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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 behavioural 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.

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).

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., 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 Cowen 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 and colleagues, (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 et al., 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 (Samll et al., 1989; Centorrino et al., 2014; De Bruijn et al., 2004). There is also evidence of benzodiazepines reducing ERP in patients with schizophrenia (de Bruijn et al., 2006) and healthy controls (Hayashi et al., 2000; Urata et al., 1996). It is therefore still unclear how medications impact EEG and may perhaps confound results.

In the present study, two subprocesses of response inhibition indexed by the NoGo N2 and NoGo P3 were investigated using a straightforward Go/NoGo task. Patients with BD in a euthymic state were compared with healthy controls in order to identify any dysfunction that may be related to the pathophysiology of the disorder. In line with previous research, patient with BD were expected to show normal performance on the inhibition task but differential neural activations relating to inhibitory processes. Specifically, reduced NoGo N2 amplitudes were expected (as in Michelini et al., 2016) and increased NoGo P3 amplitudes were expected in BD, just as cortical hyperactivations have

been proposed in euthymia (Hajek et al., 2013a). In addition, the influences of different medications on the ERP activations were investigated.

2. Method

2.1. Participants

Twenty patients with BD and 18 healthy controls participated in the study. Patients were recruited from the St. Norbertus psychiatric hospital (Duffel, Belgium) and from the Psychiatric Centre Brothers Alexians (Boechout, Belgium) and had participated in a previous research study (Morsel et al., 2014).

Diagnosis of the patients according to DSM-IV-TR criteria was confirmed using a semi-structured interview. All of the patients were in a euthymic state at the time of testing. This was assessed using the Beck Depression Inventory (BDI-II) (Beck et al., 1961) and the Hamilton depression rating scale (HDRS) (Hamilton 1960) to confirm the absence of depressive symptoms (less than 8 on the HDRS) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) to confirm the absence of manic symptoms (less than 7 on the YMRS). Patients were excluded from the study if they had a neurological disorder, history of brain injury, drug or alcohol dependence in the last year or intellectual disability. Patients with BD were taking a range of medications, specifically mood stabilizers (85%), antidepressants (35%), atypical antipsychotics (70%) and benzodiazepines (20%).

All subjects had normal or corrected-to-normal vision. Control participants were similar to the study group in terms of gender, age, education level and dominant hand. Controls were excluded from the study if they had a history of a psychiatric disorder.

Ethical approval for this study was obtained by the medical ethics committees of both hospitals and carried out in accordance with the latest version of the Helsinki Declaration. All participants gave their written informed consent.

2.2. Material

2.2.1. Go/No-Go task

All participants performed the Go/No-Go task (Donders 1969). The task consisted of Xs (Go stimuli) presented on 70% of trials and Os (No-Go stimuli), presented on 30%of trials. Each letter was

presented for 100 ms at the center of the screen. Stimulus size of the Xs and Os was approximately 18 mm x 12 mm. The stimuli were presented pseudo-randomly; each No-Go stimulus was followed by at least three Go stimuli before the presentation of the next No-Go trial. The interstimulus intervals were randomized at 2000, 2250, 2500, 2750 or 3000 msec.

Participants were instructed to respond to the letter X and not to respond when the letter O was presented. A response comprised of pressing a button on a button-box with the index finger of the dominant hand as quickly as possible following stimulus presentation. There were 3 blocks of 150 trials and in between each block, participants could take a break. Equal emphasis was placed on speed and accuracy. Subjects did not receive any feedback regarding their performance. The task lasted 20 minutes.

2.2.2. Electrophysiological measurements

The electroencephalogram (EEG) was sampled at 5000 Hz and electrophysiological signals were recorded using 32 active electrodes fixed on an actiCAP, with a DC amplifier (Brain Products GmbH (Germany)) at the Fz, FCz, Cz, Pz, Oz, F7/8, F3/4, FC5/6, FC1/2, T7/8, C3/4, CP5/6, CP1/2, P7/8, P3/4 and O1/2 sites, according to the extended international 10-20 system. In addition, horizontal electro-oculogram (EOG) was recorded from the outer canthus of each eye and vertical EOG was recorded from infra- and supraorbital electrodes placed in line with the pupil of the right eye. Electrode impedances were kept below 10kΩ.

2.3. Behavioral data analyses

Reaction times, percentage of correct hits for Go stimuli and errors of commission (incorrectly responding to NoGo stimuli) were subjected to separate independent samples t-tests to compare patients with BD and controls.

For the analysis of clinical variables (age, education, hand, gender and mood state), ANOVA (in cases of continuous variables) or Chi-square tests were performed to compare frequencies between groups.

2.4. ERP analyses

ERP data were collected using Brain Vision Analyzer 2.1. All electrodes were referred to an electrode which was situated between Cz and Pz and grounded at AFz and were later re-referenced offline to the average of T7 and T8. A band-pass filter between .02 Hz and 15 Hz was applied to the raw data and the EEG was downsampled to 250 Hz.

The EEG was corrected for EOG artifacts using the Gratton and Coles algorithm (Gratton et al., 1983). ERPs were time-locked to stimulus onset and averaged for correct responses relative to a 200 msec pre-stimulus baseline. N2 amplitudes were determined for correct Go trials and correctly inhibited NoGo trials by calculating the most negative peak in the 200-350 msec time window after stimulus onset. P3 amplitudes were determined for correct Go trials and correctly inhibited NoGo trials by calculating the most positive Go and NoGo peaks in the 250-550 msec time window after stimulus onset. Fronto-central electrodes (FCz and Cz) were investigated where maximal NoGo N2 and P3 amplitudes were expected (Bokura et al., 2001; Fallgatter et al., 1997; Tekok-Kilic et al., 2001).

Statistical analyses were performed using SPSS 20.0. In order to ascertain whether the NoGo task used in this study elicited increased fronto-central NoGo N2 and NoGo P3 amplitudes compared with Go amplitudes, repeated measures GLM were first conducted using Group (bipolar vs. control) as the between-subjects factor and Electrode (FCz and Cz) and Trial type (Go vs. NoGo) as the within-subjects factors. N2 and P3 were separately investigated.

2.5. Analysis of medication effect

Effects of medications on NoGo N2 and NoGo P3 amplitudes were examined in the patient group. Each medication (mood stabilizers, antidepressants, antipsychotics and benzodiazepines) was

coded ‘on’ or ‘off’ for each BD patient. As inhibition was the focus of this study, only the NoGo trials were analyzed. The medication analysis was conducted in the same way as the electrophysiological data analysis using repeated measures GLM with each medication separately assessed as the between-subjects factor and Electrode as the within-subjects factor.

3. Results

3.1. Clinical and Demographic data

Clinical and pharmacological treatments of the participants are presented in Table 1. The two groups did not significantly differ in age, gender, education level or dominant hand. There was a significant effect of residual depressive symptoms with higher scores on the HDRS and BDI-II scales in the BD group. Residual manic symptoms did not differ amongst the groups.

3.2. Go/ No-Go task

3.2.1. Behavioral data

Mean reaction times to Go stimuli, percentage of correct hits for Go trials and percentage of commission errors are presented in Table 2. There were no group differences in any of the conditions (RT: $t(36)=.159$, $p=.875$; error: $t(36)=1.31$, $p=.198$; correct hit: $t(36)=1.08$, $p=.288$). As expected, subjects had no difficulty correctly classifying and responding appropriately to stimuli.

3.2.2. Electrophysiological data

Figure 1 illustrates the grand averaged waveforms at the fronto-central electrodes (FCz and Cz) for Go and NoGo trials. Analysis of NoGo N2 revealed a significant main effect of Trial ($F[1,36]=19.674$, $p<.001$; $d'=.41$), indicating more negative N2 amplitudes for NoGo trials (mean= -.968µV, SD=2.78) than for Go trials (mean= -.081µV, SD=2.35). Similarly, NoGo P3 analyses revealed a significant main effect of Trial ($F[1,36]=4.781$, $p=.035$, $d'=.031$) with larger P3 amplitudes for NoGo trials (mean=5.349µV, SD=3.64) than for Go trials (mean=4.331µV, SD=2.84), indicating that the task manipulation was successful.

There was no significant main effect of Electrode for N2 ($F[1,36]=3.747$, $p=.061$) or P3 ($F<1$), nor was there a significant interaction between Electrode and Group for N2 ($F[1,36]=3.763$, $p=.060$) or P3 ($F<1$). There were no significant interactions between Trial and Group, Trial and Electrode or

between Trial, Electrode and Group for N2 or P3 (all Fs<1), nor was there a significant main effect of Group for either ERP measure (N2: F[1, 36]=2.540, p=.120; P3: F[1,36]=3.024, p=.091).

3.3. Controlling for medications

Figure 2 illustrates the effects each medication had on the NoGo N2 and NoGo P3 amplitudes in patients with BD. There were no main effects of medication on NoGo N2 amplitudes (benzodiazepines: F[1,17]=1.929, p=.183; mood stabilizers (F[1,17]=2.113, p=.163); antidepressants or antipsychotics (Fs<1)). There were no main effects of Electrode (all Fs<1), nor were there significant interactions between benzodiazepines and Electrode (F<1), mood stabilizers and Electrode site (F[1,17]=3.287, p=.087), antidepressant and Electrode or antipsychotics and Electrode (Fs<1).

However, effects of medication on NoGo P3 revealed a significant main effect of benzodiazepines on NoGo P3 amplitudes (F[1,17]=5.183, p=.036, d'=1.45). Patients taking benzodiazepines had smaller NoGo P3 amplitudes (Mean=2.99μV, SD=1.98) compared with patients who were not taking benzodiazepines (Mean=7.06μV, SD=3.45). There was no main effect of Electrode, nor was there a significant interaction between benzodiazepines and Electrode sites (both Fs <1). No significant main effects of mood stabilizers (F[1,17]=2.182, p=.157), antidepressants (F[1,17]=1.548, p=.230) or antipsychotics (F<1) were found to influence NoGo P3 activations. There were also no significant interactions between mood stabilizers and Electrode site, antidepressant and Electrode or antipsychotics and Electrode (all Fs<1).

Follow up analyses were conducted based on the significant effects of benzodiazepines on the ERP. As only 4 patients were taking benzodiazepines, behavioral and ERP analyses were re-run without these patients in order to assess for any Group differences. No differences were found amongst the behavioral results; there were still no Group differences in any of the conditions (RT: t(32)=.198, p=.844; errors of commission: t(32)=1.41, p=.168; correct Go hit: t(32)=1.04, p=.305).

Figure 3 illustrates the ERP waveforms for Go and NoGo trials among the subset of patients with BD who were not taking benzodiazepines and healthy controls. Excluding patients taking

benzodiazepines revealed a trend of enhanced NoGo N2 amplitudes among patients with BD (Mean=.142μV, SD=2.66) compared with controls (-1.672μV, SD=2.67), although this trend was not statistically significant (F[1, 32]=4.042, p=.053, d'=0.68). There was no significant main effect of Electrode nor was the interaction between Electrode and Group significant (both Fs<1). There was a significant Group difference for NoGo P3 amplitudes (F[1,32]=4.292, p=.046, d'=0.71), which was not present in the initial analysis indicating that patients with BD have increased NoGo P3 amplitudes (Mean= 6.969μV, SD=3.22) compared with controls (Mean=4.523μV, 3.65). As before, there was no main effect of Electrode (F[1,32]=1.278, p=.267), nor was the interaction between Electrode and Group significant (F[1,32]=1.519, p=.227).

3.4. Correlations with residual mood state

Residual depressive symptoms (measured by the HDRS, BDI-II) were found to be present in the BD group (see Table 1). Therefore, post-hoc correlation analyses between the BDI-II rating scale and NoGo N2 and NoGo P3 amplitudes were calculated in order to see whether there was a relationship between residual mood and electrophysiological measures. The BDI-II scale is a subjective measure which is able to tap into depressive symptoms in healthy subjects and in individuals with BD. Correlations were performed separately for each group and patients taking benzodiazepines were excluded. As there was no interaction between the ERP amplitudes and Electrode, correlation analyses were conducted on the mean NoGo N2 and NoGo P3 of electrode FCz and Cz.

None of the correlations were statistically significant. However, looking at the correlation coefficients, there was a negative relationship with a medium effect size between the BDI-II scores and the NoGo N2 amplitudes (r=-.246, p=.378) and a positive relationship with a medium effect size between the BDI-II scores and NoGo P3 amplitudes (r=.205, p=.463), indicating that as depressive symptoms increase, the NoGo N2 amplitudes decrease and the NoGo P3 amplitudes increase. These relationships were not present in the control group (NoGo N2: r=-.028, p=.001; NoGo P3: r=-.038,

p=.234). An additional relationship with a medium effect size was present between the NoGo N2 and NoGo P3 amplitudes in the BD group (r=.392, p=.133) and not in the control group (r=.171, p=.511).

4. Discussion

The current study investigated two subprocesses of response inhibition in patients with BD using a Go/NoGo task in conjunction with the NoGo N2, an early ERP measure of conflict detection and the NoGo P3, an ERP measure of inhibitory processing. Patients with BD in a euthymic state were compared with matched controls. This study additionally assessed the effects of medications on ERP activations. Results showed normal behavior on the inhibition task together with marginally reduced NoGo N2 amplitudes and *increased* NoGo P3 amplitudes in patients with BD, as expected, indicating overactivation of cortical fronto-central areas during NoGo trials. Importantly, these results were only obtained when taking the effects of medications (specifically benzodiazepines) into account.

Behavioral results of the current study are in line with previous reports of normal inhibition in euthymic BD during a simple task (Townsend et al., 2012; Ibanez et al., 2012; Kaladjian et al., 2009; Newman and Meyer 2014**)**. Although studies using more complex inhibition tasks have demonstrated aberrant inhibition in BD (Bora et al., 2009), more complex tasks may require the engagement of additional executive properties, as opposed to a simple task which may tap more directly into the inhibition process. It is thus clearly beneficial to use a simple task when investigating inhibition and the underlying neural processes in BD. Importantly, studies have shown that using easy tasks can show altered brain activity uncompromised by differences in task performance (see Kronhous et al., 2006; Van Hecke 2010), thereby allowing clear identifications of neural abnormalities.

Results of the current study showed discrepancies between normal behavior and altered neural responses during the inhibition task in BD, enabling more insight into inhibitory processing in BD. While there is robust evidence demonstrating structural alterations of the IFC in BD and reduced IFC activations during inhibition tasks (ie, Townsend et al., 2012; Blumberg et al., 2003; Stanfield et al., 2009; Hajek et al., 2013b), additional cortical activations using fMRI (Hajek et al., 2013a) and NoGo P3 (Michelini et al., 2016; Chun et al., 2013) have remained unclear due to methodological limitations. The current study was able to tap directly into cortical activity relating to different subprocesses of inhibition in euthymic BD. The finding in the current study of reduced NoGo N2

amplitudes in BD, an index of an early stage of conflict detection, taken together with previously reported evidence that NoGo N2 is generated by the IFC (Lavric et al., 2004; Pliszka et al., 2000), supports these well documented neuroimaging findings relating to abnormal activations of the IFC in BD. In addition, reduced NoGo N2 amplitudes support previous reports of impaired conflict monitoring in BD (Michelini et al., 2016; Morsel et al., 2014; Ethridge et al., 2012). The additional finding of *increased* fronto-central NoGo P3 amplitudes found in the current study, together with evidence that NoGo P3 is generated in the prefrontal cortex (Eimer et al., 1993; Kopp et al., 1996; Bokura et al., 2001) provided evidence that patients with BD compensate for abnormalities in early stages of the inhibitory process by overactivation of additional cortical areas (such as the prefrontal cortex), leading to normal performance (as suggested by Hajek et al., 2013a).

This compensatory system relating to inhibition can be explained further. Reduced NoGo P3 activations would suggest difficulties in inhibitory control, which often coincides with more behavioral errors of commission. However, results of the current study show that patients with BD could inhibit successfully in an easy task, and this coincided with increased NoGo P3 activations, suggesting that patients with BD had to invest more effort in order to perform as well as controls, corroborating the finding of Hajek and colleagues (Hajek et al., 2013a). Results of the study extend current knowledge regarding information processing capacities in BD, suggesting that equal performance on a simple task requires more effort in BD, reflected by increased cortical activity.

Reduced NoGo N2 and increased NoGo P3 amplitudes found in BD in the current study were only present when patients taking benzodiazepines were excluded from the study, suggesting that benzodiazepines reduce NoGo P3 amplitudes significantly. These findings are in support of previous findings in schizophrenia implicating that benzodiazepines reduce ERPs (i.e.,De Bruijn et al;, 2004; Hayashi 2000; Urata et al., 1996) as well as findings that other medications (lithium, antipsychotics) do not affect ERP amplitudes in BD (Strik et al., 1998; O'Donnell et al., 2004; Reeves and Struve 2005). Results of the current study are critical as most ERP studies do not take the effects of specific medications into account in the P3 analyses, and it is possible that decreased NoGo P3 amplitudes

found in a previous NoGo study in BD (Michelini et al., 2016) are simply the result of medications and not actual underlying deficits in BD. However, as only 4 patients in the current study were taking benzodiazepines, it is possible that the effects of this drug treatment on NoGo P3 amplitudes was a false-positive result or an over-estimation of the magnitude of the association. In addition, benzodiazepines are often taken as needed rather than on a daily basis, and patients taking a higher dosage (or more frequent usage) may have more adverse side effects, including depression, potentially interfering differently with cognitive abilities and ERP activations. While excluding patients using benzodiazepines from electrophysiological research may be beneficial, this may result in leaving out a population of patients with different symptoms than BD patients who are not taking benzodiazepines. Larger confirmatory studies are needed to explore the effects of benzodiazepines in the same patients, on and off the drug.

Most studies investigating ERP in BD categorize patients as a group without taking effects of symptom severity on ERP activity into account. However, in the present study, correlation analyses were additionally performed between residual depressive symptoms and ERP measures. Depressive symptoms assessed by a subjective measure were related to lower NoGo N2 amplitudes and greater NoGo P3 amplitudes with a medium effect size in the BD group and not in the control group. This increase in NoGo P3 could be related to a hypersensitivity to incorrectly responding which is found in patients with depression (Cavanagh et al., 2011) and anxiety traits (Sehlmeyer et al., 2010) and is in line with previous reports of residual depression influencing P3 activations (Maekawa et al., 2012; Kaya et al., 2007. These correlations may alternatively suggest an underlying group effect rather than a true relationship. However, the correlations need to be interpreted with caution as none were statistically significant. In addition, while results of the correlations may suggest that the NoGo P3 is state dependent rather than a compensatory mechanism in BD patients, an additional relationship found in the current study between NoGo N2 and NoGo P3 amplitudes only in the BD group supports the suggestion of the current study that the P3 is a compensation mechanism in BD.

Patients in the current study did not have more residual manic symptoms compared with healthy controls and an investigation of residual manic symptoms on NoGo P3 could not be performed. As impulsivity is a prominent clinical feature of mania with evidence of decreased inhibitory control in mania (Larson et al., 2005), residual manic symptoms may also influence the ERP relating to inhibition. For this reason, future studies should include an investigation of residual symptoms as these may have additional state related influences on inhibitory processing in BD.

Although poor inhibition is a prominent clinical feature of BD, including impulsivity and risk behavior (i.e., suicide attempts and substance abuse) (Christodoulou et al., 2006), results of the current study suggest that the underlying neural deficits cannot simply be written off as an impaired inhibitory system as proposed (Bora et al., 2009). It is possible that observed behavioral abnormalities of inhibition may be related to additional cognitive deficits present in BD, such as abnormal information processing, conflict monitoring, abnormal emotional responses to the processing of information or a combination of these. While results of the current study extend current knowledge regarding inhibitory processing in BD, further research relating to the neural underpinnings of poor inhibition is critical for the advancement of treatment targets in BD. Next to pharmaceutical interventions, cognitive remediation therapy is also emerging as an important treatment strategy in BD (see Bowie et al., 2013 for a review). Our results may suggest that in order to improve inhibitory processes, cognitive remediation needs to address other abovementioned cognitive deficits as well. However, further research is needed.

An important limitation of the current study is the small sample size. Studies including more participants are necessary in order to make more concrete conclusions. An additional limitation of the study is that the suggested compensatory inhibitory mechanism may not extend to all cases. There is evidence of increased impulsive behavior (more errors of commission) in patients with more complicated bipolar disorder, for example with many past mood episodes, substance use disorder or suicide attempts (Swann et al., 2005). It is important to note that even a simple task could include some elements of other cognitive processes, such as attention. While behavioral data of the current

study suggested that the participants appeared to have no problems attending to the current task, it would be interesting for future studies to directly manipulate attention during a Go/NoGo task, by varying attentional load, allowing further investigations into the inhibitory process uncomplicated by attention. A final limitation is that the outcome of the current study may seem to suggest that no intervention is necessary in order to improve response inhibition in patients with BD, as compensatory processes effectively deal with impairment in inhibition. However, results of the current study cannot be easily generalized to other or more difficult tasks. It is likely that complex tasks require more compensatory effort, and available resources may not always suffice. Compensatory processes may break down leading to behavioral impairments, as is commonly seen in more complex inhibition tasks (Bora et al., 2009). Therefore, despite evidence for normal inhibitory performance in BD, nevertheless patients with BD might still benefit from interventions targeting inhibitory control to accommodate for more complex real life situations.

5. Conclusion

Patients with BD in a euthymic state demonstrate marginally reduced NoGo N2 and increased NoGo P3 amplitudes at fronto-central electrodes during a simple inhibition task compared with healthy controls when patients using benzodiazepines were excluded from the study. In addition, normal task performance was found. These findings suggest that patients with BD have to invest more effort in order to perform as well as healthy controls and they appear to compensate by over-activating cortical (fronto-central) areas related to inhibitory processing.

Conflict of Interest Statement

We wish to confirm that none of the authors have potential conflicts of interests associated with this publication to be disclosed.

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Figure 1

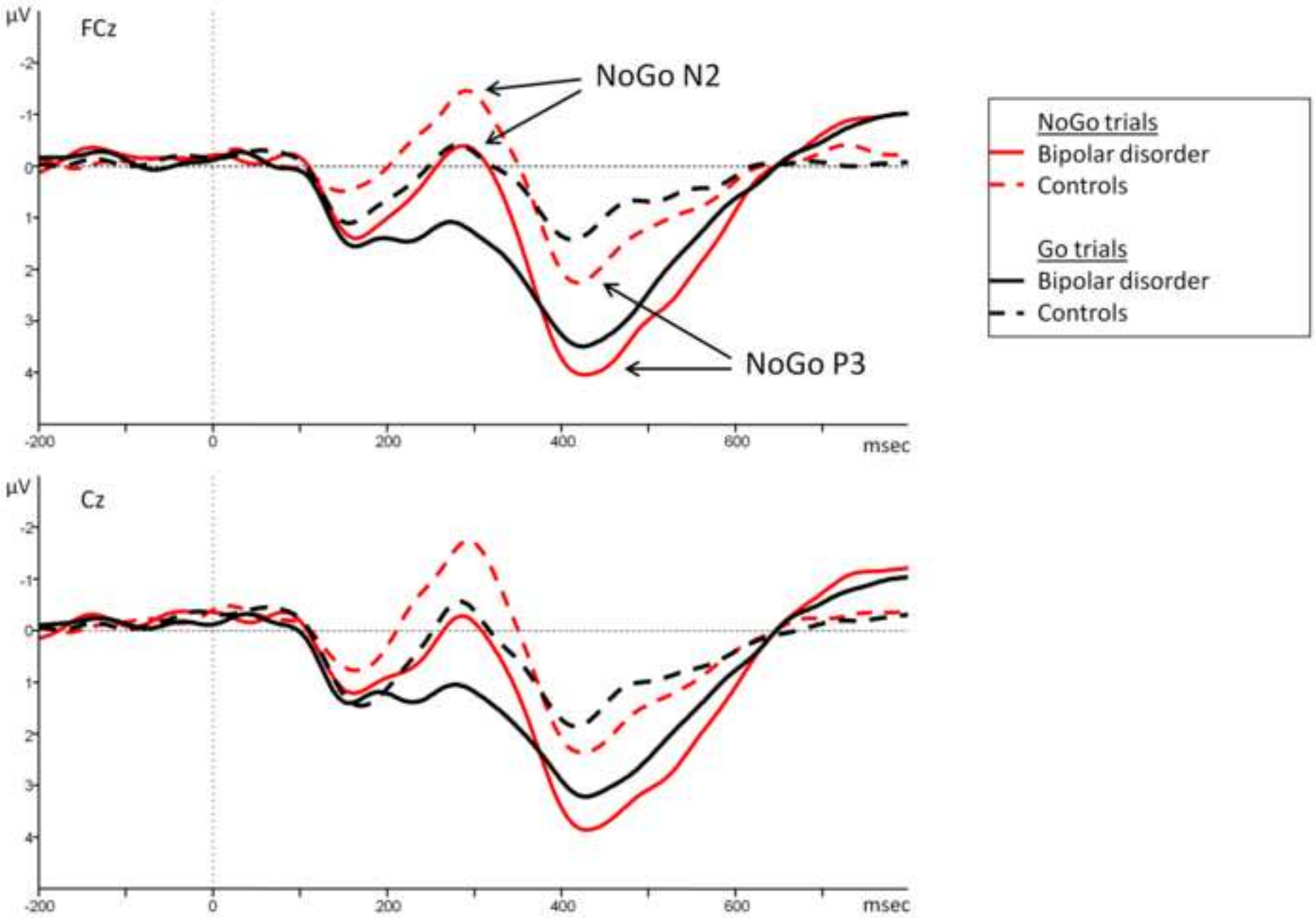

Figure 2

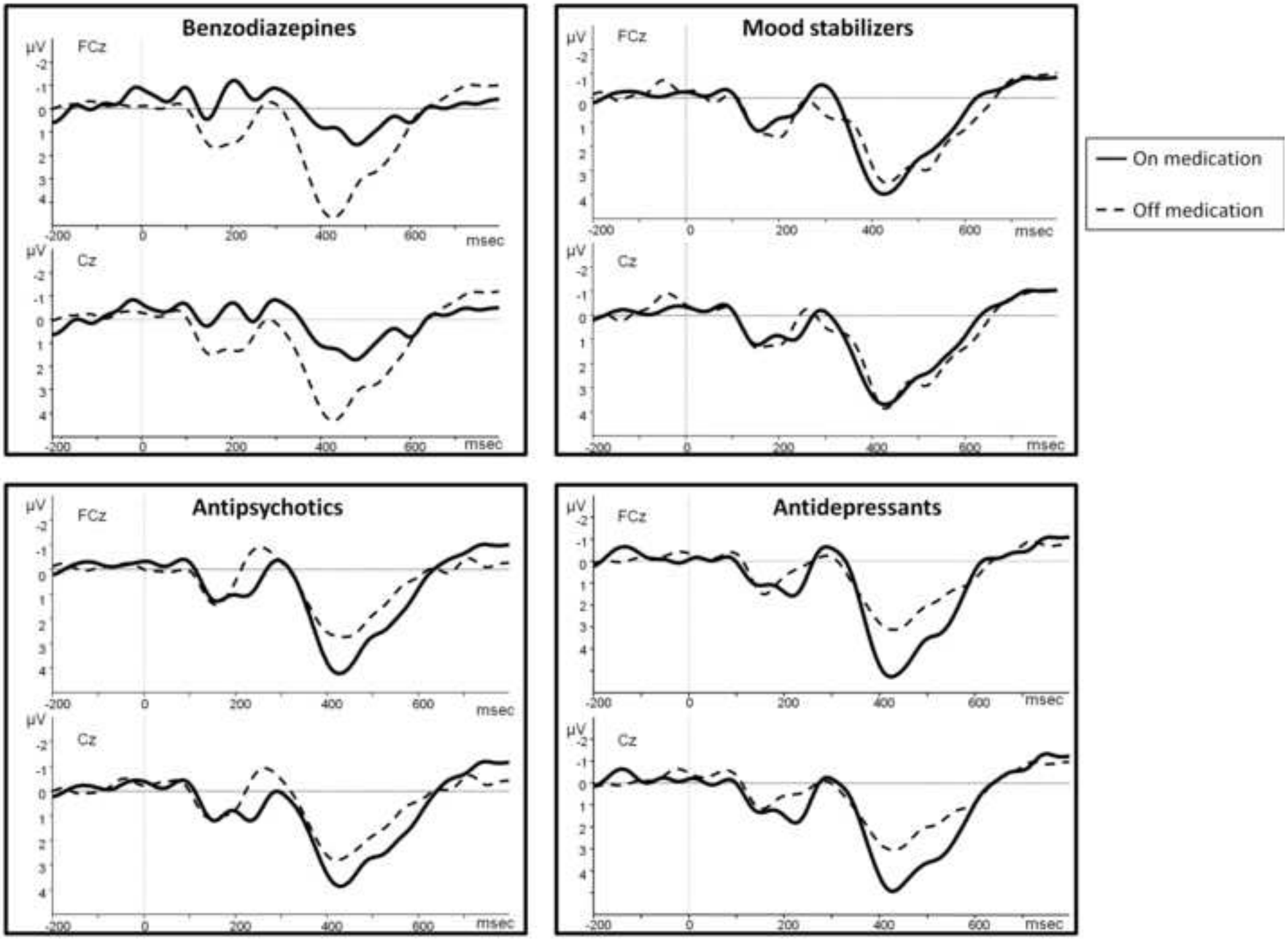

Figure 3

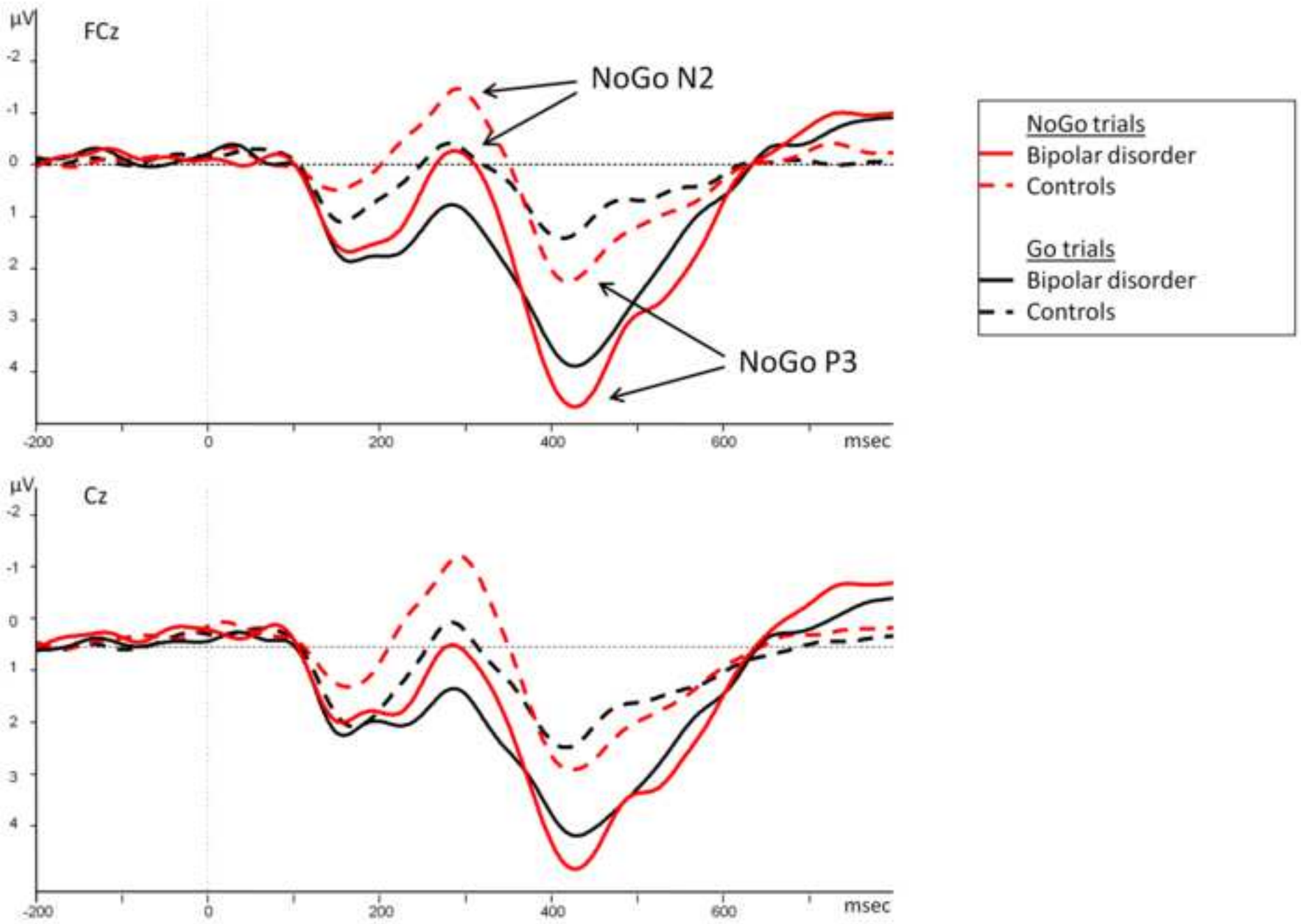

Table 1: Overview of demographic and clinical characteristics.

	Bipolar disorder (n=20)	Control (n=18)	*test statistic*	*p-value*
Gender	50% Male	40% Male	X^2=.117	.757
Age, mean years (SD)	44 (12.05)	42 (15.09)	t(36)=.463	.632
Education level (mean rank)	2.0 (.72)	2.22 (.55)	X^2=2.751	.252
Hand	75% Right	94% Right	X^2=2.694	.184
Clinical rating scale, mean, (SD)				
YMRS	2.316 (2.06)	1.222 (1.93)	t(36)=1.667	.104
HDRS	3.00 (2.62)	.722 (1.18)	t(36)=3.372	.002*
BDI-II	10.474 (9.08)	3.667 (2.89)	t(36)=3.036	.005*
Medication				
Mood stabilizers	17 (85%)			
Antidepressants	7 (35%)			
Atypical antipsychotics	14 (70%)			
Benzodiazepines	4 (20%)			
Age of onset, mean (SD)	31.84 (13.75)			
Number episodes	10.21 (9.77)			
Suicide attempts	1 (1.37)			

*p<.01, YMRS=Young Mania Rating Scale (30; Young, 1978), HDRS=Hamilton Depression Rating Scale (29; Hamilton, 1960), BDI-II= Beck Depression Inventory (31; Beck, 1966). Education level subdivided in a low (1), medium (2) and high (3) level in accordance with the Belgium education system.

Table 2: Mean (SD), reaction times (RT) to standard stimuli, percent correct hits and percent errors of commission.

	Bipolar disorder	Control
RT (ms) to standard	387.95 (55.51)	385.20 (50.43)
% correct hits	97.94% (2.32)	97.81% (3.49)
% errors of commission	9.81% (9.92)	6.26% (6.17)

Figure 1: Grand average stimulus-locked waveforms for Go and NoGo trials in patients with bipolar disorder and healthy controls. Frontocentral electrodes FCz and Cz are depicted. Stimulus onset is at 0 msec.

Figure 2: Grand average stimulus-locked waveforms of NoGo trials for patients with bipolar disorder on and off medications (benzodiazepines, mood stabilizers, antipsychotics and antidepressants). Frontocentral electrodes FCz and Cz are depicted. Stimulus onset is at 0 msec.

Figure 3: Grand average stimulus-locked waveforms of Go and NoGo trials among the subset of patients with bipolar disorder who are off benzodiazepines and healthy controls. Frontocentral electrodes FCz and Cz are depicted. Stimulus onset is at 0 msec.