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Impaired conflict resolution and vigilance in euthymic bipolar disorder

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ABSTRACT

Difficulty attending is a common deficit of euthymic bipolar patients. However, it is not known whether this is a global attentional deficit or relates to a specific attentional network. According to the attention network approach, attention is best understood in terms of three functionally and neuroanatomically distinct networks-alerting, orienting, and executive control. In this study, we explored whether and which of the three attentional networks are altered in euthymic Bipolar Disorder (BD). A sample of euthymic BD patients and age-matched healthy controls completed the Attention Network Test for Interactions and Vigilance (ANTI-V) that provided not only a measure of orienting, executive, and alerting networks, but also an independent measure of vigilance (tonic alerting). Compared to healthy controls, BD patients have impaired executive control (greater interference), reduced vigilance (as indexed by a decrease in the d′ sensitivity) as well as slower overall reaction times and poorer accuracy. Our results show that deficits in executive attention and sustained attention often persist in BD patients even after complete remission of affective symptoms, thus suggesting that cognitive enhancing treatments programmed to improve these deficits could contribute to improve their functional recovery.

1. Introduction

Bipolar Disorder (BD) is a chronic and recurrent mental illness with an overall lifetime prevalence of about 3% in the general population (Merikangas et al., 2011). Typically, BD is characterized by a cyclic pattern of mood states that includes phases of depressed and elevated mood, as well as euthymic periods (i.e., remission) (Diagnostic and Statistical Manual of Mental Disorders; 4th ed. rev. (DSM-IV-TR; American Psychiatric Association, 2000)). Growing evidence has revealed that patients with BD may have lower performance in several cognitive domains, and that these deficits persist even during clinical remission or euthymia (Malhi et al., 2007; Torres et al., 2007; Arts et al., 2008; Kurtz and Gerraty, 2009; Balanzá-Martínez et al., 2010). These cognitive dysfunctions may progressively worsen in some cases, leading to chronic functional impairment (Martínez-Arán et al., 2004; Schneider et al., 2012) and affecting long-term outcome, and quality of life in BD (Dickerson et al., 2004; Martino et al., 2009; Mur et al., 2009). One of the most frequent and earliest prodromal signs of BD is a difficulty in concentration or attention (Correll et al., 2007). Moreover, according to some researchers, a factor that might contribute to the emotional instability – a clinical feature often present in patients with BD even during the euthymic periods of the illness (Phillips et al., 2008) – is represented by a neuropsychological deficit in attention and executive functioning, which could limit the ability to effectively implement specific types of emotion regulation strategies. Consistent with this view, a growing body of evidence has underlined the critical role of the executive functions and attention in emotional regulation (e.g., Petersen and Posner, 2012) and several studies have reported impairments in sustained attention (Clark et al., 2002; Bora et al., 2006), and inhibitory control (Murphy et al., 1999; Varga et al., 2006) in BD patients. However, it is not really understood which mechanism or component of attentional system is mainly impaired. According to the attention network approach, human attentional system encompasses three functionally and anatomically independent networks, which work together in everyday life and are dissociable from perception and action: alerting, orienting, and executive control (Posner and Petersen., 1989; Fan et al., 2002; Posner and Rothbart, 2007). The orienting network is responsible for the movement of attention through space in order to select and focus on the to-be-attended stimulus; the executive network allows to the monitoring and resolution of conflict between expectation, stimulus, and response; and the alerting network is involved in achieving (phasic alerting) and maintaining (tonic

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alerting) a general state of activation of the cognitive system. Impairments of attentional processes in BD are heterogeneous; difficulties in visuo-spatial attention have been observed in bipolar patients in euthymic state, and in mildly depressed patients in one study (Jongen et al., 2007), but not in another (Barekatain et al., 2008). A marked sensitivity to interference in the Stroop (Kravariti et al., 2009; Rheenen and Rossell, 2013; Erol et al., 2014), and flanker task (Brotman et al., 2009; Patino et al., 2013), or in oculomotor paradigms such as antisaccade tasks (García-Blanco et al., 2013), which are considered to represent executive functioning, have also been observed in bipolar patients. These impaired executive functions persist in remission (Ferrier et al., 1999; Rubinsztein et al., 2000; Mur et al., 2007), and are present in first degree relatives of patients with bipolar disorder (Clark et al., 2005b). Finally, several studies have also reported impaired sustained attention in bipolar disorder during mania, remission and in first-degree relatives of patients with bipolar disorder (Liu et al., 2002; Sepede et al., 2012).

The Attentional Network Test (ANT), a combination of the Covert Orienting Task (Posner, 1980) and the Flanker Task (Eriksen and Eriksen, 1974), enables to examine individual differences in efficiency of the brain networks of alerting, orienting and executive attention discussed above within the context of a quick and simple computerized task (Fan et al., 2002). Alerting is assessed by comparing reaction times (RTs) for targets preceded by alerting cues informing the temporal onset of the target with those not preceded by any cue (i.e. warning effect). The orienting is assessed by comparing RTs for spatially cued targets with RTs for spatially uncued targets (i.e. visual cueing effect). Executive attention is assessed by comparing RTs for targets flanked by congruent distractors with those flanked by incongruent distractors (i.e., the conflicting effect). In this way, the ANT provides an appropriate index for each attentional network and it has been successfully used to address the attentional performance in healthy adults (Callejas et al., 2004, 2005; Martella et al., 2011; Federico et al., 2013; Spagna et al., 2014), children (Rueda et al., 2004), and clinical patients (Preiss et al., 2010; Casagrande et al., 2012; Orellana et al., 2012; Martella et al., 2014). To our knowledge, only one behavioural experiment has employed the ANT paradigm to assess attentional performance in bipolar patients (Gruber et al., 2007). In particular, Gruber et al. (2007) assessed attentional performance in patients with major depression, manic bipolar patients, and depressed bipolar patients and observed that manic bipolar patients showed slower reaction times in the ANT compared to both depressed patient groups, and performed significant fewer trials correctly. However, the lack of a control group of healthy subjects makes these results difficult to interpret. Indirect evidence has been provided by a recent study of Belleau et al. (2013), in which using the ANT task observed poor executive attention, but normal alerting and orienting functions, in unaffected youth at familial risk for mood disorders (bipolar disorder and major depressive disorder). This finding suggests that executive attention may represent a vulnerability marker for BD. To our knowledge, no previous study has used the ANT task to directly compare attentional performance of euthymic bipolar patients to that of healthy subjects. According to some researchers (Torres et al., 2007; Bora et al., 2008; 2009, Maalouf et al., 2010), cognitive deficits persist during remission and some types of cognitive deficits represent fundamental trait characteristics. Because of their relatively static nature, trait characteristics of cognitive and neurological manifestations may provide insights into core brain abnormalities that give rise to severe mood disorders. Therefore, testing the attentional networks during remission will help researchers to clarify the structure and course of cognitive deficit associated with bipolar disorders. In the present study, we explored whether and which of the three attentional networks are altered in euthymic BD, by directly assessing attentional functions in euthymic BD patients and age-matched healthy controls. We directly tested the following predictions: compared to controls, euthymic bipolar patients will exhibit impaired executive attention (e.g. the magnitude of the conflict effect will be larger in BD patients than controls) and a reduced vigilance (as indexed by slower reaction times and a reduced sensitivity to detect infrequent stimuli), in line with the majority of studies discussed above (for a review see also Bora et al. (2008)). In the other hand, given the scarcity and the inconsistencies of the previous data, we make no prediction about the differences between bipolar patients and healthy subjects in orienting and phasic alerting.

2. Method

2.1. Participants

Twenty-seven euthymic patients with bipolar disorder (BP-I: $n=22$; BP-II: $n=5$) were recruited from the outpatient and inpatient wards of the Department of Neurology and Psychiatry of the Policlinico Umberto I Hospital – "Sapienza" University of Rome. Diagnoses were made by well-trained psychiatrists according to DSM IV TR criteria (APA, 2000). The presence of a fully and stable euthymic condition of at least two months duration was established according to Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) scores (≤ 8) and of the Young Mania Rating Scale (YMRS; Young et al., 1978) scores (≤ 6). The inclusion criteria were normal or corrected-to-normal vision, at least middle school education, and age between 21 and 61 years. Exclusion criteria comprised: comorbid axis I and II diagnosis, according to the Structured Clinical Interview for DSM-IV TR (SCID I and II) (First et al., 2000, 2003); significant neurological or medical condition; psychiatric hospitalization within the previous six months; substance or alcohol abuse/dependence. All patients were under stabilized psychotropic medications, which were prescribed according to the most important international treatment guidelines for bipolar disorder (American Psychiatric Association, 2002; Grunze et al., 2010; Suppes et al., 2005; Yatham et al., 2009) Twenty-seven healthy volunteers with no current or past psychiatric illness and no first-degree relative with affective disorder were recruited and matched to patients on the basis of age, sex,[1] and education.

The collection of socio demographic and clinical information was performed by a team of well trained psychologists. Specific tests for IQ (Progressive Matrices of Raven; Raven, 2008) and for mood (Casagrande et al., 1997) were administered. Control participants were screened using SCID I (First et al., 2000) in order to verify that no Axis I mental disorder was present. Since none of the control subjects met diagnostic criteria for any mood disorder, HAM-D and YMRS were not used. Although fifty-four participants took part in the study, the data from six of them (5 BP-I patients and 1 control) were discarded because their percentage of errors was unusually high ($>45\%$ of the trials). In the Table 1 the main characteristics of BD patients included in the ANT analysis are reported.

Before they enrolment, participants accepted the protocol and gave written informed consent to participate and the Local Research Ethics Committee approved the study. The experiment was conducted according to the ethical standards of the 1964 Declaration of Helsinki

[1] To evaluate gender differences between BP patients and healthy controls, the Chi-square test was used. The Yates corrected formula and the Fischer's exact test were adopted. No significant difference was detected in the incidence of men as a function of group, with 7 of 22 BP patients (32%) vs. 8 of 26 healthy controls (31%) (Yates corrected $\chi^2=0.05$, $p=0.81$; Fisher's exact test: $p=0.59$).