveals an interaction effect between EAAT1 polymorphism and emotional processing on Amy–sgACC crosstalk in BD. T allele showed a different connectivity compared to C carriers during emotional processing: in TT patients Amy–sgACC coupling was negative, whereas it was absent in C carriers. In depressed [4] and euthymic bipolar patients [5], higher ACC Glu levels compared to healthy controls have been reported in magnetic resonance spectroscopy. In addition, neuroimaging studies demonstrated that the sgACC could be considered as a critical brain region in emotion processing and in the pathogenesis of mood disorders. These findings support the involvement of glutamatergic mechanisms in affecting functional connectivity between Amy and sgACC in BD. However, future studies are warranted so as to investigate the nature of this connection.

REFERENCES:


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