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Original article

Catechol-O-methyltransferase Val(108/158)Met polymorphism affects fronto-limbic connectivity during emotional processing in bipolar disorder

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ABSTRACT

Catechol-O-methyltransferase (COMT) inactivates catecholamines, Val/Val genotype was associated to an increased amygdala (Amy) response to negative stimuli and can influence the symptoms severity and the outcome of bipolar disorder, probably mediated by the COMT polymorphism (rs4680) interaction between cortical and subcortical dopaminergic neurotransmission. The aim of this study is to explore how rs4680 and implicit emotional processing of negative emotional stimuli could interact in affecting the Amy connectivity in bipolar depression. Forty-five BD patients (34 Met carriers vs. 11 Val/Val) underwent fMRI scanning during implicit processing of fearful and angry faces. We explore the effect of rs4680 on the strength of functional connectivity from the amygdalae to whole brain. Val/Val and Met carriers significantly differed for the connectivity between Amy and dorsolateral prefrontal cortex (DLPFC) and supramarginal gyrus. Val/Val patients showed a significant positive connectivity for all of these areas, where Met carriers presented a significant negative one for the connection between DLPFC and Amy. Our findings reveal a COMT genotype-dependent difference in corticolimbic connectivity during affective regulation, possibly identifying a neurobiological underpinning of clinical and prognostic outcome of BD. Specifically, a worse antidepressant recovery and clinical outcome previously detected in Val/Val patients could be associated to a specific increased sensitivity to negative emotional stimuli.

1. Introduction

The dysfunction of the fronto-limbic circuitry has been proposed as a possible underpinning of bipolar disorder (BD) mood lability, and as an endophenotype for BD [1]. The amygdala (Amy) is a critical node in this network, and is necessary in perceiving stimuli with affective salience, mainly negative [2,3]. This structure is interconnected with other regions, such as the prefrontal cortex, temporal areas, which are involved in the attribution of emotional salience to stimuli, in active self-regulation of affective states by modulating Amy reactivity [4–9], and in the implicit elaboration of emotional stimuli and attention allocation [10–13]. Neuroimaging studies confirmed that a chronic reduced or altered top-down modulation of limbic activity [14–22] and a hypoconnectivity in frontostriatal cortex, may identify a neurobiological basis for the pathophysiology and maintenance of BD [1,23,24].

Fronto-limbic circuitry is affected by dopaminergic trasmission. Catechol-O-methyltransferase (COMT) inactivates extraneuronal dopamine in the brain, and a valine (Val) to methionine (Met) transition in the *COMT* gene (rs4680) influences the enzyme activity. Compared to the Val/Val genotype, the Met homozygosis is associated with about 40% decreased enzyme activity, resulting in an increased DA level in the prefrontal cortex [25,26]. Dopamine extensively modulates higher-order information processing, and rs4680 has been shown to impact the efficiency of prefrontally-mediated cognition, with Met allele carriers showing a small advantage in healthy controls [25,27–29]. However, in healthy controls, the low-activity variant Met was also associated with a decreased resilience to negative mood states and an increased

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reactivity to conscious unpleasant and negative stimuli in amygdala, as well as in other limbic and paralimbic nodes [30–35], as well as a reduced resting state Amy-prefrontal connectivity in Met carrier compared to the Val/Val genotype [36]. These data suggest that Met allele is associated to a decreased emotional regulation, whereas from a cognitive prospective, it could contribute to an efficient prefrontal-dependent executive functioning, resulting in a possible pleiotropic effect of rs4680 on prefrontal cortex [37]. However, in an appetitive conditioning task, Val/Val healthy subjects showed an increased amygdala response, also paralleled by a decreased amygdala–ventromedial connectivity compared with Met allele group [32]. An effect of rs4680 in modulating Amy response to sad faces was also demonstrated in BD, with the Val allele showing an enhanced reactivity compared to Met/Met [38]. These data suggest that the enzyme's ability to methylate catecholamines affects the reactivity to stimuli in the prefrontal cortex and in Amy in both healthy controls and BD patients [27,32,33,36,38].

Association studies found no link between BD and rs4680 [39], but this genetic variant affects clinical and prognostic features of BD. Although in healthy controls, the low-activity variant Met has been argued to be associated with a decreased emotional regulation [37], in BD, Met allele is associated with a better response to antidepressant treatment [40–42] and a reduced recurrence of manic, but not depressive, episodes during the course of the illness [43], and relationship with Met/Met genotype and lower lifetime occurrence of illness episodes with psychotic features was also pointed out [44]. Although higher frequencies of Met allele were found in the rapid cycling variant of BD [45–47], Met allele seems to exert a protective role on clinical outcome of the disorder.

Abnormal connectivity between cortical regions and the erratic limbic activity in response to stressful life events has been proposed as a neural correlate of the mood instability in BD [1]. A specific role of COMT Val158Met polymorphism in regulating limbic responses during emotional processing in BD could be mediated by different corticolimbic connectivity profiles in genotype groups. Specifically, we hypothesized that Val/Val and Met carrier patients differ for the connectivity between Amy and cortical regions involved in its modulation, resulting in a not efficient corticolimbic regulation in Val/Val patients. We tested this hypothesis by modeling the interaction between rs4680 and task-related responses to negative emotional stimuli on the whole brain functional connectivity of the amygdala.

2. Methods

2.1. Participants and genotyping

Forty-five patients with a diagnosis of bipolar disorder type I and a current major depressive episode without psychotic features (structured clinical interview according to DSM IV-TR) were studied. Inclusion criteria were absence of mental retardation; absence of pregnancy, and major medical/neurological disorders; no treatment with long-acting neuroleptic drugs in the last three months or with neuroleptics in the last month before admission; and absence of a history of drug or alcohol dependency or abuse within the last six months. Patients had a Hamilton Depression Rating Scale (HDRS) [48] score of 18 or higher and no other diagnoses on axis I. All patients underwent magnetic resonance imaging in a Philips intera 3.0 T (Gyroscan Intera; Philips, Eindhoven The Netherlands) and COMT Val(108/158)Met genotyping. After a complete description of the study to the subjects, a written informed consent was obtained. All the research activities were approved by the local ethical committee.

All patients underwent a venous blood sample for genotypic analysis. Genomic DNA was extracted using EXTRAGEN 8C. Polymerase chain reaction was performed with the following primers: 5′-ACT GTG GCT ACT CAG CTG TG-3′ and 5′-CCT TTT TCC AGG TCT GAC AA-3′. Polymerase chain reaction product was digested using NlaIII (New England Biolabs, (UK) Ltd, Hitchin, United Kingdom); fragments were separated in 3% Seakem agarose gels (BMA; BioWhittaker Molecular Applications, Rockland, ME). The cleaved bands were visualized by ultraviolet light. Depending on the presence of 1 or 2 restriction NlaIII sites, either 2 fragments 140 bp + 29 bp (allele G or Val) or 3 fragments 114 bp + 26 bp + 29 bp (allele A or Met) were produced.

Analyses were performed by comparing rs4680 Val/Val homozygotes ($n = 11$) with pooled heterozygote and homozygote carriers of the Met allele ($n = 34$). This approach was justified by previous observations in healthy subjects showing:

- an higher functional COMT enzymatic activity in DLPFC in Val/Val subjects compared to both Met/Val and Met/Met subjects, no significant differences among Met homozygotes and heterozygotes were found [26];
- subcortical regions as amygdala have been suggested to have increased levels of tonic DA and reciprocal reduction of phasic DA in Met allele carriers compared to Val/Val [25];
- Met carriers also showed decreased resting state prefrontal-amygdala connectivity compared to Val homozygotes [36].

2.2. Image acquisition

Gradient-echo and echo-planar images (EPIs) were acquired on a 3.0 T scanner (Gyroscan Intera; Philips, The Netherlands) using a six-channel sensitivity encoding (SENSE) head coil. For each functional run, 124 $T2^*$-weighted volumes were acquired using an EPI pulse sequence [repetition time (TR) = 3000 ms, echo time (TE) = 35 ms, flip angle = 90°, field of view = 230 mm, number of axial slices = 40, slice thickness = 5 mm, matrix size = 80 × 80 reconstructed up to 128 × 128 pixels]. Two dummy scans before fMRI acquisition allowed us to obtain longitudinal magnetization equilibrium. Total acquisition time was 6 min and 11 s. On the same occasion and using the same magnet 22 Turbo Spin Echo (Philips), T2 axial slices [repetition time (TR) = 3000 ms; echo time (TE) = 85 ms; flip angle = 90°; turbo factor 15; 5-mm-thick, axial slices with a 512 × 512 matrix and a 230 × 230 mm field of view] were acquired to rule out brain lesions. A structural MRI scan was acquired at baseline using a T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR 2500 ms, TE 4.6 ms, yielding 220 transversal slices with a thickness of 0.8 mm).

2.3. fMRI paradigm

Neural correlates of implicit emotional processing were investigated with a face-matching paradigm (Fig. 1) [49], which previously allowed to define the connectivity within the emotional circuitry in healthy controls and in patients affected by bipolar disorder and schizophrenia [22,50,51]. Four blocks of six pictures each representing human faces with fearful or angry expressions, interspersed with five blocks of six pictures of geometric shapes, were shown to the participants. Each picture is made up of two faces/shapes in the lower side and one in the upper part. Participants had to push a button indicating which of the two images displayed in the lower side of the picture matched the one in the upper part. Images were displayed for 4 s interleaved by a black screen. Task performances of the subjects were recorded.