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# **Systematic review of cognitive event related potentials in euthymic bipolar disorder**

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## **Abstract**

Cognitive deficits are critical features of bipolar disorder (BD), greatly impacting quality of life. The aim is to systematically review and critically evaluate underlying event related potential (ERP) features in euthymic BD relating to differences in sensory processes, attention, inhibition and conflict monitoring compared with healthy controls. 911 unique articles were identified using the PubMed database and 14 studies met the inclusion criteria. Individuals with BD in a euthymic state have reduced P50 sensory gating and reduced P100 amplitudes compared with healthy controls. Many studies demonstrated reduced P300 amplitudes and normal P300 latencies in BD. In addition, reduced NoGo N2 and abnormal NoGo P3 activity were observed in BD. Finally, there is some evidence of reduced error-related negativity amplitudes in BD. Importantly, ERP modulations vary with stimulus factors and clinical profile. The functional significance of these findings and clinical implications are discussed. ERP differences in BD arise at various stages of cognitive processing, specifically in early auditory and visual processing, attention allocation, context updating, inhibition and conflict monitoring. Treating these deficits and their underlying neurobiological disturbances corresponding to abnormal performance on cognitive tasks may aid functional remission. This knowledge might enable personalized treatment interventions targeting specific cognitive deficits.

## **Introduction**

Bipolar disorder (BD) is a chronic psychiatric disorder characterized by recurring manic or hypomanic episodes and additional depressive episodes usually separated by periods of euthymic mood (APA 2013). Mood changes in BD are known to negatively impact cognitive performance, with evidence of cognitive abnormalities becoming more severe during manic and depressive episodes (Ferrier et al., 1999; Clark et al., 2002; Martinez-Aran et al., 2004). Disturbances in cognition affect social and occupational functioning of individuals (Green 2006; Malhi et al., 2007), with improvement in the quality of life and clinical symptoms associated with increased cognitive skills (Campanella 2013). Importantly, many neuro-cognitive abnormalities have been found to persist in euthymia, including difficulties with verbal memory, attention, executive functioning and psychomotor functioning (Arts et al., 2008; Bearden et al., 2001; Bora et al., 2009; Martinez-Aran et al., 2004). The presence of cognitive deficits during remission suggests that they are core symptoms of BD allowing for an investigation of abnormalities that may be related to the BD pathophysiology.

The identification of neural underpinnings relating to abnormal cognitive performance can be achieved through neuroimaging techniques such as fMRI, which has excellent spatial resolution (Turner and Jones 2003), allowing a broad identification of neural networks involved during specific tasks. Using fMRI in BD, differences amongst individuals in an elevated mood state compared to those in a euthymic state have been identified (see Kupferschmidt et al., 2011 for review). For example, hypo-activation of the dorsal attention network was demonstrated in euthymia compared with hyper-activation in mania (Brady et al., 2017). Persistent cognitive deficits in euthymia together with different neuronal patterns to symptomatic BD highlight the importance of identifying neurophysiological underpinnings in euthymic BD, as these may further our understanding of the pathophysiology of the disorder and have important implications for treatment strategies helping to achieve greater rehabilitation.

Unfortunately, brain activations using fMRI are averaged over seconds and are too slow to determine which specific brain activation is related to each cognitive stage involved in a task (Turner and Jones 2003). However, once cortical abnormalities have been identified via fMRI, more specific inferences can be made using electrophysiology on these components (Michel and Murray 2011). Electrophysiology, specifically

cognitive event related potentials (ERP), has the advantage of high temporal resolution (averaged over milliseconds), allowing different electrophysiological components to be observed, each representing distinct cognitive stages occurring during a task (Nunez 1981). ERP components may be considered biological markers of the disorder provided their features enable a distinction between BD and other disorders, indexing specific pathophysiological mechanisms that may or may not recover with illness remission.

In BD, ERP studies have mainly focused on early sensory processing, attention, inhibition and conflict monitoring in order to identify underpinnings related to the cognitive and behavioral deficits present in BD. The P50 is a positive component appearing 50 msec after stimulus presentation and reflects an early process of auditory perception (Picton, 1974). An early process of visual perception is reflected in the P100 which is elicited in response to visual stimuli and has a positive waveform occurring between 50-150 msec following stimulus onset (Desmedt et al., 1983). Other ERP components reflecting early sensory processing include the N100 and P200, a negative ERP component followed by a positive component, appearing 50-150 msec and 200 msec following stimulus onset respectively (Näätänen and Picton 1987). Tasks involving attention have been found to elicit the N200, a negative ERP deflection occurring 200-350 msec following stimulus presentation (Folstein and Van Petten 2008). The N200 is followed by a positive waveform P300 appearing 250-500 msec following stimulus onset which is elicited in response to the detection of rare or novel target stimuli amongst frequent stimuli, with amplitudes reflecting context and memory updating (Donchin and Coles 1988; Polich 2004) and latencies thought to reflect information processing speed (Duncan-Johnson and Donchin, 1977; Leuthold and Sommer, 1999). The NoGo N2 and NoGo P3 are two components reflecting inhibitory control (De Jong et al., 1990; Jonkman et al., 2003; Smith et al., 2006; Kok et al., 2004). The NoGo N2 is associated with conflict detection during early stages of the inhibition process (Nieuwenhuis et al., 2003) and the NoGo P3 reflects inhibition of the motor system (Kok et al., 2004). The ERN is a negative going component appearing 100-150 msec after an erroneous response, signifying the detection of an error or conflict between intended and actual response (Gehring et al., 1993; Falkenstein et al., 1990) and reflects conflict monitoring in the brain. This is followed by the Pe, a positive component occurring 150-400 msec following an error (Falkenstein et al., 2000; Van Veen and Carter, 2002;

Nieuwenhuis et al., 2001) and reflecting error awareness (Dhar et al., 2011; Endrass et al., 2012).

In an attempt to synthesize the findings in BD, a recent review of neurophysiological findings in BD was conducted (Onitsuka et al., 2013). Unfortunately, data specifically relating to ERP in euthymic BD was limited to two studies, with one discussing early sensory processing and the other attention (Sanchez-Morla et al., 2008; Fridberg et al., 2009). This underrepresentation of the data was likely due to the nature of the review. The authors included studies using a broad range of neurophysiological techniques including evoked and event related potentials, neural oscillation and synchronization and near-infrared spectroscopy studies, with the intention of reporting a general overview of major neurophysiological findings in BD (not specific to euthymia), rather than a systematic review of all ERP findings in BD. In addition, a number of studies have been conducted since 2013, warranting an updated review.

The interpretation of ERP findings is complicated by a number of confounding effects. Although individuals with BD in a euthymic state are clinically stable, the presence of low-level residual mood symptoms is common (Martinez-Aran et al., 2004). Elevated mood influences cognitive performance, which is reflected in ERP activity as well (Elliott 1998; Morsel et al., 2014; Kaya et al., 2007). In addition to residual symptoms affecting cognition and ERPs in euthymia, a lifetime history of psychosis (prevalent in 58% of BD I, see Goodwin 2007) seems to be responsible for poorer performance on neuro-cognitive tasks (Tabares-Seisdedos et al., 2003; Simonsen et al., 2009) and a greater number of ERP abnormalities (Olincy and Martin 2005; Lijffijt et al., 2009). A third potential confounding factor in the interpretation of ERP activity in BD is the influence of medication. Although it is unclear in which way medications impacts cognition and ERP, findings are limited with some studies demonstrating a decline in cognitive performance when taking antipsychotics and some evidence of lithium and antipsychotics enhancing cognition (Daglas et al., 2016; Yatham et al., 2017). In addition, while some studies did not demonstrate any influence of medication on ERP (Strik et al., 1998; O'Donnell et al., 2004) there is evidence of reduced ERP amplitudes in individuals taking benzodiazepines (de Bruijn et al., 2006), and further evidence of increased amplitudes in individuals taking lithium compared with those taking antipsychotics (Small et al., 1998).

The aim of the current article is to systematically review and evaluate visual and auditory ERP literature in euthymic BD compared with healthy controls. Studies investigating ERP components related to early sensory processing, attention, inhibition and conflict monitoring, are discussed. As ERP amplitudes and/or latencies may be modulated by residual mood, history of psychosis and medication, thereby confounding results, these factors are specifically examined in the reviewed articles. In addition, this review provides a critical discussion of limitations in the empirical literature as a guide for future investigations.

## **Methods**

### *Search strategy and selection criteria*

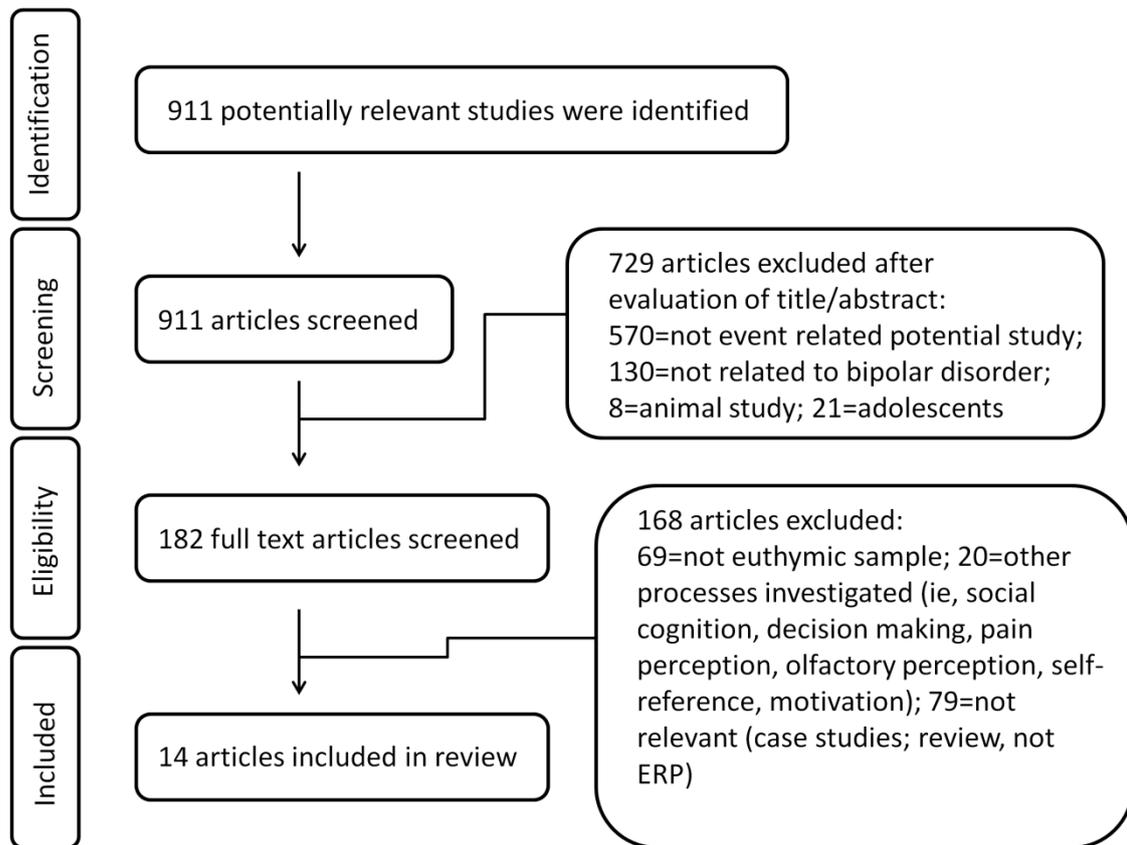
A systematic literature search was performed and article selection was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Figure 1 illustrates a flowchart of the study selection process. MEDLINE (via PubMed database) was searched in January 2018 using the search terms (bipolar disorder) AND ((ERP) OR (EEG) OR (event related potentials)) and the search was restricted to articles written in English. The search identified a total of 911 unique articles.

Articles were retained if they investigated neuro-cognitive processing and measured an ERP component in BD. Articles were included if they related to sensory processing, attention, inhibition or conflict monitoring and provided a statistical analysis of a comparison with healthy controls. In addition, studies were included if they used a sample of adults with BD who were in a euthymic state. Report of ERP component amplitudes or latencies was essential for inclusion.

Studies were excluded from the review if ERP measures were used to investigate any other processes other than cognitive impairment (i.e. sleep) or cognitive processes not specified in the aims of the review (for example, social cognition and decision making). Non-human studies were excluded as were studies that did not test adults. Case studies and reviews were also excluded.

All titles and abstracts were screened (by A.M.) to exclude any irrelevant studies. A total of 182 articles remained and these full text articles were read to determine if

they met the inclusion and exclusion criteria. In total, 14 studies met the search criteria and were reviewed in this paper. The following data was obtained from each of the selected studies: participant group and sample size, cognitive process, ERP component measured, topographical location, stimulus modality, task used, ERP amplitude and/or latency findings, relationship to mood, history of psychosis and medication.



**Figure 1:** Flow chart illustrating the steps taken in study selection

## Results and Discussion

Fourteen articles met the inclusion criteria. Table 1 presents an overview of task details and main findings of the studies reviewed and Table 2 presents an overview of demographic and clinical data of the samples investigated in each study. Amongst these 14 articles, a number of studies investigated ERPs relating to more than one cognitive process with 7 studies relating to sensory processing, 9 relating to attention, 3 studies

relating to inhibition and 2 relating to conflict monitoring. Results are reviewed and discussed according to the cognitive process under investigation.

### *Early sensory processing*

In the auditory modality, an indication of pre-attentive sensory processing can be seen as a positive peak occurring about 50 msec after the presentation of the stimulus, referred to as the P50, and is located at frontocentral regions of the scalp (Picton 1974). In terms of the stages of information processing, this component represents an early process of perception and is referred to as an 'exogenous' ERP component as it depends largely on the physical features of the stimulus. Paradigms used to elicit the P50 often use auditory clicks. In addition to P50 assessing early sensory processing, a second repetitive auditory stimulus (about 500 msec later), has been found to evoke a suppression of P50 waveforms compared with the first stimulus. A comparison of the amplitudes of the first conditioning stimulus (S1) and the second test stimulus (S2) (via their ratio or difference) can be used to measure sensory gating, a more complex stage of pre-attentive information processing. Sensory gating refers to habituation of repetitive input and requires an inhibitory response to the repetitive (or irrelevant) stimuli (Adler et al., 1982). The ability to block out irrelevant stimuli is critically important in navigating our sensory filled environment.

In the visual modality, the early exogenous ERP component P100 can be seen as a positive peak occurring about 50-150 msec after the presentation of a visual stimulus and is located at the occipital cortex.

Two other ERPs at an early stage of information processing are elicited following stimulus presentation regardless of stimulus modality; the negative peak N100 and positive peak P200. The N100/P200 components are interrelated and may reflect the convergence of sensory information (Näätänen and Picton 1987). In terms of the stages of information processing, these components may represent an integrative process of perception and attention and are referred to as mesogenous components (Picton and Stuss 1980). N100 occurs between 80 and 120 milliseconds following stimulus onset and is distributed over the fronto-central region of the scalp. It is elicited even in the absence of task demands and is larger when stimuli are new compared with repetitive or expected stimuli. The N100 is often followed by the P200 ERP which peaks

approximately 200 milliseconds after stimulus presentation and is distributed over the fronto-central and parieto-occipital regions of the brain. Evidence that the P50 does not always correlate with the N100 or P200 (Lijffijt et al., 2009) suggests that they represent different underlying mechanisms and may be differently affected in BD.

### *Main findings*

Two studies investigated auditory sensory gating in euthymic BD (Sánchez-Morla et al., 2008; Cabranes et al., 2013). A higher ratio of S2/S1 P50 amplitudes in BD was demonstrated reflecting reduced sensory gating compared with healthy controls. Cabranes and colleagues (Cabranes et al., 2013) additionally demonstrated deficits in S1-S2 difference gating which has been suggested to be more reliable than ratio gating (Dalecki et al., 2011). This implies that individuals with BD in a euthymic state have difficulties in the auditory modality inhibiting irrelevant pre-attentive sensory input. In addition, reduced P100 amplitudes were demonstrated in euthymic BD (Yeap et al., 2009) representing a dysfunction in early visual processing as well.

Individuals with BD in a euthymic state were found to have normal N100 amplitudes both in the auditory modality (Muir et al., 1991; Fridberg et al., 2009) and the visual modality (Bestelmeyer et al., 2012; Morsel et al., 2014). However, with respect to latency there is evidence of later N100s in euthymic BD (Muir et al., 1991) which reflects a disturbance of N100 timing. Early auditory processing in euthymic BD reflected by the P200 remains unclear with one study observing reduced P200 amplitudes (Fridberg et al., 2009) and another study demonstrating normal P200 amplitudes (Muir et al., 1991). It is possible that these reported differences may have been caused by differences in the BD subgroups tested (as Muir and colleagues (Muir et al., 1991) included some individuals with BD II).

There is no research on visual P200 in euthymic BD. However, in general there is little research on this component.

### *Clinical and medication influences*

Reduced sensory gating was not related to residual mood symptoms in euthymia (Cabranes et al., 2013). Two studies compared individuals with BD in a euthymic state to those in symptomatic states and did not find different N100 or P200 activity amongst the groups (Muir et al., 1999; Fridberg et al., 2009). Similarly, N100 amplitudes were not affected by residual mood symptoms (Morsel et al., 2014).

Taken together these findings suggest that mood symptoms, even mild residual symptoms, do not seem to influence these early ERP components. These findings extend results from a number of studies that investigated individuals with BD in manic and depressed states and did not find that reduced gating in BD was influenced by either manic or depressed symptoms (Lijffijt et al., 2009; Olincy and Martin et al., 2005; Schulze et al., 2007). Similarly, one study, investigating individuals with BD in manic and mixed mood states demonstrated comparable N100 and P200 amplitudes to healthy controls, suggesting that these components were not influenced by mood symptoms (O'Donnell et al., 2004).

Reduced sensory gating was demonstrated in euthymic BD with a history of psychosis (Sánchez-Morla et al., 2008) while those without a history of psychotic symptoms had normal sensory gating (Sánchez-Morla et al., 2008) or less significant reduction of gating (Cabranes et al., 2013). The influence of having a history of psychosis on P100 activity was not investigated (Yeap et al., 2009) and it did not appear to influence the N100 or P200 (Fridberg et al., 2009).

The suggestion that reduced gating in euthymia is related to a history of psychosis is in line with findings from studies that investigated individuals with BD in symptomatic states which also demonstrated that reduced gating is related to history of psychosis (Lijffijt et al., 2009; Olincy and Martin et al., 2005; Schulze et al., 2007). This suggestion is also in line with sensory gating abnormalities present in schizophrenia (see meta-analysis, Bramon et al., 2004). Schulze and colleagues (Schulze et al., 2007) suggested that reduced gating may underlie psychotic symptoms rather than be specific to BD. On the other hand, the findings of normal N100 amplitudes in euthymic BD are in contrast to the abundant evidence of reduced N100 in individuals with schizophrenia (see review, Onitsuka et al., 2013). O'Donnell and colleagues (O'Donnell et al., 2004) suggested that early sensory processing reflected by the N100 might differentiate these disorders and may be a biological index used to distinguish between BD and schizophrenia.

Medication (mood stabilizers, antidepressants, antipsychotics and benzodiazepines) did not appear to influence sensory gating (Sánchez-Morla et al., 2008; Cabranes et al., 2013), N100 or P200 activity in euthymia (Muir et al., 1991; Fridberg et al., 2009).

### *Attention*

In addition to difficulties in early sensory processing, there is evidence that individuals with BD in a euthymic state have deficits in sustained attention (Dickerson et al., 2004). This has important clinical implications for daily functioning, possibly affecting job maintenance and treatment compliance. The most commonly investigated ERP component in BD in relation to attention is the P300 (see Maekawa et al., 2012). This component is thought to reflect context and memory updating and generally P300 amplitude increases with the amount of attention allocated to the task (Donchin and Coles 1988; Polich 2004). P300 latencies on the other hand reflect information processing speed (Duncan-Johnson and Donchin, 1977; Leuthold and Sommer, 1999). In terms of the stages of information processing, these ERP components are 'later' stages requiring conscious attention and represent high-level cognitive processes. These more 'endogenous' components therefore reflect the cognitive demands of the task, irrespective of stimulus modality.

The P300 can be divided into two components, the novelty P3 (or P3a) and the classic P300 (or P3b) (Snyder and Hillyard 1976). The novelty P3 is elicited in response to orienting to novel events (independent of task relevance) (Kok 2001) and has a more frontal scalp distribution (Courchesne et al., 1975). The classic P300 is elicited in response to the detection of rare target stimuli presented amongst a train of frequent stimuli with a positive waveform occurring around 250-500 milliseconds after stimulus onset (Johnson, 1993), and is located at parietal regions of the scalp (Conroy and Polich 2007). Paradigms used to elicit the P300 often employ a traditional two-stimulus oddball paradigm, an attention task where subjects have to respond to infrequent target stimuli and not respond otherwise. In addition to the P300, attention tasks have been found to elicit an earlier component, the N200 which peaks around 200-350 msec after stimulus presentation and has been found to be generated at anterior sites (Folstein and

Van Petten, 2008). The majority of studies investigating attention reflected by P300 activity in individuals with BD have used the auditory modality.

### *Main findings*

The majority of studies investigating P300 in euthymic BD focused on P3b activity. While most studies found significantly reduced amplitudes in the auditory modality (Muir et al., 1991; Fridberg et al., 2009; Bestelmeyer et al., 2009; Bersani et al., 2015; Kaya et al., 2007), one study contradicted these findings and demonstrated comparable P3b amplitudes in euthymic bipolar disorder to healthy controls (Lahera et al., 2009). In the visual modality, two studies demonstrated comparable P3b in euthymic BD to healthy controls (Bestelmeyer et al., 2009; Bestelmeyer et al., 2012), while one study observed reduced P3b amplitudes (Morsel et al., 2014).

Regarding latencies, the majority of studies (Fridberg et al., 2009; Bestelmeyer et al., 2012; Bestelmeyer et al., 2009; Bersani et al., 2015; Kaya et al., 2007) excluding one (Muir et al., 1991) demonstrated normal P3b latencies (auditory and visual) in euthymic BD compared with healthy controls. It is important to note that task details and ERP measurements in the study of Kaya and colleagues (Kaya et al., 2007) are unknown, therefore the results need to be interpreted with caution.

Results of the studies suggest that information processing speed in euthymic BD appears to be intact, and memory and/or attention seems to be compromised. However, the exact implication of reduced P300 amplitudes in BD is under debate. Some say that this indicates a limitation of available resources (Linden, 2005), while others argue that it reflects a dysfunction in the ability to allocate these resources effectively (Wickens et al., 1983).

In an investigation of the P3a component, one study demonstrated comparable amplitudes to controls (Bestelmeyer et al., 2012). Four studies have investigated the N200 component in euthymic BD and observed normal N200 activity (Muir et al., 1991; Fridberg et al., 2009; Morsel et al., 2014; Michelini et al., 2016).

### *Clinical and medication influences*

It is possible that mood symptoms influence the ERP components relating to attention. In one study, individuals with BD in a euthymic state with residual depressive symptoms experienced larger P300 reduction (Kaya et al., 2007). On the other hand, a few studies comparing individuals with BD in a euthymic state to those in symptomatic states did not find any differences in N200 or P300 activity suggesting that mood state did not influence these ERP components (Muir et al., 1991; Fridberg et al., 2009)

Two studies compared individuals with BD in a euthymic state with a history of psychosis to those without (Fridberg et al., 2009; Lahera et al., 2009) and did not find any influence of having a history of psychosis on P300 activity. However, studies which directly compared individuals with BD in a euthymic state to healthy controls as well as individuals with schizophrenia found that the two psychotic disorders could not be differentiated based on P300 amplitudes and latencies (Muir et al., 1991; Bestelmeyer et al., 2009; 2012), suggesting that reduced P300 activity may be characteristic of all psychotic disorders rather than specific to individuals with BD. This is in line with the widely demonstrated findings of reduced P300 amplitudes in individuals with schizophrenia (see review Onitsuka et al., 2013).

It must be noted that reduced P300 amplitudes are seen in a wide range of disorders, for example depression, substance abuse, ADHD, PTSD (Roth 1981, Moeller et al., 2004; Verbaten et al., 1994; Metzger et al., 1997) and are not specific to psychotic disorders. However, the reasons behind reduced P300 amplitudes can be different. For example, amplitudes in the group average can be reduced because less attentional resources go into information processing. However, this may not be the case for all individuals and there may be great variability between individuals within the clinical spectrum. Likewise, another cause for reduced amplitudes in group comparisons can be high variability in latency within (trial-to-trial latency jitter) or between individuals of one group, which will lead to a reduction in amplitude in the group average. Furthermore, it is important to take topography into account, given that if an ERP component is more lateralized in one group, this will lead to artificially reduced amplitudes if the component is evaluated at single lead (e.g. P300 at Pz).

Unfortunately, only two studies investigating attention in euthymia using ERP investigated effects of medications (mood stabilizers, antipsychotics and

antidepressants) and did not find any drug influence on N200 or P300 activity (Muir et al., 1991; Fridberg et al., 2009).

### *Inhibition*

Behavioral deficits on neuropsychological tasks relating to inhibition are often demonstrated in BD. Difficulty to inhibit responses relates to impulsive behavior, a clinically observable phenomenon in BD and extreme manifestations of impulsivity impair everyday functioning and represent important targets for treatment interventions (Evenden, 1999; Moeller et al., 2001). Paradigms gauging inhibitory control, such as the Go/No-Go task, require subjects to respond to a visual stimulus on most trials and intermittently inhibit a prepotent response. On a neurophysiological level, an accurate reflection of inhibitory control is indexed by two distinct ERP components; the NoGo N2 and the NoGo P3 (De Jong et al., 1990; Jonkman et al., 2003; Smith et al., 2006; Kok et al., 2004). The NoGo N2 is associated with conflict detection during early stages of the inhibition process (Nieuwenhuis et al., 2003) and has been proposed to be generated in the anterior cingulate cortex (ACC) and inferior cingulate cortex (Lavric et al., 2004). The NoGo P3 is a later component reflecting actual inhibition of the motor system (Kok et al., 2004). 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).

### *Main findings*

Three studies have investigated ERPs relating to inhibition in euthymic BD, and findings remain inconclusive. One study, using a three stimulus oddball task that included elements of inhibition (subjects had to inhibit responses to a novel stimulus) and attention (P3b), demonstrated normal NoGo P3 amplitudes in euthymia (Bestelmeyer et al., 2012). This finding is in contrast to two other studies. One study (using a cued continuous performance test) demonstrated reduced NoGo N2 together with reduced NoGo P3 in euthymic bipolar disorder (Michelini et al., 2016) suggesting an overall aberrant inhibition process in BD. Another study using a Go/No-Go paradigm demonstrated marginally reduced NoGo N2 and *increased* NoGo P3 using a very simple

task (Morsel et al., 2017), suggesting that individuals with BD have difficulties in an early stage of conflict detection, but compensate for these difficulties at a later stage of the inhibition processes leading to normal performance.

These results may be related to methodological differences amongst the studies. While the NoGo P3 has been found to be more robust at fronto-central electrodes during inhibition (Bokura et al., 2001; Fallgatter et al., 1997; Tekok-Kilic et al., 2001), Bestelmeyer and colleagues (Bestelmeyer et al., 2012) focused their investigation at parietal sites, which may be the cause of the contradictory results. In addition, the tasks used in the studies varied in complexity possibly suggesting that when task demands are higher, individuals with BD are no longer able to compensate successfully, and this leads to reduced NoGo P3 and aberrant inhibition.

#### *Clinical and medication influences*

There was some evidence that symptom severity, specifically residual depression was related to reduced NoGo N2 activity, in line with evidence of a hypersensitivity to incorrectly responding in BD (Morsel et al., 2017). More research needs to be carried out to confirm effects of residual symptoms on ERP activity relating to inhibition in euthymic BD, especially residual manic symptoms as mania clearly exasperates impulsivity (Larson et al., 2005). It is important to note that in the study of Michelini (Michelini et al., 2016) only women were included. While there is no indication of gender differences in electrophysiological measures in BD, these results may not be representative of all individuals with BD. Unfortunately, the studies did not control for history of psychotic symptoms, which may influence the ERP components relating to inhibition just as it may influence the P50 and P300.

Medications, specifically benzodiazepines, were found to reduce the NoGo P3 (Morsel et al, 2017) and when effects of medications were controlled for, individuals with BD in a euthymic state demonstrated increased NoGo P3 activity. Thus, medications may have been the underlying cause of reduced NoGo P3 found in the study of Michelini and colleagues (Michelini et al., 2016).

## *Conflict monitoring*

Conflict monitoring is a cognitive control process of continuously evaluating one's performance and making subsequent behavioral adjustments to fit changing environmental demands. When an error is detected, it is important to correct performance. Abnormal error detection would result in a lack of monitoring performance and thereby result in seemingly impulsive behavior, a clinically observable phenomenon in BD (Najt et al., 2007). Conflict monitoring therefore has important implications for daily life functioning (Ullsperger, 2006).

The error-related negativity (ERN) also referred to as the error negativity (Ne) is thought to reflect error detection, an important aspect of conflict monitoring (Gehring et al., 1993; Falkenstein et al., 1990). The ERN manifests as a negative deflection in the ERP waveform that peaks 50-150 msec after error commission. Localization studies and fMRI imaging studies have shown that the ERN is generated in the anterior cingulate cortex (ACC) (Gehring et al., 1993; Dehaene et al., 1994) and is maximal at fronto-central electrodes (Gehring et al., 1995). The ERN is followed by a positive deflection known as the error positivity (Pe) which peaks 150-400 msec after an error is made (Falkenstein et al., 2000; Van Veen and Carter, 2002; Nieuwenhuis et al., 2001). Neural generators of the Pe have been localized in the ACC and insula (Dhar et al., 2011; Ullsperger et al., 2010) with maxima at central-parietal electrodes. As the Pe is enhanced when there is an awareness of errors, this component has been proposed to reflect conscious error perception (Falkenstein et al., 2000) and is triggered by the salience of errors (Dhar et al., 2011; Endrass et al., 2012).

## *Main findings*

While conflict monitoring using ERP measures has been extensively investigated in many major psychiatric disorders such as schizophrenia, depression and anxiety disorders (see Olvet and Hajcak 2008 for review), there is relatively little evidence regarding ERN (Morsel et al., 2014; Kopf et al., 2015) and Pe (Kopf et al., 2015) in euthymic BD. Using a flankers task, reduced ERN amplitudes (Morsel et al., 2014; Kopf et al., 2015) and normal Pe (Kopf et al., 2015) were found in BD subjects compared with

healthy controls, demonstrating that individuals with BD in a euthymic state have difficulties detecting errors, an important aspect of conflict monitoring.

#### *Clinical and medication influences*

Depressive symptoms were associated with increased ERN amplitudes. This was observed amongst individuals in a euthymic state who had residual depressive symptoms (Morsel et al., 2014) and amongst individuals with BD in a depressed state (Kopf et al., 2015). These findings are in line with evidence of increased ERN amplitudes in depression, which is indicative of hypersensitivity to errors in depression (Olvet and Hajcak 2008). Thus, there are likely additional state related influences on the ERN in addition to trait related ERN abnormalities.

One study observed that individuals with BD in a euthymic state with a history of psychosis did not have different ERN amplitudes compared with those without a history of psychosis (Morsel et al., 2014). Effects of medication do not appear to influence the ERN (Morsel et al., 2014; Kopf et al., 2015; Minzenberg et al., 2014).

#### *Limitations*

It is important to consider the limitations of the studies reviewed. These include methodological and publication biases, confounding variables that may have influenced ERP activity (such as bipolar subgroup and co-morbidities) and different aspects that make comparing studies difficult (such as employing different clinical profiles across studies or task differences). These limitations will be further discussed.

Firstly, there may be methodological bias amongst the studies, as unfortunately many employed very small sample sizes. Although it is not known if they are statistically underpowered (as none of the studies gave details as to how sample size was derived), underpowerment is very likely, as is the case in many neuroscience studies (Button et al., 2013). This leads to a high probability of random error with either a low chance of discovering effects or magnified effect sizes (Button et al., 2013). As such, many differences amongst the studies may be a result of this bias. It is also hard to generalize results from small studies. In addition, there may be a publication bias with published papers mostly reporting positive results. Unfortunately, it is difficult to access

unpublished papers and assess all results found, highlighting the great responsibility of researchers and journals to publish papers with null results in order to limit this bias.

Cognitive disturbances may be less severe in individuals with BD II compared with BD I, (Torrent et al., 2006), however, most studies did not take BD subgroup into account while analyzing ERP relating to cognitive disturbances in euthymia. Most studies investigated ERP in BD I or in mixed samples. However a few studies used separate BD I and BD II samples and did not find differences in ERP activity relating to sensory gating (Cabranes et al., 2013), P100 activity (including only 3 individuals with BD II: Yeap et al., 2009), N100 /P200 amplitudes (Muir et al., 1999) or P300 amplitudes (Muir et al., 1999; Bersani et al., 2015). In other words, although cognitive disturbances may be less severe in BD II, there is no neurophysiological evidence for differences in ERP activity between these subgroups.

In addition, co-morbidities such as substance abuse in BD are common (with some reports of more than 50%, see Cassidy et al., 2001) and the effects have not been adequately addressed. Only one study controlled for the effects of substance abuse (Fridberg et al., 2009) and did not find any effects of substance abuse on P300 activity. While many of studies excluded individuals with substance abuse in order to exclude possible influences on the interpretation of ERP, it is important for future studies to take co-morbidities, specifically substance abuse, into consideration as cognitive abnormalities and subsequent underlying ERP components may be influenced by this factor. For example, alcohol in low and moderate quantities affects ERN amplitudes (Easdon et al. 2005).

Individuals with different clinical profiles were included in most studies. This includes those with a history of psychosis and those without, those with residual symptoms, differences in illness duration and number of episodes. These factors may all influence both cognitive and ERP results and variability of controlling for these clinical factors across studies makes it difficult to directly compare results across studies. Presenting the data as a meta-analysis would have many benefits in quantifying the results, allowing an exploration of effects of different clinical factors and co-morbidities on ERP activity. Unfortunately, to date, there are too few studies investigating many ERP components in euthymia for a meaningful meta-analysis to be conducted. For example, only one sample of individuals with BD in a euthymic state has been used to investigate

sensory gating and only two studies were conducted investigating ERN reflecting conflict monitoring (Morsel et al., 2014, Kopf et al., 2015).

In addition to variability across subjects, the studies included employed different tasks, different variations/complexities of the tasks, different stimulus modalities and topographical locations. For example, in the investigation of P3b, both visual and auditory oddball tasks were conducted. Two studies required participants to count the oddballs while other studies required a button press. These differences add to the complexities in comparing results. The majority of studies investigating ERP in BD did not control for effects of medication. It is unclear how medication impact EEG; for example, there is some evidence that antipsychotics (haloperidol and olanzapine) and benzodiazepines reduce the ERN (De Bruijn et al., 2004; 2006). Therefore, the interpretation of ERPs may be complicated by medication effects. The numerous methodological differences amongst the studies make comparisons difficult and hamper interpretations of the results.

It must be noted that the subject samples used in the two investigations of sensory gating in euthymic BD (Sanchez-Morla et al., 2008; Cabranes et al., 2013) overlapped. Each study had a different aim; one was to compare BD with and without a history of psychosis with schizophrenia, and the other study aimed to compare BD I and BD II with healthy controls. It is not surprising that both studies demonstrated abnormal gating in euthymic BD. More studies are needed to confirm these results. Similarly, two studies (Bestelmeyer et al 2009; 2012) using different tasks and with different aims used the same sample of individuals with BD. Thus, there is less evidence of reduced P300 amplitudes than it appears.

#### *Summary of main ERP findings in euthymic BD*

Early studies investigated ERP components related to attention and early sensory processing. Abnormal sensory gating was found in euthymic BD, reflecting a difficulty in inhibiting irrelevant pre-attentive stimuli. Gating abnormalities in BD may be dependent on a history of psychosis. Reduced P300 amplitudes reflecting context and memory updating are also commonly observed in euthymic BD, and may be related to all psychotic disorders, not specifically BD. More recently there has been a shift in focus and studies have investigated ERP components relating to the executive control processes of

inhibition and conflict monitoring. Individuals with BD in a euthymic state demonstrated abnormal NoGo P3 activity relating to inhibition during an easy task. Lastly, reduced ERN amplitudes were demonstrated in euthymia reflecting difficulties detecting errors, an important aspect of conflict monitoring.

Identifying these ERP abnormalities that underlie cognitive abnormalities in euthymia suggest that these deficits may be related to the BD pathophysiology. This review highlights the numerous methodological differences across studies (such as using different clinical samples, tasks, and controlling for different confounding factors). It is important for future studies to take additional factors such as residual mood symptoms, history of psychosis and medication into account in order to compare different studies and integrate findings.

## **Conclusions**

Until recently the negative effects of cognitive dysfunction on psychosocial functioning were largely underestimated in individuals with BD in a euthymic state (Martinez-Aran et al., 2007). Clearly, individuals in remission continue to have very severe psychosocial difficulties due to cognitive deficits. Using electrophysiological measures in conjunction with cognitive tasks in BD enables direct measurement of brain activity during various stages of cognitive processing. Using this approach may largely increase our knowledge of underlying neurobiology relating to clinical symptoms in the hope of better treatment management. Abnormal ERP activity has been detected during various stages of information processing in euthymic BD, beginning with very early stages of sensory processing all the way to abnormalities in later cognitive processes.

In order to pinpoint underlying abnormalities, it is critically important to take into account any cascading effects of disrupted processing. For example, difficulties at very early stages (such as the inability to inhibit irrelevant pre-attentive sensory input) may lead to sensory overload and may underlie other abnormalities known to be present in BD such as aberrant attention (Dickerson et al., 2004). In fact, there is evidence of a direct relationship between reduced P50 gating and attentional difficulties in individuals with schizophrenia (Cullum et al., 1993; Guterman et al., 1994). Abnormal P50 gating may therefore underlie reduced P300 amplitudes in BD; however this inference needs to be made with caution as P50 and P300 have different topographical

locations (namely fronto-central and parietal respectively) and most studies focused their analyses on one specific location making comparisons difficult. Interestingly, difficulties in early pre-attentive sensory processing do not appear to influence information processing speed in BD (as normal P300 latencies have been observed).

#### *Clinical implications*

Evidence demonstrating difficulties during different levels of the information processing stream which are independent of one another has large implications for treatment. The knowledge gained from ERP studies of whether behavioral problems are perceptive, related to attention, inhibition or response related might enable personalized treatment interventions targeting specific cognitive deficits using 'ERP-oriented cognitive rehabilitation' in combination with medication and psychotherapy (Campanella et al., 2013) in order to improve the overall functional outcome of the individuals. ERP-informed cognitive rehabilitation can include an important interventional strategy of neuromodulation by brain stimulation using techniques such as repetitive Transcranial Magnetic Stimulation (rTMS) or transcranial direct current stimulation (tDCS). These non-invasive treatments stimulate brain tissue to induce currents which may normalize activity and have demonstrated cognitive improvement in individuals with psychiatric disorders (Guse et al 2010; Martis et al., 2003) and in healthy subjects (Mottaghy et al 1999; Boroojedi et al., 2001). Importantly, there is evidence of increased P300 amplitudes in euthymic BD following tDCS (Bersani et al., 2015).

In addition to ERP-guided treatment development and cognitive remediation, the clinical application of ERP may also have potential to increase diagnostic accuracy in terms of various stages of cognitive processing. For example, differences in N100 amplitudes may distinguish BD from schizophrenia, and normal P300 latencies demonstrated in BD (for example, Fridberg et al., 2009; Bersani et al., 2015) may be distinguished from commonly reported longer P300 latencies in unipolar MDD (see Olbrich and Arns 2013 for review of EEG in MDD). Further research is needed to investigate diagnostic utility and accuracy.

#### *Future developments*

Future research should focus on investigating the specificity of ERP abnormalities relating to cognitive processes occurring at later stages and their relationship to information processes occurring at earlier stages. For example, the relationship between P3b and P50 should be further investigated.

In addition, the specificity of ERP abnormalities to BD remains unclear. More studies are needed directly comparing individuals with BD in a euthymic state to those with other major psychiatric disorders such as schizophrenia and MDD.

It is also essential for future investigations to control for clinical differences, specifically residual mood and psychoses as these clearly modulate the ERP. While it is extremely difficult to control for effects of medication as all individuals with BD are on a wide range of medications, once ERP abnormalities have been identified, it may be beneficial to compare ERP activity in BD while taking different medications. As more ERP studies in euthymic BD are generated, it would be beneficial to conduct a meta-analysis allowing an exploration of effects of clinical variables, such as gender distribution, average age, medication, co-morbidity, history of psychosis, bipolar disorder type and residual mood symptoms. Including studies investigating individuals with BD in all mood states would additionally allow an exploration of the effects of mood episodes on the ERP.

Crucially, in BD the focus has been on information processing in the absence of emotionally salient contexts. There is still much to be learned from investigating information processing of emotional information or of neutral information within an emotional context (Malhi et al., 2005) in order to investigate the interaction between cognitive and emotional processing (Bush et al., 2000), which may in fact underlie differences at even the earliest stages of cognitive processing.

**Table 1:** Overview of task details and main findings of ERP studies in euthymic BD

Study	ERP investigated	Topographical location	Task	Modality	Frequent: infrequent stimulus ratio	ERP detection	Randomization	Feedback	Main finding
Bersani et al. (2015)	P3b	Fz, Cz, Pz	oddball task	auditory	4:0:1	largest peak + mean voltage	randomly presented	No	<P3b amplitudes in BD compared with control, normal P3b latency. BDI=BD II
Bestelmeyer et al. (2009)	P3b	FCz, Cz, Pz	oddball task	auditory and visual	4:0:1	largest peak	pseudo-randomized; each oddball trial followed by at least 3 standard stimuli	No	<P3b amplitudes in BD compared with controls (significant for auditory; a trend for visual)
Bestelmeyer et al. (2012)	N100, P3a, P3b	FCz, Cz, Pz	three-stimulus oddball task	visual	4:1:1 (infrequent =target oddball and meaningless distractor)	largest peak	pseudo-randomized; each target or distractor trial followed by at least 3 standard stimuli	No	BD = controls for P3a and P3b amplitudes; BD also = schizophrenia (who had <P3a, P3b amplitudes compared with controls)
Cabranes et al. (2013)	P50 sensory gating; S2/S1 ratio, S1-S2	N/A	paired click paradigm	auditory	N/A	largest peak	N/A	No	<P50 sensory gating in BD. BD I=BD II

Fridberg et al. (2009)	N100, N200 -- P200 -- P3b	Fz -- Cz -- Pz	oddball task	auditory	17:03	mean voltage	randomly presented	No	Euthymic BD =N100 amplitudes; <P200 amplitude, = N200 amplitude; <P300 amplitudes and longer latencies compared with controls
Kaya et al. (2007)	P3b	N/A	oddball task	auditory	N/A	N/A	N/A	No	<P3b amplitudes in BD previously depressed patients; = P3b latency in both groups. Residual mood influences P300
Kopf et al. (2015)	ERN -- Pe	Fcz, Cz -- Cz,Pz	Eriksen flankers task	visual	1:01	largest peak	randomly presented	visual feedback (emotional or neutral); late, error or correct	<ERN and =Pe in BD euthymia compared with controls (for errors)
Lahera et al. (2009)	P3b	Pz	oddball task	auditory	4:01	largest peak	randomly presented	No	BD=controls for P3b amplitudes and latency
Michelini et al. (2016)	NoGo N2, NoGo P3	Fz,Cz	cued CPT	visual	1:01	mean voltage	pseudo-randomization; cue-Go or cue-NoGo	No	<NoGo N2 amplitude, <NoGo P3 amplitude in BD compared with controls
Morsel et al. (2014)	ERN,N1,N2 -- P3b	FCz -- Pz	Eriksen flankers task	visual	1:01	largest peak	randomly presented	visual feedback; late, error or correct	<ERN amplitude in BD compared with controls

Morsel et al. (2017)	NoGo N2, NoGo P3	FCz, Cz	Go/NoGo task	visual	7:03	largest peak	pseudo-randomized, each NoGo trial followed by at least 3 Go stimuli	No	marginally reduced NoGo N2 amplitudes, <NoGo P3 amplitudes in BD compared with controls
Muir et al. (1991)	P3b, N100, P200, N200	Cz	oddball task	auditory	9:01	largest peak	randomly presented	No	<P3 amplitude, <P3 latency in BD compared with controls
Sanchez-Morla et al. (2008)	P50 sensory gating S2/S1 ratio and S2	Cz	paired click paradigm	auditory	N/A	largest peak	N/A	No	< P50 gating in BD; specifically with history of psychosis
Yeap et al. (2009)	P1	occipital and parietal	Go/NoGo task	visual	1:01	mean voltage	randomly presented	No	<P1 amplitude in BD

**Table 2:** Overview of demographic and clinical variables of the samples investigated in ERP studies in euthymic BD

Study	Participants	Gender (%Male)	Mean age (SD)	BD subtype	History of psychosis
Bersani et al. (2015)	10 BD euthymic 10 control	BD: 40% control: 40%	BD I: 47.2 (8.9) BD II: 48.5 (14.3) control: 46.2 (13.1)	10 BD I 10 BDII	N/A
Bestelmeyer et al. (2009)	19 BD euthymic 21 schizophrenia 35 control	BD: 37% Control: 46%	BD: 49.2 (10.6) control: 37.4 (11.9)	all BD I	N/A
Bestelmeyer et al., (2012)	19 BD euthymic 21 schizophrenia 19 control	BD: 37% Control: 46%	BD: 49.2 (10.6) control: 37.4 (11.9)	all BD I	N/A
Cabranes et al. (2013)	126 BD euthymic 95 control	BD: 44%, control: 48%	BD I: 43.5 BD II: 45.8 control: 42.4	100 BD I 26 BDII	81 BD I history of psychosis 19 BD I no history of psychosis
Fridberg et al. (2009)	62 BD euthymic 49 BD symptomatic 52 control	BD: 40% Control:46%	BD: 42.7 (12.8) control: 40.7 (11.6)	all BD I	8 history of psychosis 54 no history of psychosis/unknown
Kaya et al. (2007)	23 BD euthymic (previous episode manic) 20 BD euthymic (previous episode depressive) 22 control	BD: 56%, control 63%	BD last episode mania:36.6 (13.2) BD last episode derpression:40 (14) control: 35.5 (8.1)	all BD I	N/A
Kopf et al. (2015)	20 BD depressive episode 9 followed up when euthymic 20 control	BD whole sample: 55% control: 33%	BD: 44.3 (9.5) control: 44.2 (11.9)	9 BD I 11 BD II (not clear which ones were euthymic)	N/A
Lahera et al. (2009)	24 BD euthymic 38 control	BD: 41%, Control: 62%	BD: 43.9 (11.5), control: 48.9 (13.2)	all BD I	14 history of psychosis 10 no history of psychosis
Michellini et al. (2016)	20 BD euthymic 20 ADHD 20 control	All female	BD: 40.3 (7.7), control: 36.7 (4.3)	all BD I	N/A
Morsel et al. (2014)	16 BD euthymic 14 control	BD: 55%, control: 42%	BD: 46.9(10.8), control: 41.7 (14.6)	all BD I	N/A
Morsel et al. (2017)	20 BD euthymic 18 control	BD: 50%, control: 40%	BD:44 (12.1) control: 42 (15.1)	all BD I	N/A

Muir et al. (1991)	20 BD euthymic 14 BD depressed 24 BD manic 96 schizophrenia 46 MDD 213 control	BD whole sample: 61% control: 58%	BD: 35.2 (12.0) control: 30.5 (11.7)	75 BDI 13 BD II	N/A
Sanchez-Morla et al. (2008)	81 BD euthymic 92 schizophrenia 67 control	BD history of psychosis: 43%, BD no history of psychosis: 43% control: 66%	BD with history of psychosis: 44.7 (11), BD no history of psychosis: 46.6 (12) control: 43.8 (11.2)	No mention	51 psychosis 30 no psychosis
Yeap et al. (2009)	12 BD euthymic 12 control	BD: 50%, control: 58%	BD: 47.8 (12), control: 46 (12.7)	9 BD I 3 BD II	N/A

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