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Inhibitory control in euthymic bipolar disorder: Event related potentials during a Go/NoGo task

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HIGHLIGHTS

- Reduced NoGo N2 amplitudes in bipolar disorder reflect abnormalities in early stages of inhibition.
- Patients with bipolar disorder (BD) have increased NoGo P3 amplitudes together with normal inhibitory behavior.
- Patients with BD seem to compensate for abnormal early inhibition with increased cortical activity.

ABSTRACT

Objectives: Patients with bipolar disorder (BD) are reported to have difficulties with inhibition, even in a euthymic state. However, the literature on cortical activity associated with response inhibition in BD remains ambiguous. This study investigates inhibition in euthymic BD using electrophysiological measures, while controlling for effects of specific medications.
Methods: Twenty patients with BD were compared with eighteen healthy controls on a Go/NoGo task while electroencephalogram was recorded. Behavioral and event-related potential (ERP) measurements were analyzed for the two groups. Medication effects were controlled for in the analysis.
Results: Patients with BD had marginally reduced NoGo N2 amplitudes and increased NoGo P3 amplitudes compared with healthy controls when patients using benzodiazepines were excluded from the study. No behavioral differences between the groups were found.
Conclusions: Reduced NoGo N2 amplitudes in BD reflect aberrant conflict detection, an early stage of the inhibition process. In addition, increased NoGo P3 amplitudes in BD despite normal task performance reflect an overactive cortical system during a simple inhibition task.
Significance: Difficulties in early stages of inhibition in BD appear to have been compensated by increased cortical activation. This study extends current knowledge regarding cortical activations relating to inhibition in BD.

1. Introduction

Patients with bipolar disorder (BD) experience a broad range of cognitive deficits in acute mood states of the illness with many persisting in remission (Bearden et al., 2001). The presence of cognitive impairments during remission suggests that these deficits may be related to the pathophysiology of the disorder. Targeted neurocognitive testing often demonstrate impaired response inhibition in patients with BD in a euthymic state (Robinson et al.,

Abbreviations: BD, bipolar disorder; ERP, event related potential; IFC, inferior frontal cortex; ACC, anterior cingulate cortex; HDRS, Hamilton depression rating scale; YMRS, young mania rating scale; BDI-II, Beck Depression Inventory; EEG, electroencephalogram; EOG, electro-oculogram.

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2006; Bora et al., 2009). Inhibition is an executive function that can be defined as the ability to suppress responses when they are inappropriate in a given context (Logan and Cowan, 1984). The inability to inhibit responses relates to impulsive behavior, a clinically observable phenomenon in BD (Christodoulou et al., 2006). Extreme manifestations of impulsivity impair everyday functioning and represent important targets for treatment interventions (Evenden, 1999; Moeller et al., 2001).

While poor inhibitory control has been reported in BD (Frangou et al., 2005; Torralva et al., 2011), studies have also demonstrated normal inhibitory control in euthymia (Townsend et al., 2012; Ibanez et al., 2012). These inconsistent results are likely due to methodological differences across studies. Complex tasks (for example a Stroop task) seem to implicate poor inhibition in euthymic BD (see Bora et al., 2009 for a review). These task designs may involve additional cognitive processes, for example increasing short term memory demands and shifting attention (Buchsbaum et al., 2005), which may cause difficulties in inhibition. On the other hand, more simple tasks like the Go/NoGo task are able to tap more directly into the inhibition processes by minimizing load on other cognitive processes. Studies using the Go/NoGo task have demonstrated normal inhibitory control in euthymic BD (Kaladjian et al., 2009; see Newman and Meyer, 2014 for review). In other words, although a deficit in inhibition has been proposed in BD, using a very simple inhibition task seems to imply intact inhibition in euthymic BD.

However, despite behavioral performance, neuroimaging data have consistently demonstrated abnormal activations in BD relating to inhibition regardless of mood state (Hajek et al., 2013a). Decreased activations of the inferior frontal cortex (IFC) during inhibition tasks (Townsend et al., 2012; Blumberg et al., 2003) and structural alterations of the IFC are commonly found in BD (Stanfield et al., 2009; Hajek et al., 2013b), a region implicated for successful inhibition in healthy subjects (Horn et al., 2003). These findings are so robust that poor response inhibition mediated by changes in the IFC has been proposed to be an endophenotype in BD (Bora et al., 2009). In addition to decreased IFC activations in BD, data from a meta-analysis of neuroimaging studies related to inhibition (Hajek et al., 2013a) demonstrated that patients with BD in a euthymic state also had subcortical hypoactivations (i.e. basal ganglia) and cortical *hyperactivations* (specifically in the prefrontal cortex) together with normal performance. Hajek and colleagues (2013) therefore suggested that patients with BD in a euthymic state may compensate for subcortical hypoactivations or hypoactivations of the IFC by over activating adjacent prefrontal cortex, leading to normal performance. Unfortunately, the meta-analysis included studies with tasks of varying levels of complexity. As complex tasks recruit additional cognitive processes, many involving the prefrontal cortex, it is difficult to isolate brain regions specific to the inhibitory process. The use of complex tasks in the meta-analysis may possibly confound neurological findings. Therefore cortical activations involved in inhibitory processing in BD remain unclear and need to be further investigated.

On a neurophysiological level, an accurate reflection of inhibitory control is indexed by two distinct event related potential (ERP) components; the NoGo N2 and the NoGo P3 (De Jong et al., 1990; Jonkman et al., 2003; Smith et al., 2008; Kok et al., 2004). The NoGo N2 is associated with an early stage of the inhibition process, specifically the detection of conflict between an internal representation of a Go response and a NoGo response (Nieuwenhuis et al., 2003; Donkers and van Boxtel, 2004). The NoGo P3 is a later component reflecting actual inhibition of the motor system (Kok et al., 2004). Using source localization analysis with low resolution electromagnetic tomography (LORETA), both the NoGo N2 and the NoGo P3 have been shown to be most robust at fronto-central areas when responses have to be inhibited (Bokura et al., 2001; Fallgatter et al., 1997; Tekok-Kilic et al., 2001). Specifically the NoGo N2 has been shown to be generated in the anterior cingulate cortex (ACC) and IFC (Lavric et al., 2004; Pliszka et al., 2000; Bokura et al., 2001) and the NoGo P3 in the orbito-frontal cortex (Bokura et al., 2001). Given the inconclusive results regarding cortical activations relating to inhibition in BD, investigating inhibition using electrophysiology can be beneficial in isolating the specific cognitive subprocesses of inhibition.

Previous ERP studies in BD mainly focused on processes relating to allocation of attention to a stimulus. Many studies demonstrated lower P3 amplitudes (Bersani et al., 2015; Fridberg et al., 2009; Salisbury et al., 1999; Hall et al., 2009) in BD compared with healthy controls, yet not all studies corroborated these findings (Lahera et al., 2009; Souza et al., 1995). Importantly, most studies did not investigate inhibitory control in BD, but rather investigated stimulus processing in a standard oddball task where subjects had to respond to the rare stimuli instead of suppressing a response.

Two studies to date have investigated inhibitory control using a Go/NoGo task and ERP measures in BD (Michelini et al., 2016; Chun et al., 2013). Although both studies used a Go/NoGo task, results of these studies have been inconclusive regarding NoGo amplitudes relating to inhibition, with one study showing normal NoGo P3 amplitudes (Chun et al., 2013) and the other finding reduced NoGo P3 amplitudes together with reduced N2 amplitudes in BD (Michelini et al., 2016). Possible methodological limitations may have led to these differences. Firstly, the interpretation of ERP is largely complicated by confounding effects of mood state and as such, this may be an important factor in the interpretation of the inconclusive results regarding NoGo P3 in BD.

Elevated mood is known to influence cognition with evidence of cognitive deficits becoming more severe during manic and depressed episodes compared with euthymia (Martinez-Aran et al., 2004). In addition, state differences relating specifically to inhibitory control have been observed with decreased inhibitory control in mania (Larson et al., 2005) and hyperactive inhibition in depression (Langenecker et al., 2007). This is not surprising as impulsive behavior is a prominent symptom among individuals with mania and individuals with depression are more careful when responding in order to avoid errors. Therefore, state related inhibitory problems may have confounded the investigation. Elevated mood has been additionally found to influence ERP activity including P3 activations. Specifically, depressive state has been found to increase ERN, an ERP related to error detection and conflict monitoring (Morsel et al., 2014). Depressive state was also found to reduce P300 amplitudes relating to attention and memory (Kaya et al., 2007). Unfortunately, the study by Chun and colleagues (Chun et al., 2013) used patients with BD who were in a range of different mood states, which may have obscured their findings. While Michelini et al. (2016) used a euthymic sample to investigate NoGo N2 and NoGo P3 in BD, the variation of the Go/NoGo task used was more similar to a cued continuous performance test that in fact does not load as highly on inhibition as a Go/NoGo task where a prepotent response has to be inhibited.

An additional methodological limitation of previous NoGo studies is that neither study (Michelini et al., 2016; Chun et al., 2013) accounted for effects of medications on ERP measures. While there is some evidence demonstrating that medications, specifically lithium and antipsychotics, do not influence ERP amplitudes (Strik et al., 1998; O'Donnell et al., 2004; Reeves and Struve, 2005), there are other studies that suggest that medications may influence ERP activity. Specifically, one study demonstrated that patients taking lithium have increased amplitudes compared with patients taking antipsychotics (Small et al., 1998). In addition, some studies have demonstrated changes in EEG in response to antipsychotics (Small et al., 1989; Centorrino et al., 2014; De Bruijn et al., 2004). There is also evidence of benzodiazepines