IMPAIRED CONFLICT RESOLUTION AND VIGILANCE IN EUTHYMIC BIPOLAR DISORDER

Andrea Marotta[a], *Roberto Delle Chiaie*[b], *Alfredo Spagna*[a], *Laura Bernabei*[b], *Martina Sciarretta*[a], *Javier Roca*[c], *Massimo Biondi*[b] *Maria Casagrande*[a]

a Dipartimento di Psicologia, "Sapienza" Università di Roma, Italy

b Department of Neurology and Psychiatry, Acute Psychiatric Ward (Servizio Psichiatrico di Diagnosi e Cura - SPDC), Sapienza University of Rome, Italy

c ERI-Lectura - Departamento de Psicología Evolutiva y de la Educación, Universidad de Valencia, Spain.

Please address all correspondence to:

Maria Casagrande

maria.casagrande@uniroma1.it

Andrea Marotta

andrea.marotta@uniroma1.it

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.

Keywords: Bipolar disorders; Attention Network Test (ANT); Executive control; Alerting; Orienting; Vigilance

IMPAIRED CONFLICT RESOLUTION AND VIGILANCE IN EUTHYMIC BIPOLAR DISORDER

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 (Martinez-Aran et al.,2000; Schneider etal., 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 in BD. 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 in BD. 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 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; Callejas et al., 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 behavioral 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.

Method

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; First et al., 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 (APA, 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

[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 X2= 0.05, p= 0.81; Fisher's exact test: p= 0.59).

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

Apparatus

The experimental task was controlled by E-Prime v2.0 (Psychology Software Tools, Inc.) on a standard computer. The stimuli were presented on a 19 in. monitor and the responses were collected using a standard keyboard.

Stimuli and task procedure

The ANTI-Vigilance (ANTI-V; Roca et al., 2011; 2012) was used in the current study (Fig. 1). The following stimuli were presented: a black fixation cross, a warning tone, a black asterisk and a row of five cars pointing either left or right. The distance of the central target car was manipulated, being either centered or significantly displaced (i.e., appearing closer to one of the immediate flanker cars). Also, the vertical and horizontal location of each car was changed slightly in each trial, adding a random variability (±4 pixels) to make it more difficult to distinguish between the centered and the displaced target car. The background was grey and a two-lane road with two parking lanes was represented in the center of the screen. The target central car and its flankers appeared on one of the two parking lanes, above or below the fixation cross. The instructions presented the task to the participants as a game, in which they were working in a Centre for Traffic Management and studying the drivers' parking habits. The participants were presented for 200 ms with a row of five cars, above or below the fixation point. They had to indicate the direction of the central car, by pressing “c” (for left) or “m” (for right) on the keyboard. A period of 2000 ms was allowed for responses. The background road and the fixation point remained present until the end of the experiment. In every trial, the duration of the initial empty scene was randomly determined (400–1600 ms), and the duration of an identical final scene was adjusted so that the total trial time was 4100 ms. In half the trials the flanker cars were pointing in the same direction as the central target car (congruent condition) and in the other half, in the opposite direction (incongruent condition). Also, 100 ms before the row of cars appeared, an asterisk was briefly presented (50 ms), either in the same location as the forthcoming target central car (valid visual cue condition), in the opposite location (invalid visual cue condition), or was preceded by no asterisk (no visual cue condition). These three visual cue conditions were equally probable. In addition, either a 50 ms auditory warning signal was presented 500 ms before the target car was shown (warning tone condition) or it was not presented (no warning tone condition). Finally, in 25% of the trials, the target central car was significantly displaced to the right or to the left. The participants were encouraged to identify these infrequent stimuli by pressing an alternative response key (spacebar) and ignoring the direction of the central car in these trials. The task was composed of 5 blocks of 64 trials each (48 trials for the usual ANTI conditions and 16 vigilance trials with the displaced central target condition). In the first (practice) block, visual feedback on accuracy was provided. This first block was followed by a pause, and there were no more rest periods until the end of the task.

[INSERT FIGURE 1 ABOUT HERE]

Statistical Analysis

The gathered data were analyzed using Statistica (Statsoft, Inc Tulsa, OK) v. 6.1. To analyze sociodemographic participants' characteristics, one-way ANOVAs considering the Group as independent variable were performed on age, IQ, and years of education. To evaluate attentional performances, a four-way mixed design analysis of covariance (ANCOVA) was conducted with the following variables: 2 (Group: Bipolar vs Control) x 2 (Warning: No Tone vs. Tone) × 3 (Cue: Invalid, No Cue, Valid) × 2 (Congruency: Congruent vs. Incongruent). Due to group differences in IQ (as Measured by the Raven's Standard Progressive Matrices; Raven, 2008), IQ was entered as a covariate of no interest in all analyses. Trials with RT above or below two standard deviations (about 1% of trials) as well as incorrect responses (about 7% of trials) were excluded from the RT analysis.

Different attentional network scores were computed as a subtraction from specific average conditions: a) Phasic alertness score: no tone–tone conditions, considering only no-cue trials (i.e. warning effect); b) Orienting score: invalid–valid conditions (i.e. visual cueing effect); c) Conflict score: incongruent–congruent conditions. Regarding the vigilance task, the number of hits (proportion of correct spacebar responses to infrequent displaced targets) and false alarms (proportion of incorrect spacebar responses to frequent targets) were used to compute the sensitivity (d′) and response bias (β), following the Signal Detection Theory (SDT) procedures (Green & Swets, 1966; see Stanislaw & Todorow, 1999 for a review). If hits of false alarms were 0 or 1, these values were substituted by 0.01 or 0.99, respectively, to obtain a suitable approximation to the SDT indices. Attentional networks scores and vigilance performance indices were submitted to ANCOVAs with Group (Bipolar vs Control) as a factor.

[INSERT TABLE 1 ABOUT HERE]

Results

Mean reaction times and standard deviations are shown in Table 2. The ANCOVA showed a significant main effect of Group ($F_{1,45}$= 5.27; p< 0.03; η_p^2= 0.84) with slower RTs for the bipolar group compared to the Control Group (879 ms vs. 766 ms). The main effects of Congruency ($F_{1,46}$= 140.93; p< 0.001; η_p^2= 0.99), Warning ($F_{1,46}$= 18.23; p< 0.001; η_p^2= 0.95), and Cue ($F_{2,92}$= 21.45; p< 0.001; η_p^2= 0.96) were also significant. RTs were faster when a warning tone had been presented than when it was absent (811 ms vs. 835 ms), and when the stimuli were congruent than when they were incongruent (789 ms vs. 856 ms). Planned comparisons revealed that RTs were also faster in valid trials than in invalid ($F_{1,46}$= 35.93; p< 0.001; η_p^2= 0.44) or no cue trials ($F_{1,46}$= 11.96; p< 0.002; η_p^2= 0.21), and also faster in no cue than invalid trials ($F_{1,46}$= 11.79; p< 0.002; η_p^2= 0.20). The Warning signal × Visual cue interaction was statistically significant ($F_{2,92}$= 5.65; p< 0.005; η_p^2= 0.85). However, no differences were found in the orienting score (i.e., invalid minus valid conditions) between the no tone (51 ms) and tone trials (58 ms) (F<1). The Warning × Congruency interaction was analyzed by focusing only on the no cue condition to discard any influence of the cueing effect, and, as in the original work of Roca et al. (2011), it was not significant ($F_{1,46}$= 3.02; p= 0.09). Therefore, the Roca's ANTI-V allows clearly differenting the three attentional networks and their interactions: significant main effects, as well as main expected interactions were obtained.

Moreover, relevant to this study the critical Group x Congruency interaction was significant ($F_{1,46}$= 6.30; p< 0.02; η_p^2= 0.86): partial interactions showed that the congruency effect was higher in the Bipolar group (82 ms) than in the Control group (53 ms) ($F_{1,45}$= 4.65; p< 0.04; η_p^2= 0.82). The interaction Group × Cue and Group × Warning were not significant (F<1). No other interactions were significant. Figure 2 summarizes attentional scores in patients and controls.

Accuracy

The average percentage of errors was analyzed and all main effects were also statistically significant: Group ($F_{1,45}$= 7.19; p< 0.02; η_p^2= 0.88), Warning signal ($F_{1,46}$= 10.21; p< 0.003; η_p^2= 0.91), Cue ($F_{2,92}$= 16.48; p< 0.001; η_p^2= 0.94) and Congruency ($F_{1,46}$= 42.39; p< 0.001; η_p^2= 0.98). On average the bipolar participants made more errors (10.22%) than control participants (3.89%). Moreover, participants made more error when the warning tone was absent (7.89%) than when it was present (6.22%) and when flankers were incongruent (9.51%) versus when they were congruent (4.61%). Planned comparison of the Cue factor showed that the percentage of errors was smaller in the valid trials than in invalid trials ($F_{1,46}$= 26.06; p< 0.001; η_p^2= 0.36), or no cue trials ($F_{1,46}$= 14.02; p< 0.001; η_p^2= 0.23), and also smaller in no cue than invalid trials ($F_{1,46}$= 7.69; p< 0.008; η_p^2= 0.14). The interaction between Cue and Congruency factors was statistically significant ($F_{2,92}$= 12.33; p< 0.001; η_p^2= 0.92), showing that the congruency effect was higher in the invalid than in the valid condition.

Importantly, also in this case the critical interaction Group × Congruency was significant ($F_{1,46}$= 7.61; p< 0.009; η_p^2= 0.88), with higher congruency effect in Bipolar group than in the Control Group ($F_{1,45}$= 11.32; p< 0.002). In addition, the interaction between Group and Cue was significant ($F_{2,92}$= 3.40; p< 0.04; η_p^2= 0.88): the percentage of errors was significantly higher in the Bipolar group than in the Control group in both invalid and no-cue conditions ($F_{1,45}$= 7.75, η_p^2= 0.15; p< 0.008 and $F_{1,45}$=

6.92; $p< 0.02$, $\eta_p{}^2= 0.13$), but it was only marginally significant when a valid spatial cue was presented ($F_{1,45}= 3.71$; $p= 0.06$).

Vigilance indices

In relation to the vigilance performance indices (see Figure 3), the percentage of hits was lower in bipolar patients than in controls ($F_{1,45}= 4.07$; $p< 0.05$, $\eta_p{}^2= 0.80$).

Importantly, the sensitivity-d′ was also lower in Bipolar group as compared to the control group ($F_{1,45}= 4.60$; $p< 0.04$, $\eta_p{}^2= 0.82$). The differences in the percentage of false alarms ($F_{1,45}= 3.69$; $p= 0.061$) and the response bias ($F<1$) were not statistically significant. Additionally, the global difference in Vigilance RTs was statistically significant ($F_{1,45}= 6.79$; $p< 0.02$, $\eta_p{}^2= 0.87$): bipolar participants were slower compared to controls.

Finally, in order to evaluate whether the impairment in sustained attention was immediately evident or developed over time, one-way ANOVA on d′ sensitivity were separately conducted for each experimental block. Patients showed a reduced d′ sensitivity in block 3 ($F_{1,45}= 5.42$; $p< 0.05$, $\eta_p{}^2= 0.84$) and in block 4 ($F_{1,45}= 5.06$; $p< 0.05$, $\eta_p{}^2= 0.83$), but they showed no significant differences from controls in block 1 ($F_{1,45}= 2.51$; $p< 0.121$) and block 2 ($F_{1,45}= 3.35$; $p= 0.074$).

[PLEASE INSERT TABLE 2 AND FIGURES 2 AND 3 ABOUT HERE]

Discussion

Recent studies have clearly described the existence of a number of cognitive dysfunctions in patients with bipolar disorder, that may persist during the euthymic phases of the illness, after remission of manic or depressive symptoms (Burdick et al., 2006), and may hinder patients from reaching a complete functional recovery (Torrent et al., 2012). In this frame our results demonstrated that when compared to healthy controls, euthymic bipolar patients exhibited response slowing and accuracy decrements[2], poor executive attention, and vigilance but normal phasic alerting and orienting. These findings suggest that both executive attention and vigilance may represent fundamental trait characteristics of BD. Compared to controls, euthymic bipolar patients exhibited a greater cognitive interference as indexed by both RT and percentage of errors. This executive attention deficit may reflect an impaired ability in BD patients to perform externally focused cognitive control processes necessary for emotion regulation.

Beyond the possibility that these residual cognitive impairments may prevent bipolar patients from completely recovering their original functional levels, it may be argued that they could also be involved in the basic neural mechanisms on which mood instability is based. With reference to this hypothesis a growing body of evidence has underlined the important role of the executive functions in emotional regulation (e.g., Petersen and Posner, 2012), with a possible consequent involvement in the pathophysiology of mood disorders. In particular, different prefrontal cortical regions have been implicated in executive function, including the dorsolateral prefrontal cortex (Adolphs et al., 1996), and these regions have also been linked to effortful, voluntary emotion regulation (Phillips et al., 2008).

Regarding vigilance, our results showed that bipolar patients were less able to perform the vigilance task as compared to the control group, with a lower percentage of hits and, importantly, a reduced sensitivity (d′) to detect the infrequent stimuli. The percentage of false alarms was slightly higher in patients, although this difference did not reach statistical significance. Our findings are consistent with previous studies

[2] The accuracy decrement observed in the BP group could be attributed to the 2 sec window to complete each trial. Perhaps, BD patients might require more time to correctly execute the task as a consequence of a cognitive slowing strategy (see Ozen & Fernandes, 2012 for an example). Further research is necessary to shed light upon this issue.

indicating impaired sustained attention in euthymic individuals with bipolar disorder (Clark et al., 2002; Clark et al., 2005a). Moreover, the results of the present study extends previous findings with euthymic bipolar patients (Robinson et al., 2013), showing that such deficits only emerge with sustained processing over time (i.e. not evident in block 1). In particular, the present sample showed evidence of a reduced sensitivity (d′) to detect the infrequent stimuli which emerged as the task progressed. This impairment may reflect an underlying predisposition to distractibility or poor attentional control and lead, in particularly adverse environmental conditions, to a reduced ability to suppress impulses and actions which in turn may manifest as emotional lability - a clinical feature often present in patients with bipolar disorder even during the euthymic periods of the illness (Phillips et al., 2008). Further, consistently with previous evidence, the response bias was similar in both groups (Fleck et al., 2012). According to Fleck et al. (2012), the β index can be interpreted as a motivational factor. Thus, we may claim that despite the vigilance decrease, the motivation to perform the vigilance task was similar in both groups.

Moreover, our data regarding the orienting function of attention showed no differences between groups when reaction times were considered as dependent variable, in line with the results reported by Barekatain et al. (2008), who described comparable levels of attentional orienting effects between fully remitted BD single manic episode patients and age-matched normal control individuals. In contrast, when the percentage of errors was considered as dependent variable, results showed a greater sensitivity in patients to spatially valid cues compared to controls. However, although spatial valid cues provided a substantial positive effect on the percentage of errors of the patients, it was not enough for them to reach the performance of healthy participants. In other words, even if patients improved their performance with valid cues, they still showed lower percentage of error in every condition of the orienting cue.

Finally, we did not find differences between the groups on the phasic alerting indices. This result could be possibly explained by a sufficient level of remission of the phasic alerting in euthymic bipolar patients. However, in light of the scarcity of previous data about phasic alerting in bipolar disorder during mania and/or depression, these findings could be alternatively attributed to the intact ability in BD to achieve a state of increased sensitivity to incoming information as a consequence of a warning tone. Further research is necessary to shed light upon this issue.

Several limitations to the present study need to be acknowledged. While all bipolar patients assessed in this study were characterized as euthymic at the time of testing, persistence of residual sub-threshold symptoms of both polarities may have affected performance. We also did not control for lifestyle factors (i.e., marital status. physical activity levels, amount of social engagement) that could potentially contribute to poorer attention performance in BD. Further research will be necessary to shed light upon this issue. Moreover, the assessment of the emotion regulation (at least on a self-report level) will be required to evaluate the relation between attentional impairments and emotional lability in BD. Finally, all patients were under psychotropic medications, which could have influenced attentional processing at the time of testing. However, the study of Goswami et al. (2009) that examined the influence of medication on neurocognitive performance showed little difference between medicated and unmedicated euthymic bipolar patients.

In sum, the results of our study suggest that deficits in executive attention and sustained attention persist during remission of depressive or manic/hypomanic symptoms and lend support to research establishing executive control and sustained attention as fundamental trait characteristics of BD (Torres et al., 2007; Bora et al., 2009; Maalouf et al., 2010). In some patients, during the course of the illness this cognitive dysfunction worsens progressively, leading to a condition of chronic functional impairment (Martínez-Arán et al., 2004; Kumar and Frangou, 2010). Therefore, these patients might clearly benefit from an appropriate behavioral rehabilitation program aimed to promote vigilance and executive functions. Thus, the study of basic attention deficits should represent both an important research area in BD and a key topic for therapy in the future.

Acknowledgements

The authors would like to thank all the participants who took part in this study.

References

Adolphs, R., Tranel, D., Bechara, A., Damasio, H., Damasio, A.R., 1996.. Neuropsychological approaches to reasoning and decision-making. In: Damasio, A.R., Damasio, H., Christen, Y. (Eds.), Neurobiology of Decision-making. Springer, Berlin, pp 157-179.

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR). American Psychiatric Association.

American Psychiatric Association, 2002. Practice guideline for the treatment of patients with bipolar disorder (revision). The American Journal of Psychiatry 159 (4 Suppl), 1–50.

Arts, B., Jabben, N., Krabbendam, L., Van Os, J., 2008. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychological Medicine 38**,** 771-786.

Balanzá-Martínez, V., Selva, G., Martínez-Arán, A., Prickaerts, J., Salazar, J., González-Pinto, A., Vieta, E., Tabarés-Seisdedos, R., 2010. Neurocognition in bipolar disorders—a closer look at comorbidities and medications. European Journal of Pharmacology 626**,** 87-96.

Barekatain, M., Haghighi, M., Jahangard, L., Ranjkesh, F., Maracy, M.R., 2008. Covert orienting visual attention in full remitted single manic patients. Journal of Research in Medical Sciences 13**,** 189-195.

Belleau, E.L., Phillips, M.L., Birmaher, B., Axelson, D.A., Ladouceur, C.D., 2013. Aberrant executive attention in unaffected youth at familial risk for mood disorders. Journal of Affective Disorders 147**,** 397-400.

Bora, E., Vahip, S., Akdeniz, F., 2006. Sustained attention deficits in maniac and euthymic patients with bipolar disorder. Progress in Neuro-Psychopharmacology & Biological Psychiatry 30 (6), 1097–1102.

Bora, E., Vahip, S., Akdeniz, F., 2008. The role and importance of cognitive symptoms in bipolar disorder. Türk Psikiyatri Dergisi 19(1), 81-93.

Bora, E., Yucel, M., Pantelis, C., 2009. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. Journal of Affective Disorders 113**,** 1-20.

Brotman, M.A., Rooney, M.H., Skup, M., Pine, D.S., Leibenluft, E., 2009. Increased intrasubject variability in response time in youths with bipolar disorder and at-risk family members. Journal of the American Academy of Child & Adolescent Psychiatry 48(6), 628-35.

Burdick, K.E., Goldberg, J.F., Harrow, M., Faull, R.N., Malhotra, A.K., 2006. Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. The Journal of nervous and mental disease 194**,** 255-260.

Callejas, A., Lupiañez, J., Funes, M.J., Tudela, P., 2005. Modulations among the alerting, orienting and executive control networks. Experimental Brain Research 167**,** 27-37.

Callejas, A., Lupiañez, J., Tudela, P., 2004. The three attentional networks: on their independence and interactions. Brain and Cognition 54**,** 225-227.

Casagrande, M., Martella, D., Ruggiero, M.C., Maccari, L., Paloscia, C., Rosa, C. Pasini, A. (2012). Assessing attentional systems in children with Attention Deficit Hyperactivity Disorder. Archives of Clinical Neuropsychology 27**,** 30-44.

Casagrande, M., Violani, C., Curcio, G., Bertini, M., 1997. Assessing vigilance through a brief pencil Letter Cancellation Task (LCT): effects of one night of sleep deprivation and of the time of day. Ergonomics 40 (6), 613-630.

Clark, L., Iversen, S.D., Goodwin, G.M., 2002. Sustained attention deficit in bipolar disorder. The British Journal of Psychiatry 180**,** 313-319.

Clark, L., Kempton, M.J., Scarnà, A., Grasby, P.M., Goodwin, G.M., 2005a. Sustained attention-deficit confirmed in euthymic bipolar disorder but not in first-degree relatives of bipolar patients or euthymic unipolar depression. Biological Psychiatry 57**,** 183-187.

Clark, L., Sarna, A., Goodwin, G.M., 2005b. Impairment of executive function but not memory in first-degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression. American Journal of Psychiatry 162**,** 1980-1982.

Correll, C.U., Penzner, J.B., Frederickson, A.M., Richter, J.J., Auther, A.M., Smith, C.W., Kane, J.M., Cornblatt, B.A., 2007. Differentiation in the preonset phases of schizophrenia and mood disorders: evidence in support of a bipolar mania prodrome. Schizophrenia Bulletin 33**,** 703-714.

Dickerson, F.B., Boronow, J.J., Stallings, C.R., Origoni, A.E., Cole, S., Yolken, R.H., 2004. Association between cognitive functioning and employment status of persons with bipolar disorder. Psychiatric Service 55, 54–58.

Eriksen, B.A., Eriksen, C.W., 1974. Effects of noise letters upon the identification of a target letter in a nonsearch task. Perception & Psychophysics 16**,** 143-149.

Erol, A., Kosger, F., Putgul, G., Ersoy, B., 2014. Ventral prefrontal executive function impairment as a potential endophenotypic marker for bipolar disorder. Nordic Journal of Psychiatry *68*(1), 18-23.

Fan, J., McCandliss, B.D., Sommer, T., Raz, A., Posner, M.I., 2002. Testing the efficiency and independence of attentional networks. Journal of Cognitive Neuroscience 14**,** 340-347.

Federico, F., Marotta, A., Adriani, T., Maccari, L., Casagrande, M., 2013. Attention network test--the impact of social information on executive control, alerting and orienting. Acta Psycholica 143**,** 65-70.

Ferrier, I.N., Stanton, B.R., Kelly, T.P., Scott, J., 1999. Neuropsychological function in euthymic patients with bipolar disorder. The British Journal of Psychiatry 175**,** 246-251.

First, M.B., Spitzer, R.L., Gibbon, M.,Williams, J.B.W., 2000. The Structured Clinical Interview for DSM-IV Axis I Disorders. Giunti OS, Firenze.

First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W., Benjamin L.S., 2003. The Structured Clinical Interview for DSM-IV Axis II Disorders. Giunti OS, Firenze.

Fleck, D.E., Eliassen, J.C., Durling, M., Lamy, M., Adler, C.M., Delbello, M.P., Shear, P.K., Cerullo, M.A., Lee, J.H., Strakowski, S.M., 2012. Functional MRI of sustained attention in bipolar mania. Molecular Psychiatry 17**,** 325-336.

García-Blanco, A.C., Perea, M., Salmerón, L., 2013. Attention orienting and inhibitory control across the different mood states in bipolar disorder: An emotional antisaccade task. Biological Psychology 94**,** 556-561.

Goswami, U., Sharma, A., Varma, A., Gulrajani, C., Ferrier, I.N., Young, A.H., Gallagher, P., Thompson, J.M., Moore, P.B., 2009. The neurocognitive performance of drug-free and medicated euthymic bipolar patients do not differ. Acta Psychiatrica Scandinavica 120**,** 456-463.

Green, D.M., Swets, J.A., 1966. *Signal detection theory and psychophysics*. Wiley, New York.

Gruber, S., Rathgeber, K., Braunig, P., Gauggel, S., 2007. Stability and course of neuropsychological deficits in manic and depressed bipolar patients compared to patients with Major Depression. Journal of Affective Disorders 104**,** 61-71.

Grunze, H., Vieta, E., Goodwin, G.M., Licht, R.W., Möller, H.J., Kasper, S., 2010. WFSBP task force on treatment guidelines for bipolar disorders. the world federation of societies of biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. World Journal of Biological Psychiatry 11, 81-109.

Hamilton, M., 1960. A rating scale for depression. Journal of neurology, neurosurgery, and psychiatry 23(1)**,** 56.

Jongen, E.M.M., Smulders, F.T.Y., Ranson, S.M.G., Arts, B.M.G., Krabbendam, L., 2007. Attentional bias and general orienting processes in bipolar disorder. Journal of Behavior Therapy and Experimental Psychiatry 38**,** 168-183.

Kravariti, E., Schulze, K., Kane, F., Kalidindi, S., Bramon, E., Walshe, M., Marshall, N., Hall, M.-H., Georgiades, A., McDonald, C., 2009. Stroop-test interference in bipolar disorder. The British Journal of Psychiatry 194**,** 285-286.

Kumar, C.T.S., Frangou, S., 2010. Clinical implications of cognitive function in bipolar disorder. Therapeutic Advances in Chronic Disease 1**,** 85-93.

Kurtz, M.M., Gerraty, R.T., 2009. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology 23(5)**,** 551.

Liu, S.K., Chiu, C.-H., Chang, C.-J., Hwang, T.-J., Hwu, H.-G., Chen, W.J., 2002. Deficits in sustained attention in schizophrenia and affective disorders: stable versus state-dependent markers. American Journal of Psychiatry 159**,** 975-982.

Maalouf, F.T., Klein, C., Clark, L., Sahakian, B.J., Labarbara, E.J., Versace, A., Hassel, S., Almeida, J.R.C., Phillips, M.L., 2010. Impaired sustained attention and executive dysfunction: Bipolar disorder versus depression-specific markers of affective disorders. Neuropsychologia 48**,** 1862-1868.

Malhi, G.S., Ivanovski, B., HadziPavlovic, D., Mitchell, P.B., Vieta, E., Sachdev, P., 2007. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. Bipolar disorders 9**,** 114-125.

Martella, D., Casagrande, M., Lupiáñez, J., 2011. Alerting, orienting and executive control: the effects of sleep deprivation on attentional networks. Experimental Brain Research 210**,** 81-89.

Martella, D., Manzanares, S., Campoy, G., Roca, J., Antúnez, C., Fuentes, L.J., 2014. Phasic and tonic alerting in mild cognitive impairment: A preliminary study. Experimental Gerontology 49**,** 35-39.

Martínez-Arán, A., Vieta, E., Colom, F., Torrent, C., Sánchez-Moreno, J., Reinares, M., Benabarre, A., Goikolea, J.M., Brugue, E., Daban, C., 2004. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar disorders 6**,** 224-232.

Martino, D.J, Marengo, E., Igoa, A., Scápola, M., Ais, E.D., Perinot, L., Strejilevich, S.A., (2009). Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. Journal of Affective Disorders 116, 37–42.

Merikangas, K.R., Jin, R., He, J.-P., Kessler, R.C., Lee, S., Sampson, N.A., Viana, M. C., Andrade, L.H., Hu, C., Karam, E. G., 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Archives of General Psychiatry 68**,** 241-251.

Mur, M., Portella, M.J., Mártinez-Arán, A., Pifarré, J., Vieta, E., 2007. Persistent neuropsychological deficit in euthymic bipolar patients: Executive function as a core deficit. Journal of Clinical Psychiatry 68(7), 1078-86.

Mur, M., Portella, M.J., Martinez-Aran, A., Pifarre, J, Vieta, E., 2009. Influence of clinical and neuropsychological variables on the psychosocial and occupational outcome of remitted bipolar patients. Psychopathology 42, 148–156.

Murphy, F.C., Sahakian, B.J., Rubinsztein, J.S., Michael, A., Rogers, R.D., Robbins, T.W., Paykel, E.S. 1999. Emotional bias and inhibitory control processes in mania and depression. Psychological Medicine 29(6), 1307–1321.

Orellana, G., Slachevsky, A., Peña, M., 2012. Executive attention impairment in first-episode schizophrenia. BMC Psychiatry, 12**,** 154.

Ozen, L.J., Fernandes, M.A., 2012. Slowing down after a mild traumatic brain injury: a strategy to improve cognitive task performance? Archives of Clinical Neuropsychology 27, 85–100.

Patino, L.R., Adler, C.M, Mills, N.P., Strakowski, S.M., Fleck, D.E., Welge, J.A, DelBello, M.P., 2013. Conflict monitoring and adaptation in individuals at familial risk for developing bipolar disorder. Bipolar Disorders 15(3), 264-71.

Petersen, S.E., Posner, M.I., 2012. The attention system of the human brain: 20 years after. Annual Review of Neuroscience 35**,** 73-89.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Molecular Psychiatry 13**,** 833-857.

Posner, M.I., 1980. Orienting of attention. Quarterly Journal of Experimental Psychology 32**,** 3-25.

Posner, M.I., Petersen., S.E., 1989. The attention system of the human brain. (No. TR-89-1). WASHINGTON UNIV ST LOUIS MO DEPT OF NEUROLOGY.

Posner, M.I., Rothbart, M.K., 2007. Research on attention networks as a model for the integration of psychological science. Annual Review of Psychology 58**,** 1-23.

Preiss, M., Kramska, L., Dockalova, E., Holubova, M., Kucerova, H., 2010. Attentional networks in euthymic patients with unipolar depression. European Psychiatry 25**,** 69-74.

Raven J.C., 2008. Standard Progressive Matrices. Firenze, Giunti OS.

Rheenen, T.E., Rossell, S.L., 2013. An empirical evaluation of the MATRICS Consensus Cognitive Battery in bipolar disorder. Bipolar disorders *16*(3), 318-325.

Robinson, L.J., Thompson, J.M, Gallagher, P., Gray, J.M., Young, A.H., Ferrier, I.N. 2013. Performance monitoring and executive control of attention in euthymic bipolar disorder: employing the CPT-AX paradigm. Psychiatry Research 210, 457-464.

Roca, J., Castro, C., López-Ramón, M.F., Lupiáñez, J., 2011. Measuring vigilance while assessing the functioning of the three attentional networks: The ANTI-Vigilance task. Journal of Neuroscience Methods 198**,** 312-324.

Roca, J., Fuentes, L.J., Marotta, A., López-Ramón, M.-F., Castro, C., Lupiáñez, J., Martella, D., 2012. The effects of sleep deprivation on the attentional functions and vigilance. Acta Psychologica 140**,** 164-176.

Rubinsztein, J.S., Michael, A., Paykel, E.S., Sahakian, B.J., 2000. Cognitive impairment in remission in bipolar affective disorder. Psychological Medicine 30**,** 1025-1036.

Rueda, M.R., Fan, J., McCandliss, B.D., Halparin, J.D., Gruber, D.B., Lercari, L.P., Posner, M.I., 2004. Development of attentional networks in childhood. Neuropsychologia 42**,** 1029-40.

Schneider, M.R., DelBello, M.P., McNamara, R.K., Strakowski, S.M., Adler, C.M., 2012. Neuroprogression in bipolar disorder. Bipolar Disorders 14, 356–374.

Sepede, G., De Berardis, D., Campanella, D., Perrucci, M.G., Ferretti, A., Serroni, N., Moschetta, F.S., Del Gratta, C., Salerno, R.M., Ferro, F.M., 2012. Impaired sustained attention in euthymic bipolar disorder patients and non-affected relatives: an fMRI study. Bipolar disorders 14**,** 764-779.

Spagna, A., Martella, D., Sebastiani, M., Maccari, L., Marotta, A., Casagrande, M., 2014. Efficiency and interactions of alerting, orienting and executive networks: The impact of imperative stimulus type. Acta Psychologica 148**,** 209-215.

Stanislaw, H., Todorov, N., 1999. Calculation of signal detection theory measures. Behavior Research Methods, Instruments, & Computers 31(1), 137-149.

Suppes, T., Dennehy, E.B., Hirschfeld, R.M., Altshuler, L.L., Bowden, C.L., Calabrese, J.R., Crismon, M.L., Ketter, T.A., Sachs, G.S., Swann, A.C., 2005. Texas consensus conference panel on medication treatment of bipolar disorder. the Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. Journal of Clinical Psychiatry 66, 870–886.

Torrent, C., Martinez-Arán, A., Del Mar, B.C., Reinares, M., Daban, C., Sole, B., Rosa, A.R., Tabares-Seisdedos, R., Popovic, D., Salamero, M., 2012. Long-term outcome of cognitive impairment in bipolar disorder. The Journal of clinical psychiatry 73**,** 899-905.

Torres, I.J., Boudreau, V.G., Yatham, L.N., 2007. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatrica Scandinavica 116**,** 17-26.

Varga, M., Magnusson, A., Flekkoy, K., Ronneberg, U., Opjordsmoen, S., 2006. Insight, symptoms and neurocognition in bipolar I patients. Journal of Affective Disorders 91 (1), 1–9.

Yatham, L.N., Kennedy, S.H., Schaffer, A., Parikh, S.V., Beaulieu, S., O'Donovan, C., MacQueen, G., McIntyre, R.S., Sharma, V., Ravindran, A., Young, L.T., Young, A.H., Alda, M., Milev, R., Vieta, E., Calabrese, J.R., Berk, M., Ha, K., Kapczinski, F., 2009. Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disorders, 11 225–255.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. The British Journal of Psychiatry 133**,** 429-435.

5. Table(s)

Table1. Participants' characteristics and ANOVA results of age, education, and IQ.

Variables	**Bipolar Group**			**Control Group**			**ANOVA results**	
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	$\mathbf{F}_{(1,42)}$	**p**
Sex (male/female)			7/15			8/18		
Age (years)	40.59	13.11		42.31	12.36		<1	
Education (years)	12.32	3.14		12.2	3.55		<1	
IQ	110.94	15.65		122.58	7.69		10.72	<0.005
Diagnosis (BDI/BDII)			17/5					
YMRS	4.73	1.52						
HAM-D	3.14	1.28						
Age at onset (years)	28.45	10.06						
Duration of illness (years)	12.3	10.42						
Mood stabilizers			13					
Antipsychotics			19					
Antidepressants			9					
Benzodiazepines			3					
Other			7					

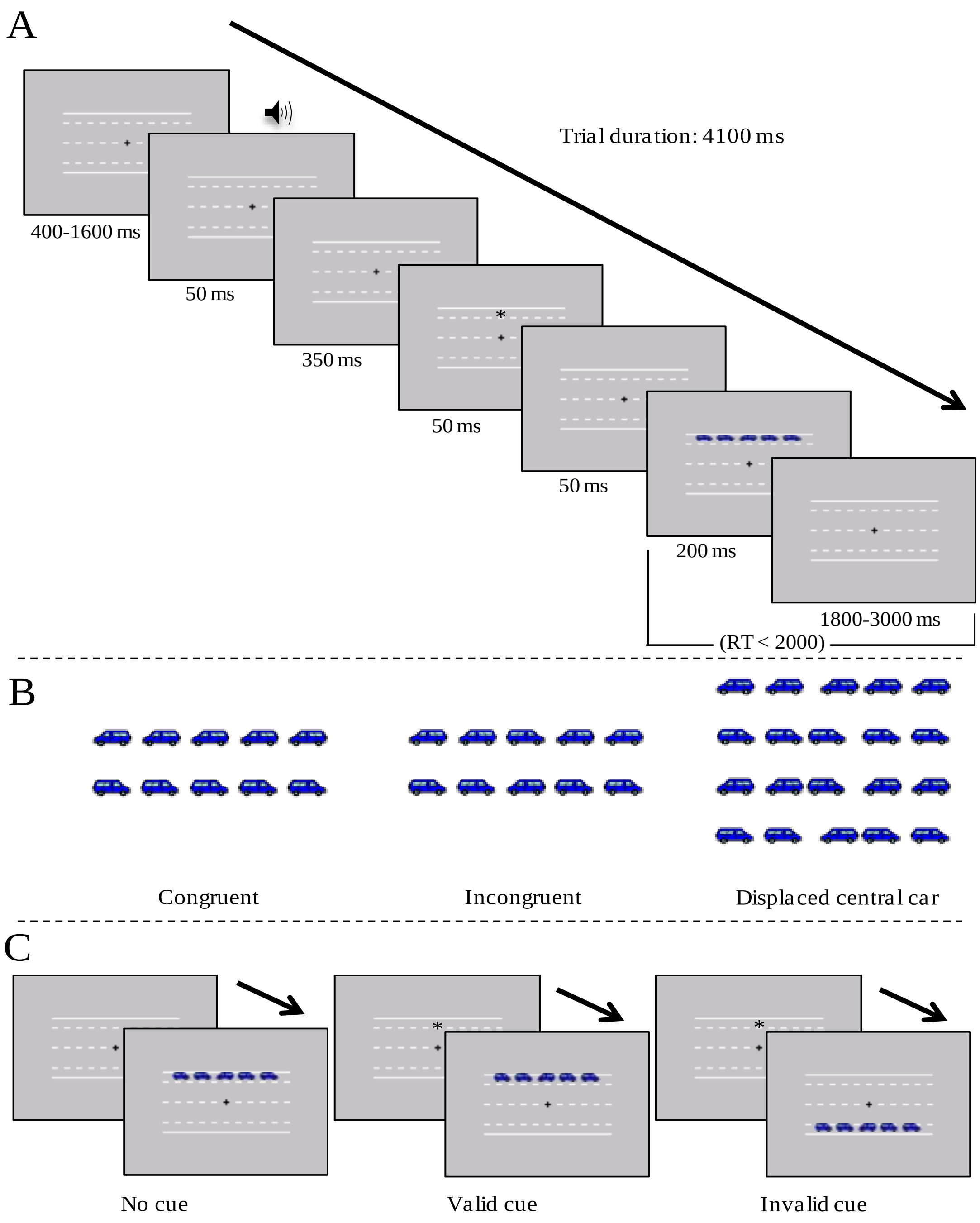
IQ: Intelligence Quotient; SD: Standard Deviation; YMRS: Young Mania Rating Scale; HAM-D: Hamilton Depression Rating Scale

5. Table(s)

	Bipolar Group				Control Group			
	No Tone		Tone		No Tone		Tone	
	Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent
Reaction Time								
Invalid	863.19 (175)	944.38 (164)	847.08 (183)	957.15 (205)	776.48 (199)	836.35 (202)	755.15 (165)	820.2 (212)
No cue	872.32 (200)	930.49 (144)	811.42 (165)	906.36 (158)	768.94 (186)	807.72 (197)	707.12 (171)	775.15 (165)
Valid	832.7 (190)	890.88 (180)	801.54 (178)	891.24 (201)	714.21 (175)	777.53 (201)	714.55 (176)	740.55 (174)
Percentage of error								
Invalid	10.30 (12)	18.30 (18)	6.68 (9)	20.06 (20)	2.07 (4)	9.57 (12)	5.08 (6)	2.27 (5)
No cue	7.85 (10)	14.80 (16)	6.84 (11)	11.34 (16)	4.08 (5)	4.83 (4)	8.39 (14)	3.17 (6)
Valid	6.14 (9)	11.22 (13)	2.59 (5)	6.58 (12)	1.52 (3)	5.08 (6)	3.16 (6)	3.12 (5)

Table 2 Mean correct reaction time, percentage of errors and standard deviations (between parentheses) in the two Groups: Bipolar patients and Controls. Warning signal (No tone/Tone), Visual cue (Invalid/No cue/Valid) and Congruency (Congruent/Incongruent) experimental conditions have been differentiated.

6. Figure(s)



Attention Networks Subtractions

Executive Control: RT for Incongruent – RT for Congruent trials (i.e. Conflict effect)

Orienting: RT for Invalid – RT for Valid trials (i.e. Visual cue effect)

Alerting: RT for No Tone – RT for Tone trials (i.e. warning effect)

Figure 1. Procedure and stimuli used in the Attention Network Test for Interactions and Vigilance (ANTI-V). (A) Schematic representation of the procedure. (B) The target stimuli. (C) The visual cue conditions.

6. Figure(s)

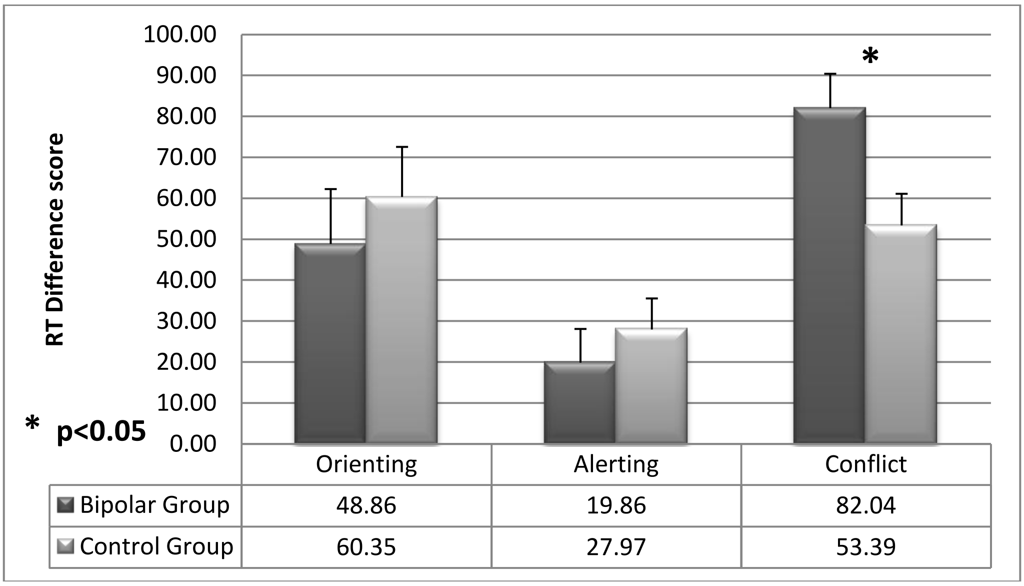


Figure 2. Alerting effect (RT no-tone trials minus RT tone trials), Orienting effect (RT valid cue trials minus RT invalid cue trials), and Control effect (RT incongruent trials minus RT congruent trials) in bipolar patients and controls.

6. Figure(s)

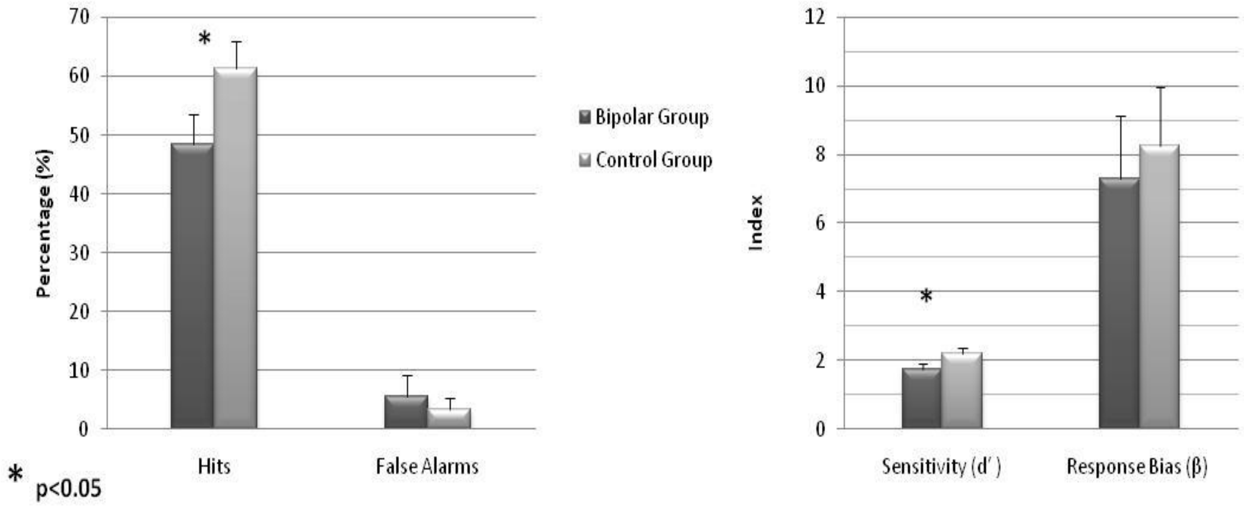


Figure 3. Vigilances indices in bipolar patients and controls: percentage of hits and false alarms (left) and sensitivity and response bias indices (right)