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Research report

COMT Met (158) modulates facial emotion recognition in bipolar I disorder mood episodes

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ABSTRACT

Background: One of the many cognitive deficits reported in bipolar disorder (BD) patients is facial emotion recognition (FER), which has recently been associated with dopaminergic catabolism. Catechol-O-methyltransferase (COMT) is one of the main enzymes involved in the metabolic degradation of dopamine (DA) in the prefrontal cortex (PFC). The *COMT* gene polymorphism rs4680 (Val^{158}Met) Met *allele* is associated with decreased activity of this enzyme in healthy controls. The objective of this study was to evaluate the influence of Val^{158}Met on FER during manic and depressive episodes in BD patients and in healthy controls.
Materials and methods: 64 BD type I patients (39 in manic and 25 in depressive episodes) and 75 healthy controls were genotyped for *COMT* rs4680 and assessed for FER using the Ekman 60 Faces (EK60) and Emotion Hexagon (Hx) tests.
Results: Bipolar manic patients carrying the Met *allele* recognized fewer surprised faces, while depressed patients with the Met *allele* recognized fewer "angry" and "happy" faces. Healthy homozygous subjects with the Met *allele* had higher FER scores on the Hx total score, as well as on "disgust" and "angry" faces than other genotypes.
Conclusion: This is the first study suggesting that COMT rs4680 modulates FER differently during BD episodes and in healthy controls. This provides evidence that PFC DA is part of the neurobiological mechanisms of social cognition. Further studies on other COMT polymorphisms that include euthymic BD patients are warranted.
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1. Introduction

There is a growing body of evidence pointing to impaired facial emotion recognition (FER) in bipolar disorder (BD) during mood episodes and euthymia (Harmer et al., 2002; Lembke and Ketter, 2002; Summers et al., 2006; Venn et al., 2004). Recently, the dopaminergic system, through catechol-O-methyltransferase (COMT), has been implicated in the neurobiology of FER by genetic association studies with functional magnetic resonance imaging (fMRI) in healthy subjects and euthymic BD patients (Lelli-Chiesa et al., 2011; Mier et al., 2010). Most data from healthy subjects have provided system-level evidence supporting a behavioral dissociation by showing an effect of the COMT single nucleotide polymorphism (SNP) rs4680 (Val^{158}Met) on amygdala activation during tasks with emotional processing components. Despite the available data, it is unclear if or how the COMT functional polymorphism modulates FER capacity in healthy populations and BD patients during episodes.

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Social cognition refers to the mental operations underlying social interactions, which can be relatively independent from other aspects of cognition and is not assessed by traditional neurocognitive tasks (Pinkham et al., 2003). One of the key aspects of social cognition is the ability to discriminate accurately between different facially expressed emotions. The ability to process and identify facial emotions is an essential component of human communication and social interaction. Although social interaction may vary according to cultural norms and customs, cross-cultural studies have repeatedly provided evidence in favor of the universality of facial emotions. Six universal emotions have since been established, including happiness, sadness, anger, fear, disgust and surprise, each of which corresponds to a specific arrangement of facial muscles and has partially separable neurocircuitry processes (Ekman and Friesen, 1971; Gosselin and Kirouac, 1995). BD patients, even during remission, have psychosocial problems caused not only by residual symptoms, but also by cognitive deficits and difficulties in social cognition (Burdick et al., 2010; Jabben et al., 2010; Rocca et al., 2009; Solé et al., 2011).

Evidence for BD deficits in FER varies in the literature from reports of no alterations and improved recognition for disgust (Harmer et al., 2002), isolated fear recognition impairment (Lembke and Ketter, 2002; Venn et al., 2004), to a selective effect of mood state (Rich et al., 2008; Rocca et al., 2009) on surprise recognition. In a recent meta-analysis however, Kohler et al. (2011) concluded that FER impairment in BD represents a moderate and stable deficit that appears to be moderated by a limited number of demographic and clinical factors such as self-reported depression, age at time of testing and years of education. BD patient impairments in FER have been the focus of intense study with fMRI disclosing differentiated activation of ventromedial prefrontal cortex (PFC), cingulate, hippocampus, amygdala and limbic region (Chen et al., 2006; Dickstein et al., 2007; Foland et al., 2008; Lelli-Chiesa et al., 2011; Malhi et al., 2007). Chen et al. (2006) reported a significant increase in amygdala activity among BD patients versus control subjects emotion labeling tasks. In this regard, Foland et al. (2008) showed that compared to healthy subjects, manic patients had significantly reduced ventrolateral PFC regulation of amygdala response during the emotion labeling task.

COMT is an important regulator of PFC dopaminergic (DA) levels (Lachman et al., 1996). This role renders COMT one of the main enzymes involved in the metabolic degradation of extraneuronal DA in glial cells and postsynaptic neurons (Lachman et al., 1996). Genetic studies have shown that COMT activity levels can vary considerably. The rs4680 SNP in the *COMT* gene leads to a 3 to 4-fold reduction in COMT enzyme activity in A *allele* (Met) carriers (Lachman et al., 1996). As a result, they have high levels of PFC DA due to lower enzyme activity while heterozygous subjects have an intermediate level of enzyme activity (Lachman et al., 1996; Weinshilboum et al., 1999). Thus, the COMT polymorphism rs4680 is responsible for genetically modulating DA levels in PFC. Recently, genetic association fMRI studies confirmed that COMT SNP rs4680 influenced emotion stimulus processing, showing that the Val *allele* was associated with greater amygdala activation and that signal change was greater for the Met *allele* in the ventromedial PFC and ventrolateral PFC (Lelli-Chiesa et al., 2011). Furthermore, studies in healthy carriers of the Val *allele* reported impaired performance (Bosia et al., 2007; Egan et al., 2001; Joober et al., 2002) coupled with increased dorsal PFC activation during executive function tasks (Bertolino et al., 2006; Blasi et al., 2005; Mattay et al., 2003; Mier et al., 2010; Schott et al., 2006; Winterer et al., 2006). Nonetheless, healthy subjects with the Met *allele* are associated with greater reactivity to emotionally negative stimuli, as evidenced by increased activation in the ventral PFC and associated limbic regions (Drabant et al., 2006; Mier et al., 2010; Smolka et al., 2005). Despite all this information, it is unclear if/how the COMT polymorphism impacts FER in healthy controls or in BD patients during manic and depressive episodes.

Based on the potential association revealed by fMRI studies between COMT and FER, the objective of this research was to investigate how/if the lower activity of the Met *allele* of COMT influenced FER scores in BD patients (mania and depression states) and healthy controls.

2. Materials and methods

2.1. Sample

The patient sample comprised sixty-four medication-free individuals with BD I, aged between 18 and 40 years old (28.16 ± 5.24 years) and currently in manic or depressive episodes according to DSM-IV TR criteria (DSM-IV, 2000). All patients were participants in the *LICAVAL* clinical trial (Campos et al., 2010) and were evaluated immediately after a wash-out period of four weeks for antidepressants, mood stabilizers and antipsychotics, or eight weeks for *depot* medications. Diagnoses were determined by trained psychiatrists using the Structured Clinical Interview (SCID-I) (First et al., 1997) for DSM-IV TR (DSM-IV, 2000). The Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1960) were used to evaluate the intensity of symptoms. The cut-off point for mania was YMRS ≥ 12 and for depression was HDRS ≥ 15. The 39 manic patients had a mean YMRS of 15.67 (± 3.44), while the 25 depressive patients had a mean HDRS score of 21.70 (± 7.18). Subjects with neurological disorders, previous head trauma, any illness requiring medical intervention, current substance abuse, or that had undergone electroconvulsive therapy in the preceding six months, were excluded.

2.2. Control group

Seventy-five healthy volunteers (predominantly medical students) aged between 18 and 35 years old (23.54 ± 3.53) were recruited from the University of São Paulo. All control subjects had no current or past history of psychiatric disorder according to the evaluation conducted by trained psychiatrists using The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Similarly, all subjects had no family history (first degree relatives) of mood or psychotic disorders and had not been in recent use of psychotropic medicine or indulged in substance abuse over the last three months. Only women with a regular menstrual cycle were included. The YMRS (Young et al., 1978) and HDRS-21 (Hamilton, 1960) instruments were used to evaluate