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Modulation of fronto-limbic activity by the psychoeducation in euthymic bipolar patients. A functional MRI study

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ABSTRACT

Bipolar disorders (BD) are mainly characterized by emotional and cognitive processing impairment. The cerebral substrate explaining BD impairment and the action mechanisms of therapies are not completely understood, especially for psychosocial interventions. This fMRI study aims at assessing cerebral correlates of euthymic bipolar patients (EBP) before and after psychoeducation therapy. Sixteen EBP and 16 matched healthy subjects (HS) performed a word-face emotional Stroop task in two separate fMRI sessions at 3-month interval. Between fMRI sessions, EBP underwent psychoeducation. Before psychoeducation, the comparison of EBP vs. HS in fMRI data revealed (a) significant decreased activity of cognitive control regions such as bilateral inferior and left superior frontal gyri, right insula, right fusiform gyrus and bilateral occipital gyri and (b) significant increased activity of emotion-related processing regions such as bilateral hippocampus, parahippocampal gyri and the left middle temporal gyrus. After psychoeducation, EBP showed significant clinical improvement, increased activity of inferior frontal gyri and a tendency toward decreased activity of right hippocampus and parahippocampal gyrus. These results suggest that the imbalance between cognitive control and emotion processing systems characterizing BD acute episodes may persist during euthymic periods. Moreover, this imbalance may be improved by psychoeducation, which enhances the cognitive control and modulates emotional fluctuations in EBP.

1. Introduction

Bipolar disorders (BD) are characterized by abnormal emotional and cognitive processing during thymic critical episodes (mania and depression) and inter-critical (euthymic) periods (Soreca et al., 2009; Leboyer and Kupfer, 2010). Thymic episodes are associated with socio-professional disability, deterioration in the illness' evolution, increased risk of comorbidities, addictions, and suicide (Goldstein et al., 2011; Undurraga et al., 2011). Inter-critical periods are nevertheless not free of residual cognitive and/or emotional symptoms (Judd et al., 2005; Torrent et al., 2006; Bauer et al., 2010). Some of these symptoms actually represent *trait* characteristics of the illness. The identification of trait abnormalities in BD and the related cerebral substrate is particularly important as it may contribute to early diagnosis of BD thus reducing the latency to adequate treatment and improving outcome (Cusin et al., 2000; Altamura et al., 2010).

Current neurophysiological models suggest that mood dysregulation in BD may be explained by the imbalance between the limbic and prefrontal cerebral networks: first, an overactivation of both limbic and prefrontal regions involved in emotional perception and identification. It includes subcortical (ventral striatum, thalamus) and medial temporal (amygdala, hippocampus and parahippocampal gyrus) regions, and also some prefrontal regions such as the orbitofrontal cortex (OFC) and the rostral part of the anterior cingulate cortex (rACC). Second, an hypoactivation of prefrontal areas responsible for executive functions, attention and emotion regulation, including the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC) and the dorsal part of the anterior cingulate cortex (dACC) (Phillips et al., 2003, 2008a; Strakowski et al., 2005b, 2012). However, it has not been clearly demonstrated whether these fronto-limbic abnormalities persist during euthymic states, which would constitute trait abnormalities of BD (Hariri, 2012).

Previous functional magnetic resonance imaging (fMRI) studies that compared cerebral activity of euthymic bipolar patients (EBP)

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to healthy subjects (HS) usually used two broad classes of activation paradigms: *emotional* or *cognitive* (Chen et al., 2011). With respect to emotional paradigms, the majority of previous studies used emotional facial expressions under various tasks. Some of them exhibited increased limbic activity in EBP compared to HS by using stimuli varying in emotional intensity. Specifically, EBP vs. HS showed increased activity of left striatum in response to mild happy faces (Hassel et al., 2008), of the left amygdala and left hippocampus for emotional vs. neutral faces processing (Chen et al., 2010), and of the left putamen in response to mild fearful faces (Surguladze et al., 2010). However, decreased limbic activity was also showed in EBP compared to HS during emotional tasks. Particularly, decreased activity was found within bilateral amygdala and temporal pole by using backward masking paradigm (Van der Schot et al., 2010) and within ventral ACC, OFC and striatum in response to happy and neutral faces (Liu et al., 2012). The use of a face matching task did not reveal significant amygdalar activity between EBP and HS (Robinson et al., 2008). Considering the prefrontal cortex (PFC), the use of a face matching task (Robinson et al., 2008) increased the activity of the right inferior frontal gyrus (IFG) in EBP compared to HS. Moreover, in response to fearful and happy faces the medial PFC showed increased activity in EBP (Surguladze et al., 2010). Furthermore, compared to HS, the EBP showed decreased activation of the right IFG in the labeling emotion condition of a face matching task (Foland-Ross et al., 2012), decreased activation of the left IFG and the left middle PFC in response to facial expression of disgust (Malhi et al., 2007b), decreased activation of the right dorsolateral PFC (dlPFC) in response to neutral, mild and intense happy faces as well as within the left dlPFC in response to neutral, mild and intense fearful faces (Hassel et al., 2008).

Similarly, previous fMRI studies testing cognitive control processes showed increased IFG activity in EBP compared to HS during a color-word Stroop task (Blumberg et al., 2003) and a Continuous Performance Task (CPT) (Strakowski et al., 2004). Other studies found decreased right middle PFC activation in EBP compared to HS by using a counting Stroop interference task (Strakowski et al., 2005a) and decreased activity of left IFG and dlPFC during a color-word Stroop task (Kronhaus et al., 2006). In respect with limbic regions, increased activation of left parahippocampal/amygdala during a CPT (Strakowski et al., 2004) and decreased activation of left fronto-polar cortex and bilateral amygdala during a Go/Nogo task (Kaladjian et al., 2009a) have been shown in EBP compared to HS.

These inconsistencies may be due to several factors such as medication effect or comorbidities (Phillips et al., 2008b), but the variability of task paradigms used may probably be the most important factor. Indeed, most fMRI studies used either cognitive or emotional tasks but few of them employed tasks that involved both cognitive and emotion processes that may better approach the emotion regulation processes (Malhi et al., 2005, 2007a; Lagopoulos and Malhi, 2007; Wessa et al., 2007). However, using an emotional Stroop task, both increased (Lagopoulos and Malhi, 2007) and decreased (Malhi et al., 2005) activations of the limbic system were shown in EBP compared to HS. With an emotional go/nogo task an increased overall activation of the fronto-striatal network in EBP was reported (Wessa et al., 2007). Consequently, it is necessary henceforth to more precisely identify trait characteristics of the BD using tasks designed to involve both emotional and cognitive processing that may also assess emotion regulation processes in BD patients (Phillips et al., 2008a). An emotional word-face Stroop adapted from Etkin et al. (2006) was used in the current study. By using emotional words and faces that may be congruent or not, this task permits to implicitly distract attentional control by emotional material and therefore examine neural systems involved in emotional processing and cognitive control interaction. Because this task included fearful, happy and neutral facial stimuli, it also allows assessing the impact of the emotional valence and arousal dimensions in emotional processing.

Furthermore, next to a better understanding of the pathophysiology of BD, the development of therapeutic strategies constitutes a real challenge. Indeed, despite relative effectiveness in a majority of patients, pharmacological treatments are insufficient on a functional level, as well as on residual depressive, dysthymic and dysphoric symptoms (Tohen et al., 2000; Huxley and Baldessarini, 2007). Consequently, in parallel with pharmacological progress, psychosocial interventions have recently undergone great development (Swartz and Frank, 2001; Zaretsky, 2003; Colom and Vieta, 2004; Miklowitz, 2008). Most of these interventions target emotional and cognitive processes in order to improve adaptive processes and reach functional recovery (Honig et al., 1997; Bernhard et al., 2006). Among various therapeutic approaches, clinicians, therapists and researchers have recently shown a particular interest in psychoeducation for BD treatment (Colom et al., 2003a; Rouget and Aubry, 2007). The aim of this approach is to teach patients to better manage BD symptoms in everyday life, to improve coping strategies and to optimize compliance with pharmacological treatment in order to prevent thymic relapses and improve functioning (Perry et al., 1999; Colom et al., 2003b). Positive outcomes of psychoeducation in BD have been observed rapidly and are long lasting (i.e., five years), particularly in terms of risk, duration and severity of relapses (Colom et al., 2003a, 2009; Rouget and Aubry, 2007). Moreover, positive effects have been observed in terms of quality of life (Michalak et al., 2005) and social functioning (Perry et al., 1999). Psychoeducation benefits in BD are similar to those revealed by CBT (Miklowitz, 2008; Costa et al., 2010), which are nevertheless more time- and care- consuming to allow detection positive effects (Zaretsky et al., 2008). Despite significant improvements in clinical symptoms, the behavioral and neural mechanisms associated with psychoeducation are not completely understood (Miklowitz and Scott, 2009). It has been suggested that the mechanism of psychotherapeutic action would be *top-down* (Mayberg et al., 1999) as it first involves modulation of cortical activity with a subsequently impact on subcortical regions. In contrast, pharmacological treatments could act in a *bottom-up* way (Mayberg et al., 1999; Mayberg, 2009) as they act first on a subcortical level (neurotransmitters brain centers), then modulating activity at a higher cortical level.

The present study compares EBP and HS cerebral activity during performance of a task involving both cognitive and emotional processes, a word-face emotional Stroop (Etkin et al., 2006). Two objectives have been defined. First, we aimed to better identify neurofunctional abnormalities in EBP that could be the trait characteristics of BD. At the behavioral level, we assumed an increased emotional interference in EBP compared to HS, which may result in lower task performances in emotionally incongruent condition compared to congruent condition. At the cerebral level, EBP would reveal decreased activity in prefrontal regions during emotional conflict processing and increased activation of limbic regions during emotional processing. Second, we aimed to assess the effect of psychoeducation at the cerebral level. In order to answer this question, we compared EBP cerebral activity before and after psychoeducation. We assumed that psychoeducation modulates the activity of prefrontal and limbic networks underlying cognitive control and generation of emotional responses, respectively.

2. Methods

2.1. Participants

Sixteen EBP (mean age ± SD: 40.4 ± 11.8 years, nine females) and 16 HS matched on age and gender (mean age 40 ± 12.5 years, nine female) were included in the study. EBP were right-handed and four HS were left-handed. All participants