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Effects of mood state on divided attention in patients with bipolar disorder: Evidence for beneficial effects of subclinical manic symptoms

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ABSTRACT

A relatively small number of studies have been dedicated to the differential effects of the current mood state on cognition in patients with a bipolar disorder (BD). The aim of the current study was to investigate the effect of current mood state on divided attention (DA) performance, and specifically examine possible beneficial effects of the (hypo-) manic state. Over a maximum period of 24 months, medication use, divided attention test (a subtest of the Test for Attentional Performance (TAP)) was assessed every 6 months in 189 outpatients with BD. Data were analyzed with multilevel regression analysis (i.e. linear mixed models). DA performance varied considerable over time within patients. Corrected for psychotropic medication a significant quadratic relationship between manic symptoms and DA performance was found, with mild hypomanic symptoms having a positive influence on divided attention scores and moderate to severe manic symptoms having a negative influence. No association between depressive symptoms and DA performance was found. In future research on mania and cognition as well as in the clinical practice both the beneficial and negative effects of mania should be taken into account.

1. Introduction

Bipolar disorder (BD) is an 'episodic illness' which is characterized by alternating episodes of depression and (hypo-) mania. Besides the recurrent mood disturbances numerous studies indicate that patients with bipolar disorder suffer from cognitive impairments (Quraishi and Frangou, 2002; Glahn et al., 2004; Robinson et al., 2006; Henin et al., 2009). Attention problems, slowing of processing speed, and deficits in visual and working memory and executive functioning appear to be most consistently observed (Torres et al., 2007). A growing number of studies found evidence that cognitive impairments persevere in the euthymic state (Arts et al., 2008; Bora et al., 2009; Kurtz and Gerraty, 2009), giving rise to the ideas that cognitive impairments may represent a trait or an endophenotype of the disorder (Wichers et al., 2010). However, it is also widely suggested that cognitive performance is affected by bipolar mood symptoms. Nevertheless, studies investigating this association are rather scarce and limited by cross-sectional designs and small sample sizes. We are aware of only two longitudinal studies on the effects of bipolar mood on cognition, performed by Malhi et al. (2007) and Arts et al. (2011). Mahli et al. investigated 25 bipolar I patients for a maximum of 30 months and found that compared to the euthymic state of the patients, verbal memory was more impaired during the depressive state. No significant effect of manic state (mean YMRS score > 10) on cognition was found after adjusting for confounders, but a manic state only occurred in 12 patients. Arts et al. (2011) included a total of 76 bipolar I and II patients, who were neuropsychologically assessed every 2 months, for a period of 2 years. In this study cognitive functioning varied substantially over time and depressed mood had a negative impact on performance in several cognitive domains but no relation was found with mania.

It is rather remarkable that in the above described longitudinal studies no distinct association was found between (hypo) manic symptoms and cognitive performance, while a number of cross-sectional neuropsychological studies found cognitive impairment in (hypo) manic BD patients (Murphy et al., 1999, 2001; Fleck et al., 2003). The fact that longitudinal studies failed to find this association may be due to a) a lack of power because of the small

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number of currently (hypo)manic patients,(Malhi et al., 2007) or b) the occurrence of only subclinical or mild hypomanic symptoms, as seen in the study of Arts et al. (2011) in which mean Young Mania Rating Scale (YMRS) (Young et al., 1978) scores were 1.6 during cognitive assessment. In contrast, the cross sectional studies (Murphy et al., 1999, 2001; Fleck et al., 2003) were able to examine cognitive functioning during mild to severe manic episodes (YMRS mean scores ranging from 18.2 to 23.6). Or c) that non-linear models better model the relationship between manic symptoms and cognitive functioning, as suggested by the findings of Kravariti et al. (2012). In their cross-sectional study they found a non-linear association between mild manic symptoms and executive control and processing speed among 31 BD patients with mild manic symptoms. These results indicate that mild levels of mania are related to better cognitive functioning compared to moderate levels. This is in line with findings suggesting that low levels of manic symptoms are related to reports of mental alertness, goal directed activity, increased self-confidence and increased self-efficacy in non-clinical samples (Seal et al., 2008; Brand et al., 2011). Further, creativity is known to be associated with hypomanic traits or hyperthymia (Vellante et al., 2011), and hypomania (Furnham et al., 2008), underlining the possibility of increased or special performance levels during hypomania. Recent studies found that adolescents developing BD premorbidly have already normal or even better than average cognitive abilities regarding intelligence quotient (IQ) and reading abilities compared to healthy controls (Reichenbert et al., 2002; Zammit et al., 2004). It is widely suggested (Thys et al., 2012), but poorly investigated, that among talented people, BD is a well known phenomenon. This suggests that manic symptoms may both enhance and worsen performance.

Another complicating factor in studying cognitive performance in patients with a bipolar disorder is the impact of medication use. There are indications that especially antipsychotics (Torrent et al., 2011; Donaldson et al., 2003), benzodiazepines (Stewart, 2005), antidepressants (Jamrozinski et al., 2009), and the use of multiple types of medication (polypharmacy) (Martinez-Aran et al., 2005) have a negative effect on cognition. The majority of the before mentioned studies failed to adjust for potential confounding by medication. However, separating the effects of mood fluctuation and (fluctuations in) medication use on cognitive performance in patients of whom almost all use some kind of psychotropic drug is a challenge.

In this current longitudinal study, we aimed to investigate the natural variability of divided attention (DA) performance in outpatients with bipolar disorder. In addition, we examined the association between mood state, including euthymia, depressive and (hypo)manic mood, with objectively assessed DA performance adjusted for medication use.

There are several reasons studying DA in BD patients. First, DA is an essential component of everyday living (Loose et al., 2003) and is thought to be crucial for the ability to drive in traffic (Brouwer et al., 2002b), to establish and maintain joint attention and to avoid confusion when confronted with unfamiliar situations. Second, with respect to bipolar and unipolar depression was found that the divided attention performance predicted response to treatment, remission of symptoms, and risk of relapse in depressed patients (Majer et al., 2004). Furthermore in longitudinal studies both impairments in executive functioning (Mur et al., 2007, 2008) and attention (Arts et al., 2011) has been pointed out as possible endophenotypes of BD. Functional imaging research indicates that attending to both visual and auditory stimuli requires a recruitment of the frontal lobe (Johnson and Zatorre, 2006). This means that the task involves besides attentional also executive processes. Deficits in these two domains are both frequently associated with BD (Goodwin et al., 2008). As a part of executive function as well as attention, therefore, divided attention can be considered as a sensitive marker in mood disorders.

In the current study, we hypothesized that DA performance will be variable over time within patients, depending partly on the current fluctuating mood states, with increases of manic and depressive symptoms being associated with a decline in cognitive performance. Since low levels of manic symptoms could be associated with better performance, we also assessed potential non-linear relationships between level of manic symptoms and cognitive performance.

2. Methods

2.1. Study design

This is a 2-year prospective follow-up study among 189 bipolar outpatients with a diagnosis of BD I or BD II (also including BD not otherwise specified and cyclothymia) according to DSM-IV-TR diagnostic criteria. All participants were older than 18 years. They were all treated in the Program for Mood Disorders at PsyQ in The Hague, The Netherlands. Exclusion criteria in this study were schizoaffective disorder, neurological disease and substance abuse disorders. All participants gave full informed consent and this study was approved by the Medical Ethical Committee (METTIG) in Utrecht, The Netherlands, and was carried out in accordance with the declaration of Helsinki.

Diagnoses of BD and psychiatric co-morbidities were based on DSM-IV criteria and were assessed with a standardized diagnostic interview developed by Sheehan et al. (1998) using the Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS) (van Vliet and de Beurs, 2007b). The Questionnaire for Bipolar Illness, Dutch translation (Leverich et al., 2001a; Suppes et al., 2001a) was used to specify subtypes of BD, its course over time and detailed information about age of onset of first symptoms regarding hypomanic, manic, and depressive episodes.

Of the total sample 90.2% of the patients ($N=156$) completed at least 1 year follow-up, eventually a cumulative number of 62 (32.8%) patients dropped out before the end of the study. The most common reasons for patients to quit prematurely were being too unstable, being hospitalized, deeming the research too burdensome, discontinuing treatment at our outpatient clinic, and not showing up at an appointment more than 2 times. Patients missing more than one measurement were excluded from the current study. Fig. 1 shows the number of patients who dropped out at the different time points. Between the group that participated until the end of the study ($n=127$) and the group that dropped out during the study ($N=62$) no significant differences in the demographic and clinical characteristics were found.

2.2. Assessment

2.2.1. Divided attention test

Divided attention performance in this study was assessed by means of the TAP (Test for Attentional Performance, version 2.1) (Zimmerman and Fimm, 1993). The TAP is a widely used computer-based standardized test battery and easy to use in clinical practice (Hofer et al., 2007; Jamrozinski et al., 2009; Riecher-Rossler et al., 2009). At baseline a total of 8 subtests of the TAP were assessed, including the divided attention (DA) subtest. During the follow-up only the DA test of the TAP was repeatedly assessed, and this test will be the focus of this study. The divided attention TAP subtest is a crossmodal task, with both visual and auditory input. During the task a visual and an auditory task must be processed in parallel. Four different visual stimuli are separately presented on the screen of which two are the target stimuli to which the patient has to react by pressing a key. At the same time the patient hears high and low pitched tones alternately. When the high or low pitched tones emitted twice in succession the patient has to respond by pressing the key. Errors and omissions are the most important indicators for performance. To create a score for total performance, both errors and omissions are combined in one score. First, both variables were log-transformed because of their right-skewness. The log-transformed omission and error scores were then standardized as z-scores. Subsequently, the mean of those two z-scores was calculated, representing the overall performance on the divided attention test. This procedure resulted in one z-index-score for divided performance for every of the up to five waves, with a higher score indicating better performance

2.2.2. Assessment of mood states, clinical characteristics and medication use.

All 189 patients who participated in the neurocognitive assessment at the baseline were invited every 6 months for follow-up assessment during 24 months, at which divided attention was assessed, resulting in up to 5 time points. In those 6-monthly assessments, the current mood states were assessed using the self-