COGNITIVE EVENT-RELATED POTENTIALS IN PSYCHOPATHOLOGY: NEW EXPERIMENTAL AND CLINICAL PERSPECTIVES

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COGNITIVE EVENT-RELATED POTENTIALS IN PSYCHOPATHOLOGY: NEW EXPERIMENTAL AND CLINICAL PERSPECTIVES

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EDITORIAL
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Editorial: Cognitive Event-Related Potentials in Psychopathology: New Experimental and Clinical Perspectives

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The Editorial on the Research Topic

Cognitive Event-Related Potentials in Psychopathology: New Experimental and Clinical Perspectives

A common feature of many psychopathological states (going from anxiety, depression to schizophrenia, or addictive states) is to be associated with large-scale cognitive impairments, which have a clear impact on the onset and maintenance of clinical symptoms (Menon, 2011). Therefore, studies have shown that the training and rehabilitation of cognitive skills lead to positive effects on patients' quality of life, centrally by decreasing the severity of these clinical symptoms (e.g., Pilling et al., 2002). However, beyond patent cognitive impairments, some minor cognitive restrictions can also be present and, even if not observable at the behavioral level, may induce a state of "vulnerability" that can, in some circumstances, facilitate the persistence of the psychopathology (Levit Binnun and Golland, 2012). In alcohol-related disorders for example, it is well-known that, despite a well-structured detoxification treatment encompassing psychiatric, psychological and pharmacological therapies, 50–90% of patients will relapse or restart consuming alcohol in the year following detoxification (Boothby and Doering, 2005). In this view, it appears urgent to find biological markers which can go beyond classical behavioral assessment to detect even minor cognitive alterations. These new tools would help clinicians to identify which patients are more at-risk to develop or extend psychopathologies, and would thus significantly improve treatment through best suited medication as well as specialized and individualized cognitive rehabilitation programs (Campanella, 2016).

In this topic, our aim is to illustrate how and why cognitive event-related potentials (ERPs) may help, across various psychopathological populations, to specify the neuro-cognitive alterations presented by each patient in order to adapt the treatment. With this in mind, different authors will describe how ERPs may be helpful to better understand the pathophysiological mechanisms involved in diverse mental diseases and to adapt the therapeutic proposals accordingly. In this view, discriminating early and late ERPs modifications is thought to be of the greatest relevance in child psychopathology (Chronaki). A major focus on ERP correlates of attentional control is presented as a crucial aspect in child social anxiety (Wauthia and Rossignol). It is also suggested to include self-referential negative contexts when studying ERP correlates of adult social anxiety (Wieser and Moscovitch), while Cao et al. proposed a major focus on social feedback processes. Combining cognitive training and neuromodulation is also thought to have a positive impact on ruminations in major depression by increasing ERPs subtending inhibitory processes (Monnart et al.). Electroencephalogram (EEG) is also presented as a useful tool to predict outcome treatment

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in obsessive-compulsive disorders (Krause et al.). Moreover, Brion et al. suggested that ERPs may help to differentiate the successive steps, envisaged as a continuum, leading patients from an addictive state (alcohol-dependence) to Korsakoff syndrome. Finally, combining ERPs with hemodynamic data may help to better tag to pathological emotional disturbances indexing schizophrenia (Balconi et al.).

Overall, the rationale of this approach is that a better understanding of the underlying brain neurophysiological activities, by means of ERPs which are a quite cheap and easy to implement tool, could be highly useful to clinicians to install a best suited individualized treatment (specifically addressing the individual deficits of the patient). Two other papers finally propose to go one step further by presenting new "perspective" tools offering innovative possibilities to further extend the understanding of the electrophysiological correlates of psychopathological states. First, Karch et al. shed light on the measurement of neural oscillations to enlight the understanding of intentional actions. Second Schröder et al. suggest that the "bimodal" P300 component could offer an interesting add-on tool in a near future to enhance our understanding of the pathophysiology subtending mental diseases. We thus hope that this research topic will simultaneously illustrate: (1) *what can already be done*, i.e., the direct potential outcomes that can be expected right now from developing the use of electrophysiology in clinical psychopathology; (2) *what will soon be possible*, particularly following the development of new methodological and experimental proposals which will offer new perspectives for clinicians.

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All authors listed have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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MINI REVIEW
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Event-Related Potentials and Emotion Processing in Child Psychopathology

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In recent years there has been increasing interest in the neural mechanisms underlying altered emotional processes in children and adolescents with psychopathology. This review provides a brief overview of the most up-to-date findings in the field of event-related potentials (ERPs) to facial and vocal emotional expressions in the most common child psychopathological conditions. In regards to externalizing behavior (i.e., ADHD, CD), ERP studies show enhanced early components to anger, reflecting enhanced sensory processing, followed by reductions in later components to anger, reflecting reduced cognitive-evaluative processing. In regards to internalizing behavior, research supports models of increased processing of threat stimuli especially at later more elaborate and effortful stages. Finally, in autism spectrum disorders abnormalities have been observed at early visual-perceptual stages of processing. An affective neuroscience framework for understanding child psychopathology can be valuable in elucidating underlying mechanisms and inform preventive intervention.

Keywords: ERPs, emotion, children, adolescents, psychopathology

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INTRODUCTION

The worldwide prevalence of mental disorders in children and adolescents is about 13% and continues to rise (Polanczyk et al., 2015). As the majority of adult mental health disorders begin in childhood and adolescence, it is important to gain a better understanding of the causal mechanisms as well as the factors reducing risk and increasing resilience in the young to help develop effective prevention strategies. In the recent years, there has been a renewed interest in emotion dysregulation as a mechanism increasing the risk for a range of psychopathological conditions (Kret and Ploeger, 2015). Understanding the neurobiology of emotion processing in child psychopathology can advance knowledge of underlying mechanisms and aid the identification of intervention targets (Pine, 2007).

Understanding other's emotions is critical in social interaction. Theoretical debates have focused on whether brain structures are specialized for processing social information or whether social cognition is part of general cognitive processes applied to social behavior (Adolphs, 2009). Empirical research has supported the proposal that there is a network of specific brain areas preferentially involved in the processing of social information, a network often referred to as the 'social brain' (Brothers, 1990; Johnson et al., 2005; Adolphs, 2009). Developmental psychology has demonstrated that the ability to understand other's feelings and mental states develops in the first 4 years of life (Frith and Frith, 2003). Developmental neuroscience frameworks can be valuable

for the study of emotion processing. Development provides a unique opportunity to study the neural correlates of emotion processing as they emerge at different ages (De Haan et al., 2003; Grossmann et al., 2007). This approach can provide answers to the question of 'when' the developing brain begins to become 'tuned' to its social environment. Event-related potentials (ERPs) represent a useful, non-invasive methodology to understand the timing (in a millisecond resolution) of the sensory, perceptual, and cognitive processes underlying social information processing (Nelson and Luciana, 2001). As neural substrates implicated in social processing become more specialized over development (Johnson et al., 2009), ERPs can inform our understanding of whether neurally separate components have the potential to be specialized for processing emotional information (De Haan and Gunnar, 2009). Finally, ERP methods are useful in conceptualizing not only typical but also atypical development as they can reveal individual differences which may not be evident in observable behavior. Developmental transitions in particular, such as early childhood and adolescence, represent important landmarks in mental health trajectories and are accompanied with a unique set of opportunities and challenges (Blakemore, 2010) which overlap with important neurobiological changes in emotion processing.

This mini-review aims to briefly summarize the ERP components implicated in facial and vocal emotion recognition in typical and atypical development. For this mini-review, computerized searches of articles published until 2015 were conducted using the PubMed, Psycinfo, Science Direct and Nature journals online databases. The following terms ERPs, facial, vocal, emotion recognition, child, adolescent, psychopathology, externalizing, internalizing, ADHD, CD, ASD, anxiety, depression, were entered into the databases. In addition, the table of contents of journals that often publish articles relevant to this topic were reviewed including Journal of Child Psychology and Psychiatry, Frontiers in Neuroscience, Human Brain Mapping, Biological Psychiatry, Nature Neuroscience, Developmental Science, Social Neuroscience and American Journal of Psychiatry. Finally, the reference lists of relevant articles were scanned for pertinent studies. Only studies written in English were included (see **Table 1**).

TYPICAL DEVELOPMENT

Theoretical models for recognizing facial emotional expressions emphasize that conceptual knowledge of emotion signaled by the face is preceded by early perceptual processes by salient stimuli (Bruce and Young, 1986; Haxby et al., 2000). The N170 is an occipitotemporal potential traditionally linked to sensitivity in processing information from human faces (Bentin et al., 1996; Taylor et al., 1999). Some studies have shown that the N170 is sensitive to facial emotion in adults (Batty and Taylor, 2003; Blau et al., 2007), although other studies have not found facial emotion modulation of the N170 (Eimer and Holmes, 2002; Herrmann et al., 2002; Eimer et al., 2003). Infant research has identified the N290 as a developmental precursor to the adult N170 (Halit et al., 2003, 2004). Emotion effects on the N170 have been observed in older (14–15-years-old) compared to younger (4–12-years-old) children, with N170 amplitudes being larger for negative (anger, sad) compared to positive (happy) and neutral faces in emotion recognition tasks (Batty and Taylor, 2006). Compared to the N170 proposed to index 'fine-grained' sensitivity to facial emotion emerging during adolescence, a parietal–occipital P1 component (∼120 ms) has been suggested to reflect global and 'superficial' processing of facial emotion that is present in younger children (Batty and Taylor, 2006; Vlamings et al., 2010). Beyond early components, later components such as the late positive potential (LPP), a parietal–occipital component evident from around 300 ms, show sensitivity to the emotional content of human faces and are proposed to signify elaborative or effortful processing of emotionally significant stimuli in healthy adults (Hajcak et al., 2010). The LPP has been shown to be sensitive to facial emotion in children. In particular, the LPP was larger in amplitude to angry compared to happy faces in 7-year-old children in emotion recognition tasks (Kestenbaum and Nelson, 1992) and sad compared to neutral faces at occipital areas in 6-year-old children in a passive viewing paradigms (Kujawa et al., 2012).

Despite a number of studies using facial stimuli, considerably less is known about the neural development of vocal emotion processing. This is surprising given the prominent role of vocal emotional expressions in children's social interactions. Brain potentials in response to voice compared to non-voice sounds emerge between 160 and 200 ms on frontocentral (positivity) and occipital (negativity) sites in healthy adults (Charest et al., 2009). This suggests that the neural processing of voices and faces ('face-specific' N170) occur at similar time points explaining the integration of such signals in real-life social interactions (Campanella and Belin, 2007). In healthy adults, the recognition of emotion from vocal signals (i.e., 'prosody') is represented in the brain by a series of ERP components. According to a three-process model of emotional prosodic-processing, a temporal N100 component is suggested to reflect early sensory processing of vocal expressions, followed by a P200 component, proposed to reflect integration of prosodic acoustic cues and finally, frontal late latency components (i.e., P300, N400) reflecting cognitive-evaluative judgments such as labeling emotional expressions (Schirmer and Kotz, 2006). In adults, vocal emotion effects have consistently been observed in the N400 component (Bostanov and Kotchoubey, 2004; Paulmann and Kotz, 2008). The human brain begins to become sensitive to vocal signals of emotion from the first months of life (review by Grossmann and Johnson, 2007). Despite a number of infant studies, very little is known about the neural development of vocal emotion processing in childhood. In typically developing 6–11-year-old children differential ERPs to distinct vocal expressions of emotion (angry, happy, and neutral) have been identified in an emotion recognition task (Chronaki et al., 2012). These consisted of an early, N100 (90–180 ms) and a later, N400 (380–500 ms) component observed in more posterior (parietal–occipital) regions compared to adults (Chronaki et al., 2012). Further research is needed in the neural development of vocal emotion processing in children and adolescents.

TABLE 1 | A summary of empirical findings of altered ERP responses to facial and vocal emotional stimuli in children and adolescents with psychopathology.

Psychopathology type	*n*	Age (Years)	Sample	Task	Emotion	ERP effect
ADHD						
Facial cues						
Williams et al., 2008	51 ADHD 51 controls	8–17	Clinical	Emotion recognition	A, H, S, F, Di, N	↓ P120, ↑ N170, ↓ P300 amplitudes to anger in ADHD
Chronaki et al., 2010	41 children	6–11	Community	Emotion recognition	A, H, N	↓ Slow Wave to anger with increased hyperactivity
Tye et al., 2014	18 ADHD 26 controls	8–13	Clinical	Emotion recognition	A, H, F, Di, N	Reduced fear and happy N400 modulation in ADHD
Köchel et al., 2014	16 ADHD 16 controls	8–12	Clinical	Emotional Go/NoGo	A, H, S, N	↓ P300 amplitude in ADHD
Vocal cues						
Chronaki et al., 2015a	25 ADHD 25 controls	6–11	Clinical	Emotion recognition	A, H, N	↑ N100 amplitude to anger in ADHD
Conduct disorder						
Vocal cues						
Hung et al., 2013	20 CD 20 controls	13–19	High-secure offenders	Oddball Neutral-'standards' Fear/sad-'deviants'	F, S, N	↑ MMN amplitude to fear in CD
Anxiety and depression						
Facial cues						
DeCicco et al., 2012	32 children	5–7	Community	Reappraisal	Pleasant, unpleasant, N	↑ LPP amplitude to unpleasant in high anxiety
Solomon et al., 2012	39 children	5–7	Community	Passive viewing	Pleasant, unpleasant, N	↑ LPP amplitude to unpleasant in fearful Children
Kujawa et al., 2015	53 Anxiety 37 controls	7–19	Clinical	Emotional face-matching	A, H, F, N	↑ LPP amplitude to anger and fear in anxiety
Autism spectrum disorder						
Facial cues						
Dawson et al., 2004	29 ASD 22 controls	3–4	Clinical	Emotion recognition	F, N	No emotion N300 and NSW modulation in ASD
Batty et al., 2011	15 ASD 15 controls	5–16	Clinical	Implicit emotion processing	A, H, S, F, Di, Sur, N	↑ P1 and N170 latency across emotions in ASD
Wagner et al., 2013	18 ASD 20 controls	13–21	Community (with ASD diagnosis)	Passive viewing	A, F, N	No emotion P1 and N170 modulation in ASD
Apicella et al., 2013	10 ASD 12 controls	6–13	Clinical	Passive viewing	H, H, N	↓ P1 and N170 amplitude ↑ P1 and N170 latency in ASD
Tye et al., 2014	19 ASD 26 controls	8–13	Clinical	Emotion recognition	A, H, F, Di, N	↓ N170 amplitude across emotions in ASD
Vocal cues						
Chin-hsuan, 2011	23 ASD 23 controls	NA	Clinical	NA	A, H	↓ MMN amplitude to anger in ASD
Korpilahti et al., 2007	13 Asperger syndrome 13 controls	9–12	Clinical	Passive oddball Happy-'standard' Angry – 'deviants'	A, H (tender)	↑ N100 and MMN latency across emotions in Asperger
Multimodal						
Lerner et al., 2013	34 ASD No controls	10–16	Clinical	Emotion recognition	A, H, S, F (faces and voices)	N100 and N170 latencies were positively correlated with emotion recognition errors in ASD

A, anger; H, happy; S, sad; F, fear; Di, disgust; Sur, surprise; N, neutral. ERP effects relate to findings in the experimental group (i.e., ADHD).

ATYPICAL DEVELOPMENT

An emerging body the ERP literature supports the idea that sensory, perceptual, and cognitive processing stages of emotion recognition may be altered in children with psychopathology. The section that follows reviews some landmark studies in children with externalizing and internalizing problems and autism spectrum conditions.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity (Americal Psychiatric Association [APA], 2013). Motivational processes (Sonuga-Barke and Fairchild, 2012) are implicated in ADHD and emotion dysregulation is recognized as an important clinical feature of the condition (Shaw et al., 2014; Bunford et al., 2015).

Although, some theories suggest that emotion processing difficulties in children with ADHD may result from general inattention or impulsiveness, socio-cognitive models have argued in favor of emotion-specific difficulties (review by Uekermann et al., 2010). Behavioral studies have shown that individuals with ADHD present deficits in the recognition of emotions (especially negative emotions) from facial expressions (see Uekermann et al., 2010) and that these deficits can be independent of cognitive functions such as attention (Bisch et al., 2016) and performance in non-emotion tasks (Rapport et al., 2002). Emotion recognition deficits are associated with behavior problems already in preschool (Chronaki et al., 2015b) and school-aged children (Pelc et al., 2006; Yuill and Lyon, 2007). ERP correlates of these deficits have only recently been identified. Adolescents with ADHD have been shown to display reduced occipital P120, followed by increased N170 and reduced temporal P300 amplitudes to anger and fear in a facial emotion recognition task (Williams et al., 2008). These findings may suggest reduction in occipital activity during the early perceptual processing of anger (120 ms), followed by increased activity during structural encoding stages (∼170 ms) and later reduction in temporal activity reflecting context processing of anger (∼300 ms). Similarly, hyperactivity was negatively associated with occipital Slow Wave amplitudes to facial anger in an emotion recognition task in a community sample of 6–11-year-old children (Chronaki et al., 2010). Similar work has shown that impairments in response inhibition to angry faces have been associated with reduced P300 amplitudes in a Go/Nogo task in boys with ADHD compared to controls (Köchel et al., 2014).

The only ERP study to date using vocal stimuli has shown enhanced N100 and attenuated P300 amplitudes to vocal anger in 6–11-years-old with ADHD in an emotion recognition task using pure prosodic stimuli (Chronaki et al., 2015a). The N100 effect persisted after excluding children with comorbid Conduct Disorder. This pattern of results possibly reflects hyper-vigilance to vocal anger in ADHD at early and almost automatic processing stages consistent with an automatic and less controlled processing style in ADHD (Oades et al., 1996). These findings are consistent with near-infrared spectroscopy work showing stronger supramarginal gyrus activation to sentences with angry intonation in children with ADHD (Köchel et al., 2015) and functional magnetic resonance imaging (fMRI) work showing enhanced frontal and posterior cingulate cortex activation to anger from facial expressions in 10–17-years-old with ADHD compared to controls (Marsh et al., 2008). Results should be interpreted in the context of recent conceptual models of emotional dysregulation in ADHD involving a circuitry underpinning deficits in rapid early orienting to emotion (i.e., ventral striatum, amygdala; Shaw et al., 2014).

CONDUCT DISORDER

Conduct disorder (CD) is a condition at the severe end of a continuum of oppositional defiant behaviors (Americal Psychiatric Association [APA], 2013). The majority of studies in emotion processing in CD and associated conditions have employed behavioral and fMRI methods and have shown pervasive deficits in the recognition of a range of emotions from facial and vocal modalities (meta-analysis by Dawel et al., 2012). A recent ERP study has shown that young offenders with CD displayed stronger mismatch negativity (MMN) to fearful syllables in a passive listening task with no difference found in controls. This findings may reflect enhanced pre-attentive auditory change detection for distressful stimuli in youth with CD (Hung et al., 2013). Despite methodological differences, these results are generally inconsistent with evidence from behavioral (Blair et al., 2005; Dadds et al., 2008; Fairchild et al., 2009) and functional neuro-imaging (Jones et al., 2009) studies which show *reduced* sensitivity to fearful facial expressions in active-attention tasks. These findings should be considered in the context of theoretical frameworks suggesting that failure to inhibit antisocial behaviors may be the result of lower sensitivity to distress-related cues from others such as fear (Blair, 2001).

There is a striking lack of empirical studies on the temporal processing of emotion in youth with CD. Further research is necessary before drawing any conclusions. In addition, given the high rates of comorbidity between CD and ADHD, future research should examine the electrophysiological correlates of emotion processing in ADHD, ADHD+CD, and CD to clarify the role of common or distinct neural pathways.

ANXIETY AND DEPRESSION

The experience of negative affect (i.e., anxiety and depression) in children and adolescents has been closely associated with emotion processing (Hadwin and Field, 2010). Behavioral work in this area has predominantly been guided by theoretical frameworks of attentional biases to threat (Bar-Haim et al., 2007). The ERP literature points to the direction of enhanced neural response to threat (i.e., anger) stimuli in anxious children, as reflected by larger amplitudes of the LPP component, proposed

to reflect elaborative or effortful processing of emotional stimuli (Schupp et al., 2000; Hajcak et al., 2010). Recently, Kujawa et al. (2015) found that relative to healthy controls, 7–19-year-old diagnosed with social anxiety, separation anxiety, and generalized anxiety disorders showed enhanced LPP amplitudes to angry and fearful faces during an emotional face-matching task. This is consistent with earlier research using pictorial stimuli which has found increased processing of unpleasant compared to neutral pictures (reflected by the posterior LPP amplitudes) in a community sample of 5–7-year-old with high anxiety (DeCicco et al., 2012). Similar results have been found in 5–7-year-old children with inhibited and fearful behavior (Solomon et al., 2012). ERP research in emotion processing in childhood depression is more limited. In the study by Kujawa et al. (2015), higher depressive symptoms were associated with reduced LPP amplitudes to angry faces in 7–19-years-old diagnosed with an anxiety disorder (Kujawa et al., 2015). Results partly support adult studies linking depression to blunted or reduced emotional response (as reflected by the LPP), consistent with theories suggesting disengagement from emotional stimuli more generally in depression (Proudfit et al., 2015). In summary, preliminary findings support the LPP as a neural marker of neurobiological vulnerability to threat in childhood internalizing symptoms. Future work should aim to disentangle the role of anxiety and depression in the neural processing of threat and explore whether existing effects generalize to vocal modalities.

AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) refers to a range of conditions characterized by impairment in social interaction and communication (Americal Psychiatric Association [APA], 2013). Children with ASD find social stimuli less salient than non-social stimuli (Stavropoulos and Carver, 2014) and present difficulties in recognizing other people's emotions (see meta-analysis by Uljarevic and Hamilton, 2013). However, not all studies have supported emotion processing deficits in ASD (Jones et al., 2011). Further, it is not clear from behavioral studies whether existing deficits are emotion-specific or whether they are secondary to domain-general processing abnormalities (i.e., attention, sensory-perceptual processing).

Event-related potentials research has partly supported an atypical pattern of facial emotion processing in ASD. Typically developing 3–4-years-old displayed larger N300 amplitudes to fearful than neutral faces, while children with ASD did not show this effect in a passive viewing task (Dawson et al., 2004). Similarly, the amplitude of the face-sensitive N170 component varied with emotional expression only in typically developing adolescents aged 13–21 but not in adolescents with ASD who showed reduced neural differentiation between angry, fearful, and neutral facial expressions in a passive viewing task (Wagner et al., 2013). In an implicit emotional task, 10-years-old children with autism displayed longer P100 and N170 latencies and smaller P100 amplitudes to facial expressions of emotion including anger, disgust, happiness, sadness, surprise and fear. In this study, only the P1 amplitude remained affected in autism, after children with autism were matched by verbal equivalent age to controls, suggesting abnormalities at early stages of rapid visual perceptual processing (Batty et al., 2011). These findings are consistent with a slowed neural speed of face processing (McPartland et al., 2004) already present at 3 years in ASD (Webb et al., 2006). Recent research has shown that relative to controls, 6–13 years-old with ASD presented delayed latencies and reduced amplitudes of early components (P100, N170) regardless of emotion type in an implicit face-perception task whereby children viewed fearful, happy, and neutral faces and were asked to press a button when a cartoon stimulus was presented (Apicella et al., 2013). Results are consistent with fMRI work showing no impairments in the cognitive labeling of basic facial emotions in adolescents with ASD (Wang et al., 2004). More recently, children with ASD and comorbid ADHD have been shown to display reduced N170 amplitude across a range of facial emotions and particularly for fearful compared to neutral expressions in an emotion discrimination task (Tye et al., 2014), confirming work showing abnormalities at an early structural encoding processing stage.

Few studies have investigated the neural processing of vocal emotion in children with ASD, although recent infant fMRI work suggests that some infants at high-risk for ASD may present atypical neural responses to emotional (i.e., sad) vocalizations (Blasi et al., 2015). A first study has shown lower Mismatch negativity (MMN) amplitudes in response to angry but not happy voices in individuals with ASD, possibly reflecting atypical early sensory processing of negative emotion (Chin-hsuan, 2011). A second study examined the electrophysiological correlates of vocal emotion processing in 10–16-years-old with ASD using an emotion recognition task. Stimuli consisted of the phrase "I'm leaving the room now, but I'll be back later" spoken in happy, angry, sad and fearful tone of voice (Lerner et al., 2013). This study found a significant correlation between emotion recognition errors and N100 latency, suggesting that participants with longer N100 latencies made more recognition errors. The findings were interpreted as indicating difficulties with speed of sensory processing of social information in ASD as reflected by N100 latency (Lerner et al., 2013). An important limitation of this study, however, was that it lacked a group of typically developing children to inform our understanding of the degree of abnormality of this processing. Similar work has investigated the neural correlates of vocal anger processing in 14 9–12-years-old boys with Asperger syndrome (AS) and 13 controls using a passive oddball paradigm (Korpilahti et al., 2007). Vocal stimuli consisted of the word *'Anna!'* spoken with tender and angry tone of voice. Although the study did not report a differential neural response to emotion condition in any group, the N100 component peaked later in children with AS compared to controls (Korpilahti et al., 2007).

In summary, findings provide some evidence that impaired automatic discrimination of facial and vocal expressions may be a candidate neural marker of the social impairments observed

in ASD. A limitation in existing research using vocal stimuli is that they include semantic or lexical confounds in the tasks. This raises the possibility that findings are influenced by differences in language comprehension (Paul et al., 2005). Future studies should employ pure prosodic stimuli devoid of semantic or lexical content.

Implications for Early Detection and Preventive Intervention

Future research should aim to elucidate the sensory, perceptual and cognitive processes (i.e., mechanisms) underlying emotion processing. Emotion-specific neural markers can be useful in identifying individuals most in need of preventive intervention as well as identifying risk and resilience factors for disorder-specific outcomes. Targeted prevention programs can help children read emotions in others successfully or help implement strategies to compensate for emotion-related abnormalities. This can help reduce the risk for later emerging psychopathology. It is critical to intervene early in order to prevent a number of problems before they manifest and help reduce the economic and social burden of mental disorders for individuals and society.

AUTHOR CONTRIBUTION

The author confirms being the sole contributor of this work and approved it for publication.

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REVIEW
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Emotional Processing and Attention Control Impairments in Children with Anxiety: An Integrative Review of Event-Related Potentials Findings

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Anxiety disorders in adults have been associated with biased processing of emotional information which may be due to a deficit in attentional control. This deficit leads to an hypervigilance and a selective attention toward threatening information. Event-related potentials (ERPs) have been used to study this topic in anxious adults. Similar biases have been reported in children with anxiety but researches investigating the ERPs components underpinning these biases are more scarce. However, the understanding of the neural correlates of attentional biases in anxious children seem quite important since they could play a role in the etiology and the maintenance of this disorder. This review summarizes the results of researches having used ERPs to index emotional processing and attention control in children suffering from anxiety. We will focus on the P1, indexing basic visual perceptual processing, the N2, thought to reflect cognitive control process, the P3 typically associated with response inhibition, and the late positive potential (LPP) that indicates sustained attention toward motivationally salient stimuli. We will also examine the error-related negativity (ERN) that indexes monitoring system for detecting errors. Electro-physiological studies generally reported increased amplitudes of these components in anxious children, even when they did not differ from typically developing children at a behavioral level. These results suggest diminished cognitive control that influences children's selective attention mechanisms toward threatening information. Theoretical perspectives and implications for future researches will be discussed in the framework of current models of childhood anxiety.

Keywords: Anxiety, P1, N2, P3, ERN, LPP, attentional control, emotion

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INTRODUCTION

Anxiety is a frequent and incapacitating psychiatric disorder that affects 15–20% of children and adolescents (for a discussion on the prevalence and the definition of anxiety in youths, see Beesdo et al., 2009). Pathological anxiety is defined by persistent or extensive anxiety and avoidance behavior, associated with subjective distress and impairments in daily life. These features make it possible to distinguish pathological anxiety from normative and developmental fears and concerns that often emerge during childhood and adolescence, but which are transient and do not interfere with the functioning of youths (Beesdo et al., 2009). Anxiety disorders in children ranges from

high temperamental trait anxiety to clinical anxiety disorders, including separation anxiety disorder (SEP), social anxiety disorder (SAD), generalized anxiety disorder (GAD), panic disorder (PD), and agoraphobia disorder (AD) (Beesdo et al., 2009). Without intervention, anxiety is often a lifelong problem that persists into adulthood and significantly affects personal and professional achievements (Beesdo et al., 2009).

Anxiety significantly impairs cognition and anxious individuals consistently show a biased cognitive processing of emotional information (for a review, see Bar-Haim et al., 2007). Biases in the processing of emotional stimuli, such as threatening words or angry faces, have been reported in healthy children with a high level of temperamental trait anxiety and in children diagnosed with clinical anxiety disorders (for a review, see Puliafico and Kendall, 2006), suggesting that anxiety acts as an on/off filter in the cognitive processing of emotional information. As cognitive biases are postulated to play a role in the etiology and maintenance of anxiety, researchers have attempted to defined the exact stages of information processing that are affected by anxiety. Notably, Richards et al. (2014) distinguished between hypervigilance to threat, corresponding to the fast selection of threatening information in the environment, and selective attention to threat, which refers to the preferential processing of this information.

Given their high temporal resolution, event-related potentials (ERPs) constitute a very suitable method for exploring the dynamics of emotional processing (for a review, see Olofsson et al., 2008; Carretié, 2014). Numerous studies in anxious adults have demonstrated elevated amplitudes of early and late parietal components (Holmes et al., 2009; Michalowski et al., 2009; Mueller et al., 2009; Rossignol et al., 2012). However, studies in children are scarce and, to our knowledge, there has been no attempt to date to integrate the existing findings.

Accordingly, a first aim of this review is to summarize results stemming from electrophysiological studies that have explored ERP correlates of attention to threat in children suffering from clinical anxiety disorders and subclinical anxiety. A second aim of this review will be to discuss the role of attention and particularly attentional control in these biases. Indeed, contemporary models of attention postulate the coexistence of two neural systems, namely an automatic, stimulus-driven attentional system, and a more strategic, goal-directed attentional system (Posner and Petersen, 1990; Corbetta and Shulman, 2002). The balance between these two systems is ensured by attentional control (Eysenck et al., 2007). According to the Attention Control Theory (ACT, Eysenck et al., 2007), anxiety disrupts attentional control, leading to orientation of attention toward threatening but irrelevant events in a bottom-up manner, and disables the inhibition of such processing in a top-down manner. The hypothesis of an impoverished attention control in high anxiety has been supported by research showing reduced activity of the prefrontal cortex (PFC) (Bishop, 2009) and disrupted attentional control during emotional processing (Ansari and Derakshan, 2011a,b; Osinsky et al., 2012). Consistently, Telzer et al. (2008) have shown that adolescents (11–18 years-old) with a high level of anxiety demonstrate a selective attention bias toward angry faces associated with an enhanced recruitment of the right dorsolateral PFC, suggesting that that high anxiety requires increased cognitive control to reorient attention after processing threatening cues. Accordingly, an interesting question concerns the efficiency of attentional control in children and its role in the emergence of cognitive biases, since this process gradually develops during childhood. According to Lonigan and Phillips (2001), low effortful control abilities mediate the development of negative affectivity by shaping stimulus selection and then the subsequent cognitive and emotional processing (Lonigan and Vasey, 2009). Moreover, this model argues that children with high levels of negative affectivity demonstrate an automatic attentional bias for threat, but they may vary in their capacity to use voluntary attentional control to override this bias (Lonigan et al., 2004).

Hence, good attentional control may be protective against the development of pathological anxiety; it should therefore be important to examine the consistency of results between children suffering from subclinical and clinical anxiety, as well as in young children with high levels of shyness or behavioral inhibition (BI), described as a precursor of anxiety emergence (Van Ameringen et al., 1998; Muris et al., 2011).

Accordingly, this review will focus on five ERP components in order to evaluate their value in understanding the attentional biases present in children with anxiety. First, after the presentation of a visual stimulus, one may record the following component: (1) the P1, which indexes early automatic, exogenous attention (Carretié, 2014); (2) the N2, which is associated with conflict detection, and (3) the P3, reflecting motor control and response inhibition (Enriquez-Geppert et al., 2010; Luijten et al., 2014); (4) the LPP component, which indexes sustained attention toward motivationally salient information (Cuthbert et al., 2000). Finally, after the response production stage, (5) the error-related negativity (ERN) is also associated with response evaluation and cognitive control mechanisms (Hajcak et al., 2003). For each component, we will describe its development in childhood, its functions, and its relevance in studying emotional attention, before reviewing results stemming from empirical ERP studies (summarized in **Table 1**). Finally, we will discuss the implications for future research and theoretical perspectives in the framework of current models of childhood anxiety.

THE P100

The P100, or P1, is an exogenous component elicited in extrastriate areas of the visual cortex when a visual stimulus is detected (Csibra et al., 2008). The P1 indexes basic visual perceptual processing and peaks approximately 90–110 ms after the occurrence of the stimulus (Allison et al., 1999; Sass et al., 2010). While the P1 indexes early, pre-attentive processes, it may be modulated by a top-down attention processes and its amplitude increases with stimuli appearing in an attended location (Luck et al., 2000). Moreover, P1 amplitude is enhanced when viewing emotional as compared to neutral faces, indicating that emotional load globally enhances basic visual processes (Batty and Taylor, 2003). While an attention preference for emotional, and particularly negative, faces seems to develop from the first year of life (Peltola et al., 2009; Hoehl and Striano, 2010;

TABLE 1 | Results from empirical ERP studies in children with anxiety.

Reference	N	Diagnoses	Age	Questionnaires	Behavioral measures	Electrophysiological measures	Results
Buss et al., 2011	35 (19♂)	Healthy controls	4- to 8-years-old	CBQ	The ANT test	EEG ERP (N2)	N2 effect in children older than 6 years old [$F_{(1, 11)} = 9.05$, $p < 0.01$] Increase in N2 was associated with less efficient executive attention and lower temperamental effortful control.
Carrasco et al., 2013	13 26 27	GAD and/or SAD and/or OCD OCD Healthy controls	8- to 16-years-old	K-SADS-PL CBCL CDI MASC	Eriksen Flanker Task	EEG ERP	Compared to healthy controls, ERN amplitude was increased in patients with either OCD or other anxiety disorders [$F_{(2, 62)} = 7.16$, $p = 0.0016$] Scored from the CBCL had a correlation with ERN amplitude in all subjects ($r = -0.30$, $p = 0.013$; $p = -0.33$, $p = 0.007$)
Davies et al., 2004	151 (89♀)	Healthy controls	7- to 18-years-old		Visual Flanker task	EEG EOG ERP (ERN, CRN, Pe)	ERN amplitude in error trials increased with age [$F_{(1, 122)} = 20.9$, $p < 0.001$] The Pe amplitude did not change with age. CRN amplitude was larger in children than in adults [$F_{(1, 116)} = 8.6$, $p = 0.004$]
DeCicco et al., 2012	34 (13♀)	Healthy controls	5- to 7-years-old	CBCL CBQ	IAPS The black box task	EEG EOG ERP (LPP)	Larger LPP amplitude for unpleasant pictures [$F_{(2, 60)} = 11.85$, $p < 0.001$] LPP was not sensitive to reappraisal [$t_{(31)} = -0.80$, $p = 0.42$]
Dennis and Hajcak, 2009	25 (13♀)	Healthy controls	5- to10-years-old	The Emotion Regulation Checklist CBCL	IAPS	EEG EOG ERP (LPP)	Smaller LPP following neutral interpretations at posterior recording sites, [$F_{(1, 16)} = 7.93$, $p = 0.01$) except for younger girls (aged 5–6 years) [$F_{(1, 16)} = 5.32$, $p < 0.05$]. Greater LPP modulation of the LPP by neutral interpretations was associated with reduced anxious-depressed symptoms ($r = 0.49$, $p < 0.05$)
Henderson, 2010	46 (24 ♀)	Extreme Shyness	9- to 13-years-old	EATQ-R SASC-R CASQ SPPS	Eriksen Flanker Task	EEG ERP (N2)	Shyness and N2 amplitude alone and in combination were associated with measures of social adjustment: -Negative attribution style: $\beta = 0.66$, $t = -3.09$, $p = 0.004$/$\beta = -0.45$, $t = -2.24$, $p = 0.03$) -Self-perception of social acceptance: $\beta = 0.28$, $t = 2.24$, $p = 0.03$ -Social anxiety: $\beta = 0.89$, $t = 3.89$, $p < 0.001$ Shyness was associated with larger N2 amplitude or enhanced N2 responses.

(Continued)

TABLE 1 | Continued

Reference	N	Diagnoses	Age	Questionnaires	Behavioral measures	Electrophysiological measures	Results
Hum et al., 2013a	29 34	Clinically anxious Typically developing	8- to 12-years-old	MASC CBCL STAIC-S	Go/NoGo	EEG ERP (P1, N2, ERN, CRN)	Greater P1 [$F_{(1, 57)} = 5.56$, $p = 0.022$) and N2 [$F_{(1, 57)} = 9.48$, $p = 0.003$] amplitudes in anxious children Greater ERN and CRN in anxious children [$F_{(1, 56)} = 6.67$, $p = 0.012$] No differences between faces types or trials in anxious children. N2 amplitudes for calm faces predict self-reported anxiety levels [$F_{(1, 61)} = 5.16$, $p = 0.027$]
Hum et al., 2013b	24 (8♂) 16 (7 ♂)	Anxious Non-anxious	8- to 12-years-old	MASC STAIC-S CBCL GIS	Go/NoGo	EEG ERP (P1, N2)	Greater P1 activation in non-improvers at both sessions ($p < 0.022$) Greater P1 amplitudes at pre-treatment predicts non-improvement following treatment ($p = 0.030$) Greater N2 activation for improvers at post-treatment ($p = 0.043$).
Jonkman et al., 2007	16 17 17	Healthy controls	6- to 7-years-old 9- to 10-years-old 19 to 23-years-old	CBCL	Go/no-go (CPT-AX task)	EEG EOG ERP (N2)	In children and adults, a bilateral source pair in the medial frontal cortex was involved in the generation of the N2. Children need and additional posterior source. In 6- to 7-year-old children, this posterior source was localized in the occipito-temporal areas. In 9- to 10-years-old children, the posterior sources shifted to parietal locations.
Kujawa et al., 2015	90 (41♂)	53 anxiety disorders (AD) 37 healthy controls (HC)	7- to 19-years-old	K-SADS PARS CDI	Emotional face-matching task	EEG EOG ERP (LPP)	Response accuracy: AD = HC ($p > 0.46$) Response time: AD = HC ($p > 0.30$) Enhanced LPP amplitude to threat in AD in late stage of processing ($p = 0.03$)
Ladouceur et al., 2006	19	9 anxious 10 control	11- to 12-years-old 12- to 16-years-old	K-SADS-PL CBCL SCARED CDI BDI	Visual Flanker task	EEG ERP (ERN, Pe)	Increased ERN amplitude in anxious children [$F_{(1.17)} = 7.84$, $p < 0.05$] Neural generators of the ERN in the anxious group is localized to the ACC. No group differences in Pe [$F_{(1, 17)} = 0.25$, $p = 0.62$]
Lahat et al., 2014	291 (125♂)	Behavioral inhibition (BI) Longitudinal study	4 months 24 and 36 months 7-years-old	CBCL SCARED-R K-SADS-PL TBAQ	Visual Flanker Task	EEG ERP (ERN/CRN, Pe)	Children with high BI displayed at age 7 years larger ERN amplitude than those with low BI [$F_{(1, 62)} = 8.12$, $p < 0.01$]

(Continued)

TABLE 1 | Continued

Reference	N	Diagnoses	Age	Questionnaires	Behavioral measures	Electrophysiological measures	Results
Lamm et al., 2014	108 (48♂)	Healthy controls	2- to 7-years-old	TBAQ CBQ CBCL	The Zoo game (Go/no-go task)	EEG ERP (N2)	BI was associated with increased performance accuracy, longer reaction times, greater N2 activation and higher estimated doral ACC and DLPFC activation.
Meyer et al., 2012	55 (31♂)	Anxiety disorders	8- to 13-years-old	Child SCARED Parent-SCARED	Visual Flanker Task	EEG ERP	Among older children (≥12.43- years old) a larger ERN was related to increased anxiety based on parent report ($r = -0.35$, $\beta = -0.53$, $t = 2.69$, $p < 0.01$).The relationship is opposite among younger children ($r = 0.23$, $\beta = 0.35$, $t = 1.67$, $p = 0.90$)
Meyer et al., 2014	295 parents and children	Anxiety disorders	3-years-old	PSDQ	Go/No go task	EEG ERP (ERN and Pe)	Children with anxiety disorders are characterized by an increased ERN [$F_{(1, 294)} = 6.13$, $p < 0.01$ ERN amplitude is mediated by the relationship between harsh parenting and anxiety disorders in children.
Meyer et al., 2015	96	48 anxiety disorders 48 healthy controls	6-years-old	PAPA The Structured Clinical Interview for DSM-IV	Go/ No Go task	EEG ERP (ERN)	Larger ERN in anxious children [$F_{(1, 95)} = 1.41$, $p = 0.24$] Maternal history of anxiety disorder was associated with a smaller ERN [$F_{(1, 92)} = 4.47$, $p < 0.05$]
Moser et al., 2008	42	21 (15♀) high level-socially anxiety 21 (11♀) low level socially anxiety		SPIN DASS	Eriksen Flanker Task	EEG EOG ERP (N2, P3, LPP, CRN)	No group differences emerged on the behavioral measures Enhanced P3 amplitude for high socially anxious individuals [$F_{(1, 40)} = 12.49$, $p = 0.001$, $*^2 = 0.24$] Enhanced P3 for threatening faces [$t_{(20)} = 4.42$, $p < 0.001$, $d = 0.96$]
Pollak and Tolley-Schell, 2003	28 (17♂)	14 physically abused 14 non-physically abused	8- to 11-year-old	PCCTS RCMAS CBCL	Selective attention paradigm	ERP (P1) EEG EOG	Enhanced P1 response to angry faces [$F_{(1.24)} = 4,62$; $p < 0.05$] Threatening cues affect the flexibility and the control of selective attention [$F_{(1, 2)} = 4.42$, $p < 0.06$]
Santesso et al., 2006	37 (16♂)	Healthy controls	10-years-old	CBCL	Visual Flanker Task	EEG ERP (ERN and Pe)	More reported OC behaviors were associated with larger ERN ($r = -0.35$, $p = 0.02$) and larger Pe amplitude ($r = 0.43$, $p < 0.005$) The more error that were committed the less pronounced the ERN ($r = 0.46$, $p < 0.01$) and Pe component ($r = 0.33$, $p = 0.02$)

(Continued)

TABLE 1 | Continued

Reference	N	Diagnoses	Age	Questionnaires	Behavioral measures	Electrophysiological measures	Results
Santesso et al., 2005	39 (16♂)	Control	10-years-old	JEPQR-S	Visual Flanker Task	EEG ERP (ERN and Pe)	High scores on the Psychoticism and low scores on the Lie scale were associated with smaller ERNs. Smaller ERNs are associated with committing more errors on incongruent trials ($r = 0.41$, $p < 0.01$)
Solomon et al., 2012	39 (22♂)	Healthy controls	5- to 7-years-old	CBQ CBCL	IAPS The black box task	EEG EOG ERP (LPP)	Larger LPP amplitude for pleasant and unpleasant stimuli Association between LPP amplitude for unpleasant stimuli and fearful behaviors ($r = 0.38$, $p < 0.05$)
Wiersema et al., 2007	13 children (7♂) 14 adolescents (9♂) 17 young adults (10♂)	Control	7- to 8-years-old 13- to 14-years-old 23- to 24-years-old	Abbreviated WISC-III and short version of the WAIS-III	Go/no-go task	EEG ERP (ERN and Pe)	Group did not differ in the ability to adjust to response strategies after making an error. The ERN amplitude increased with age $[F_{(2, 36)} = 5.49, p < 0.008$ The Pe amplitude did not change with age

Jessen and Grossmann, 2016), few studies have examined the P1 in response to emotional stimuli in normatively developing preschool to school-aged children (Taylor et al., 2004; Batty and Taylor, 2006; Todd et al., 2008).

During an implicit processing task involving emotional faces, Batty and Taylor (2006) found that negative emotions (fear, disgust and sadness), in comparison to neutral or positive (happy and surprised) emotions, elicited later P1 latencies in 4- to 6-year-old children, but not in older children or adults, and postulated that young children rely on a rapid global processing for detecting emotion. This result was not replicated in a go/no-go study with children in the same age range, but those authors postulated that the faces used in their study may have been insufficiently disturbing to elicit emotional effect (Todd et al., 2008). Although inconsistent, these first results confirm the existence of a P1 response in preschool children, and emphasize the role of stimuli in modulating this brain response.

A second important result concerns the constant reduction of the P1 amplitude with age (Taylor et al., 2004; Batty and Taylor, 2006; MacNamara et al., 2016) which has been interpreted as indexing a reduction in cortical activity due to the increasing automaticity and efficiency of visual processing with age (MacNamara et al., 2016). Accordingly, the P1 amplitude may indicate the amount of cognitive resources devoted to processing a visual stimulus, with higher P1 indicating more attention and allocation of more cognitive resources.

Despite being of much interest, only few studies have investigated the P1 response in children with anxiety disorders. Preliminary results are described by Pollak and Tolley-Schell (2003), who recruited 8- to 11-year-old physically abused children. Maltreated children showed important levels of anxiety and biases in their abilities to recognize, express, and regulate their emotional states (Pollak et al., 2000). Pollak and Tolley-Schell (2003) used a selective attention paradigm where participants had to detect targets cued by emotional (angry and happy) faces. Behavioral results showed that maltreated children displayed hypervigilance toward angry faces, indicated by a faster response time (RT) for a target appearing in the location previously occupied by an angry face, and difficulties in disengaging from threat (i.e., a longer RT for targets appearing on the other side of the screen). Interestingly, physically abused children displayed enhanced P1 responses for angry faces, suggesting that threatening cues capture early attention and creates difficulty in control its allocation (Pollak and Tolley-Schell, 2003). More recently, Hum et al. (2013a) proposed a go/no-go task using angry, calm and happy expressions for typically developing children and clinically anxious children. They showed that, as compared to their age-matched peers, anxious children demonstrated greater P1 amplitudes in responses to faces, irrespective of their emotional content, showing heightened attention and/or arousal in response to these stimuli. The authors suggested that anxious children may have been more sensitive to the demands of the task, leading them to experience heightened arousal and to attribute more attentional resources to facial stimuli (Hum et al., 2013a).

A comparable hypothesis of general hypervigilance/hyperarousal was proposed by Peschard et al. (2013) who

reported enhanced P1 amplitudes in SAD adults while processing neutral and emotional faces, but also colored frames. Hence, anxiety could lead to an enhanced neural activation when performing experimental tasks. Unfortunately, the study by Hum et al. (2013a) did not allow attribution of the P1 enhancement to a particular type of anxiety disorders or even to a specific dimension of anxiety since participants in their study presented different types of anxiety disorders (GAD, SAD, and SEP) and comorbid anxiety disorders.

In a second study, Hum et al. (2013b) examined the changes induced by a cognitive behavioral therapy (CBT) program by measuring ERP responses before and after the intervention, in children presenting clinical anxiety disorders (SEP, SAD, GAD). They showed that higher P1 amplitudes at pre-treatment predicted non-improvement after the therapy. Moreover, children who did not improve in terms of anxiety levels after treatment had greater P1 amplitudes in both sessions, in comparison to children for whom anxiety levels decreased after treatment (Hum et al., 2013b). Unfortunately, this study encountered the same limitations as the previous one, as participants with various and comorbid anxiety disorders were recruited. Moreover, some children participating in the CBT protocol also had other pediatric conditions, such as ADHD, which may have reduced their response to a therapy targeting anxiety. Nevertheless, one may conclude that these results suggest that enhanced perceptual vigilance, representing heightened attention and arousal processes, limits the response to CBT strategies that are focused on more explicit strategies. Accordingly, it would be interesting to evaluate if P1 can be enhanced by a retraining of the attention processes, as proposed in the Attention-Bias Modification (ABM) programs that has been shown to reduce attention biases and anxiety symptoms in anxious children (Bar-Haim et al., 2011).

THE N200

The N200 or N2 is a fronto-central negativity observed at 200–300 ms post-stimulus which is generated by frontal structures, such as the anterior cingulate cortex (ACC) and the orbito-frontal cortex (Banich et al., 2001; Nieuwenhuis et al., 2003). The N2 is thought to index conflict monitoring and its amplitude reflects the extent to which attentional control is required to resolve conflict and inhibit incorrect responses (Van Veen and Carter, 2002; Nieuwenhuis et al., 2003; Dennis and Chen, 2007). The N2 is evoked during tasks in which two or more incompatible response tendencies are activated simultaneously, requiring the inhibition of a pre-potent response, or including incongruent stimuli, such as go/no-go or Flanker tasks. Thus, the N2 is linked to effortful control, i.e., individual differences in the ability to engage executive processes to inhibit dominant responses (Posner and Rothbart, 2007).

From a developmental perspective, the N2 is already seen at the age of 4 in the context of cognitive emotional challenges (Nelson and Nugent, 1990; Todd et al., 2008). The N2 amplitude is larger in young children, particularly under conditions that require cognitive control (Lamm et al., 2006; Todd et al., 2008; Buss et al., 2011) and decreases with age. This decline correlates with better achievement in cognitive tasks (Lewis and Stieben, 2004; Henderson, 2010). Henderson (2010) demonstrated that the age-related changes in the N2 components are due to the ongoing development of the ACC and the PFC. Moreover, the structures involved in cognitive control processes evolve with time. Using a go/no-go task, Jonkman et al. (2007) identified a bilateral source pair in the medial frontal cortex that was involved in no-go N2 activity in both children and adults. However, an additional posterior source was needed to explain the N2 distribution in children. This posterior source was localized in occipito-temporal areas in 6- and 7-year-old children, to shifting to parietal locations in 9- and 10-year-olds. The additional activation of posterior sources in the youngest children might indicate that executive control performance is less automatic or requires more effortful and attentional control (Jonkman et al., 2007). Recently, Buss et al. (2011) suggested that the N2 is a good biomarker for conflict-monitoring efficiency for children older than 6 years, who show larger N2 amplitude to incongruent compared to congruent flankers, but not in preschool-aged children. Indeed, after controlling for age, the N2 enhancement was associated with less efficient executive attention and a resource depletion that corresponded to interference with executive attention interference (Buss et al., 2011). To summarize, studies have considered enhanced N2 amplitude as reflecting less efficient monitoring of cognitive and emotional conflict.

In line with this concept, enhanced N2 amplitudes have been reported in conditions that are precursors to of anxiety disorders. In a first study, Henderson (2010) showed that shyness was unrelated to behavioral performances or ERP measures in a sample of typically developing 9- to 13-year-old children when performing an Eriksen Flanker task, but an extremely shy temperament in combination with larger N2 amplitudes predicted social anxiety outcomes. These results suggest that conflict sensitivity may alter the regulation of attention and emotion and reinforce the negative influence of temperamental factors. Recently, Lamm et al. (2014) observed that early reports of BI (at age 2 or 3) was associated with social reticence in 7-year-old children who demonstrated enhanced N2 amplitudes and higher activation of the ACC and the dorsal lateral PFC for no-go trials. Although these results did not allow a conclusion as to whether N2 activation results from social reticence or if it is a predictive factor for social reticence, they do suggest that a high level of control-related neural activation in childhood may be a biomarker for future anxiety symptoms, particularly in conjunction with an inhibited temperament.

Results in clinically anxious children are more controversial. Hum et al. (2013a) showed that anxious children had greater frontal N2 amplitudes to faces showing all emotions, while age-matched peers showed enhanced N2 amplitudes specifically for angry faces. Moreover, the differences observed in neural activation were not due to variations in task performance since anxious and non-anxious children had comparable behavioral performances (Hum et al., 2013a). Hum et al. (2013a) proposed that this enhancement indicated heightened neural activation due to emotional regulation processes, either because all emotional

faces were appraised as threatening by anxious children, or because they felt anxious throughout the experiment and were less sensitive to the actual emotion load of the stimuli. Interestingly, more negative N2 amplitudes for neutral faces predicted increased self-reported anxiety, consistent with the idea that neutral faces may be perceived as threatening in anxious individuals (Hum et al., 2013a). However, in a second study using the same paradigm in children of the same age, the authors did not replicate their finding and found that anxious children did not have greater N2 amplitudes relative to the comparison group (Hum et al., 2013b). Since this second study compared relatively small groups of participants with various types of anxiety disorders in the clinical groups, a lack of statistical power may be the reason for the lack of replication, but the existence of the N2 enhancement in anxiety states should be confirmed in future studies. More disturbing, in their second study in which they measured ERP responses before and after a CBT treatment, Hum et al. (2013b) reported an increase in N2 amplitude from pre- to post-treatment in those who improved.

THE P300

The P300 or P3 is a positive component that peaks 300–500 ms after stimulus onset at parietal and midline scalp sites (Segalowitz et al., 2010; Hajcak et al., 2013). The PFC seems to be the primary generator of the P3 (Halgren et al., 1998). Classically, the P3 is measured in go/no-go conditions (Bokura et al., 2001). The literature has associated the P3 with response inhibition (Falkenstein et al., 1999; Righi et al., 2009; Enriquez-Geppert et al., 2010). In go conditions, the P3 is maximal at centro-parietal sites whereas in no-go conditions, the P3 is maximal at fronto-central sites (Fallgatter and Strik, 1999; Weisbrod et al., 2000). Weisbrod et al. (2000) showed that the P3 was lateralized to the left side of the PFC during no-go trials highlighting the importance of this area in attentional control. In this review, we will mainly focus on the no-go-P3.

Bruin et al. (2001) showed that the P3 amplitude was enhanced when responses required stronger inhibition. The P3 follows a slow developmental course in childhood. Davies et al. (2004) used ERPs to investigate the response inhibition through the P3 in 6-year-old children, in comparison to a group of adults. During this task, participants performed a task that required selective responses to target stimuli while inhibiting responses to equally salient non-target stimuli. The results of Davies et al. (2004) showed that the neural activity measured by P3 differed between adults and children, suggesting that they may use different processes to perform an inhibition task (Davies et al., 2004).

Using a go/no-go task, Jonkman et al. (2003) compared the performance and ERP activity of 9- to 10-year-old children with those of adults. They observed that, in comparison to adults, children showed reduced or absent frontal P3, which would be due to an immature response inhibition processing in middle childhood (Jonkman et al., 2003). From a behavioral point of view, significant age effects were observed on hits, false alarms, impulsivity and inattention scores. Indeed, adults had more hits and less false alarms than children and were less impulsive and inattentive (Jonkman et al., 2003). Jonkman (2006) wanted to extend these results on neurocognitive development of the response inhibition measured by the P3 in a go/no-go task. Jonkman (2006) compared a group of 6- to 7-year-old to a group of 9- to 10-year-old and a group of adults of 19–23 year of age. The author observed a linear increase in the P3 effect with age. Indeed, a small effect was observed in late childhood at the midline frontal-central electrodes, but not in 6- to 7-years-olds. Furthermore, after 11-years-old, the P3 was recorded at frontal electrodes (Jonkman, 2006). These studies highlighted the fact that the P3 has a late development starting at about 10 years of age and are in agreement with previous studies (Jonkman et al., 2003; Okazaki et al., 2004). These data can be related to the late development of the networks involved in the regulation of motor preparation and response inhibition (Jonkman, 2006) and with the increase of the cortical efficiency with age (Lewis et al., 2006).

While the P3 presents a major interest in studies of motor response preparation (in go trials) and inhibition (in no-go trials), only few studies have measured this component in children with anxiety. Some preliminary results may be found in the study by Shackman et al. (2007), who, using a modified recognition oddball task, investigated how physically abused children process conflicting visual and emotion cues posed by their mothers or a stranger. They found that abused children showed enhanced P3 amplitudes in response to anger expressed by their own mother. Authors concluded that abused children exert more cognitive effort both to engage their attention toward salient anger cues and concurrently to inhibit the processing of irrelevant affective cues in the environment.

Éismont et al. (2009) examined the characteristics of amplitudes and frequencies of ERPs in 10- to 11-year-old children suffering from low and high anxiety levels with a two-stimulus go/no-go paradigm. They showed that the P3 wave for children with high anxiety levels were lower than for those of the same age with low-anxiety levels, suggesting that there are particularities in the functioning of the cerebral systems in anxious individuals. These authors supported the idea that decreased EP amplitudes in high anxiety children reflect insufficient maturity and unbalanced functioning of the brain structures (Éismont et al., 2009).

THE LATE POSITIVE POTENTIAL (LPP)

The late positive potential (LPP) is a slow positive wave appearing at midline parietal sites at 400–600 ms after the onset of a relevant stimulus (Cuthbert et al., 2000). The LPP reflects sustained attention toward motivationally salient information (Kujawa et al., 2015). It has been proposed that the LPP reflects the same mental processes as the P3 (Kok, 1997) but unlike the P3, the LPP has been shown to be sustained throughout and even after picture presentation (Cuthbert et al., 2000; Hajcak and Olvet, 2008). Furthermore, the scalp topography is different between the LPP and the P3. Indeed, there is a scalp shift in the LPP from a parietal positivity in the 100–1000 ms range to a more superior positivity in the 1000–2000 ms range suggesting that the LPP is a slow wave (Hajcak et al., 2007; Foti and Hajcak, 2008) whereas

the P3 is a peak (Foti et al., 2009). Furthermore, Foti et al. (2009) showed that the LPP reflects emotionally relevant processing, which is distinct from the P3. The LPP has been demonstrated to be associated with the activation of the visual cortex, as well as subcortical structures including the amygdala, ventral striatum, ACC and anterior insula (Liu et al., 2012).

The LPP has been demonstrated to be larger for emotional, both pleasant and unpleasant, stimuli (Cuthbert et al., 2000). Using an emotional face-matching task, MacNamara et al. (2013) has demonstrated that the LPP is larger for pictures of faces than of geometric shapes. Previously, Grasso and Simons (2012) has demonstrated that personally salient social stimuli, such as pictures of a relative, also elicit larger LPPs. Finally, the LPP has been demonstrated to be larger for stimuli described as negative in comparison to stimuli described as neutral (MacNamara et al., 2009).

In children, the LPP appears maximal at slightly more occipital recording sites as compared to adults, and was not evident in the ERP beyond 1500 ms. Recently, Kujawa et al. (2012) studied the electro-cortical reactivity to emotional faces in a sample of 3- to 6-year-old children and showed that the LPP arose in response to emotional faces in children who were only 6 years of age. Three studies evaluated the LPP in response to emotional pictures from the International Affective Picture System (IAPS, Lang and Bradley, 2007). First, Solomon et al. (2012) examined whether the LPP is sensitive to emotional content in healthy young children and whether this varies with affective individual differences. To do so, they measured neural responses to 30 unpleasant pictures (e.g., air crashes, snakes), 30 neutral pictures (e.g., household objects) and 30 pleasant pictures (e.g., Disneyworld, ice-cream) in 5- to 7-years-old children. They found that children showed larger LPP amplitudes for emotional stimuli. Second, Hajcak and Dennis (2009) confronted 5- to 8-year-olds with developmentally appropriate pictures and they recorded an increased amplitude of the LPP in response to unpleasant pictures. The differences in these studies may be partly due to the arousal by these stimuli. Indeed, Hajcak and Dennis (2009) found that pleasant stimuli were rated as more arousing than unpleasant stimuli in 5- to 10-years-olds. However, in the study by Solomon et al. (2012), the results can be interpreted as indicating the increased effort needed to interpret neutral facial expressions, because they are perceived as ambiguous and that this ambiguity is thought to convey emotion in anxious children.

Finally, Kujawa et al. (2012) found larger LPPs to emotional and neutral scenes in 8-to 10-year-olds than in a group of 11-to 10-year-old children. According to the authors, the age-related decrease suggests a shift in attentional allocation and stimulus processing which may be due to maturation of the cortical structures (Kujawa et al., 2012). In another study, these authors investigated the same children 2 years later, and confirmed the decrease of the LPP amplitude over time (Kujawa et al., 2013). MacNamara et al. (2016) replicated these finding while studying age-related change in ERPs elicited by emotional faces across an age span of 7- to 19-years-old. Kujawa et al. (2013) also investigated the stability of the LPP across development. They assessed this component during an emotional-interruption task following pleasant, unpleasant and neutral images in 8-to 13-year-old children that the results indicated that the LPP is quite reliable across ages. Thus, LPP appears to be a stable measure of emotional processing across a large period of development (Kujawa et al., 2013).

An important study by Kujawa et al. (2015) recruited children of 7-to 19-year-old with anxiety disorders who were exposed to an emotional face-matching task in which participants were shown fearful, happy or angry faces. Kujawa et al. (2015) observed a persistent enhancement of LPP amplitudes in the relatively late stages of processing (until 1000–2000 ms after the presentation of angry and fearful faces). Kujawa et al. (2015) compared the impact of different types of anxiety disorders on the LPP. They highlighted that LPPs to threatening faces were enhanced for SAD, compared to GAD or SEP. The results of this study suggest that the LPP may be a useful measure of threat reactivity in children with anxiety disorders and they confirmed the hypothesis of the early development of attentional biases toward threat in youths (Bar-Haim et al., 2007). The enhancement of the LPP in reaction to threats and particularly with subject-specific stimuli has also been demonstrated in adults suffering from anxiety disorders (Kujawa et al., 2015).

Moreover, higher LPP amplitudes to unpleasant stimuli were associated with longer RTs in a specific task called "the black box task" (Goldsmith and Rothbart, 1999). In this task, 5-to 7-year-old children were asked to put their hands inside a box that had "something scary inside" and the independent measure was the time required for the children to do so. These results suggest a relationship between a more positive LPP and fearful behaviors in children of these ages. Finally, given the high comorbidities between anxiety disorders and phobias (James et al., 2013), Leutgeb et al. (2010) studied the LPP in response to symptom provocation in 8- to 12-year-old spider-phobic girls, using a behavior avoidance test (BAT). Their results showed that phobic girls showed enhanced LPP amplitudes in response to spider pictures, reflecting motivated attention to emotionally salient stimuli.

The LPP can also be used to study the development and the maintenance of emotional regulation in anxiety disorders (Hajcak and Dennis, 2009). Interestingly, LPP amplitudes can be increased or attenuated if participants are asked to direct their attention to less or more arousing portions of emotional stimuli (Dunning and Hajcak, 2009) using a technique called reappraisal (Wessing et al., 2015). DeCicco et al. (2012) questioned reappraisal and LPP down-regulation in a group of 5- to 7-year-old children: the LPP amplitudes were larger in response to unpleasant than to neutral pictures and correlated with greater maternal-reported anxiety and observed fearful behaviors, but reappraisal did not modify LPP. The authors concluded that young children do not yet have the neural maturity to use reappraisal strategies effectively in order to regulate the affective and attentional processes measured by the LPP (DeCicco et al., 2012).

Consistently, Dennis and Hajcak (2009) recruited older children from 5 to 10 years and found that reappraisal led to a reduction of the LPP amplitude in response to IAPS stimuli (Dennis and Hajcak, 2009), supporting the idea that

reappraisal capabilities evolve with the maturity of the fronto-parietal network (Wessing et al., 2015). Finally, Hua et al. (2015) examined changes in LPP amplitudes following simplified interpretations of unpleasant pictures in preschoolers. They showed that LPP amplitudes, after neutral interpretations, were lower than after negative interpretations, suggesting that preschoolers as young as 4 years have developed the ability to use cognitive reappraisal strategies following instructions.

Even though there have been no studies investigating the reappraisal abilities in anxious children to date, the empirical data presented here suggest that the LPP may be an useful measure of cognitive emotion regulation, threat reactivity and emotion processing biases in youths with anxiety, in relation to age.

COMPONENT RELATED TO ANSWER PROCESSING: THE ERN AND THE PE

The ERN is a negative deflection that occurs at fronto-central sites approximately 60–110 ms after a wrong response (Falkenstein et al., 1991, 2000; Luu et al., 2003; Pailing and Segalowitz, 2004). The concept of "errors" may refer to incorrect responses in choice-reaction time tasks (errors of choice) and uninhibited responses, for instance on no-go trials (errors of commission; Scheffers et al., 1996) or to the lack of an answer in a target trial (errors of inaction). The ERN is not affected by the type of the stimulus (Bernstein et al., 1995) or the modality in which the stimulus is presented (Falkenstein et al., 2000) and is output-independent (Holroyd et al., 1998). The ERP wave is considered to be a signal resulting from the mismatch between a response and the outcome of this response (Falkenstein et al., 2000; Wiersema et al., 2005). Taken together, the ERN reflects a "monitoring system" for detecting errors (Wiersema et al., 2005; Santesso et al., 2006). This monitoring system is essential for preventing undesirable actions and optimizing task performance (Wiersema et al., 2007).

The production of an error may also be followed by a second component, the error positivity (Pe, Falkenstein et al., 1991). This late positive deflection occurs at centro-parietal sites approximately 200–400 ms after response execution (Falkenstein et al., 2000; Ladouceur et al., 2006) and has been observed for corrected and uncorrected responses, as well as on false-alarm trials (Nieuwenhuis et al., 2001). Thus, the Pe cannot be considered as a correlate of the error correction process but is more likely to be a conscious process of the error event (Falkenstein et al., 2000). According to Falkenstein et al. (2000), the Pe may be related to the controlled adjustment of response strategies after the recognition of an error, or may reflect the recognition of the error (Wiersema et al., 2007). Furthermore, the Pe may reflect the emotional significance of the error to the participant (Santesso et al., 2006).

Error monitoring underlined by the ERN and the Pe is associated with activation in the ACC (Kiehl et al., 2000), which is centrally involved in controlling or directing attention and actions (Wiersema et al., 2007). However, the ERN and the Pe may be functionally and anatomically distinct (Wiersema et al., 2007) as studies have localized the generator of the Pe in the rostral part of the ACC and the parietal cortex whereas the ERN is generated in the caudal part of the ACC (Van Veen and Carter, 2002).

From a developmental point of view, the ability to identify error production seems to have matured at the age of 4 years and undergoes its maximal development during early adolescence (Davies et al., 2004; Ladouceur et al., 2004; Hogan et al., 2005; Grammer et al., 2014). Using a go/no-go task, Wiersema et al. (2007) found that latencies of incorrect responses compared to correct responses were shorter in children and adolescents than in adults. Indeed, they showed that children (age 7–8 years) have much smaller ERN than adolescents (age 13–14 years) and adults (age 23–24 years) and thus ERN seems to increase with age. The same effect was observed for ERN latencies: latencies for incorrect compared to correct responses were shorter in children and adolescents than in adults (Wiersema et al., 2007). These findings are in line with those of Davies et al. (2004), and those of Ladouceur et al. (2004), who did not find a difference between children (age 9–14 years) and adolescents (age 14–17 years) in ERN and Pe amplitudes and latencies. Taken together, these results suggest that the ERN and the Pe do not seem to appear until late adolescence suggesting that the ability to detect error-related conflict which involves the modulation of cognitive control, develops in adolescence (Ladouceur et al., 2004).

Anxiety disorders in children, similar to high levels of negative affect or depression, have been associated with increased ERN amplitudes resulting from altered maturational patterns of ACC circuitry (Ladouceur et al., 2006). Three studies used a visual flanker task to reveal higher ERN amplitudes in children with anxiety. Ladouceur et al. (2006) demonstrated increased ERN amplitude in 10- to 12-year-old anxious children as compared to children with no affective disorders, and attributed this result to higher levels of negative affect in anxious children. This result was replicated in 8- to 16-year-old children with obsessive–compulsive disorders, GAD and SEP (Carrasco et al., 2013). Moreover, Santesso et al. (2006) showed that parent-reported obsessive–compulsive behaviors were associated with larger ERN and Pe components at fronto-central sites in clinically normal 10 year-old children. Using a go/no-go task with facial stimuli depicting angry, neutral, and happy expressions, Hum et al. (2013a) confirmed that anxious children produced greater ERN amplitudes and thus greater error-related negativities and correct-response negativities than typically developing children. At a behavioral level, there was no significant differences in accuracy, response duration, go response times or error no-go response times, suggesting that the neural activation is not due to variation in task performance (Hum et al., 2013a).

The hypothesis of a relationship between negative affect and an enhanced ERN is congruent with the model developed by Luu et al. (2004). This model assumes that the ERN indexes an affective signal of distress when an individual detects a discrepancy between action and an emotionally-salient goal (Weinberg et al., 2012).

Interestingly, enhanced ERN amplitudes at age 6 years predicted the onset of anxiety disorder by age 9 (Meyer et al., 2015). Moreover, Meyer et al. (2012) found the relation between anxiety disorders and ERN amplitudes is also moderated by

age: increased anxiety based on parent report was correlated to a larger ERN in older children (age 11–13 years), but this relation was opposite for younger children (age 8–10). These results indicate that ERN evolves with development to increase in anxious children around age 12 years (Davies et al., 2004).

Finally, the ERN appears to be modulated by early childhood temperament (Lahat et al., 2014). Using a visual Flanker task, these authors found that a high BI at age 7 years is associated with increased ERN amplitudes and predicts social phobia symptoms at age 9 years (Lahat et al., 2014). Increased ERN amplitude may index enhanced vigilance and fear of negative evaluation, and rigid and over-controlled behaviors, in social situations which, in turn, could lead to maladaptative social–emotional behaviors including phobia symptoms.

That relationship between a history of inhibited temperament and subsequent altered reward processing is congruent with the functional magnetic resonance (fMRI) results from Bar-Haim et al. (2009), who demonstrated heightened response monitoring and increased performance concerns in 14- to 18-year-old adolescents (Bar-Haim et al., 2009). The association between negative affect and the perceived distress with error commission may be reinforced by punitive parenting, as suggested in a longitudinal study by Meyer et al. which followed children over a period of 3 years (2013, 2014, 2015). These authors evaluated parenting behavior and parenting style in parents of 3-year-old children and they used a go/no-go task in a follow-up assessment, which included evaluation of child psychopathology 3 years later (Meyer et al., 2013, 2015). Moreover, in children, a larger ERN could be predicted by observational and self-reported harsh parenting, possibly because a hostile parenting style intensifies the threatening value and salience of errors and caused children to pay increased attention to their own error production, which is a risk for anxiety (Meyer et al., 2014).

In conclusion, although little information is available on Pe in children with anxiety, the ERN appears to be consistently modulated by anxiety, and could therefore constitute a promising biomarker for exploring defensive reactivity in children with anxiety symptoms or those who are at risk of anxiety.

DISCUSSION

The aims of this paper was to present the electro-physiological components underpinning the processing of emotional information and to discuss the role of an attentional control deficit in the development and maintenance of attentional biases in anxious children. First, we will present the results for each component of interest highlighted in this review.

The results of this paper showed that very few studies have investigated the automatic visual processing in anxious children and thus the P1. However, the studies that have investigated this component showed a larger P1 amplitude when anxious children were confronted with emotional face regardless of the emotional valence of the face. These results suggest an increased attentionnal processing of emotional faces in anxious children (Hum et al., 2013a). Thus, we can conclude that faces are considered as threatening by anxious children regardless of their emotional valence. Furthermore, there is a selective attention bias toward these faces (Richards et al., 2014) and the automatic attentional subsystem in anxious children would have superiority due to a deficit in attentional control (Eysenck et al., 2007). These results are in line with those observed in adults with high trait anxiety, who showed an enhancement of the P1 in response to angry faces (Fox et al., 2008; Frenkel and Bar-Haim, 2011), but also to phobia-relevant stimuli in phobic adults (Michalowski et al., 2009), and to all emotional stimuli in socially anxious adults (Mueller et al., 2009; Muhlberger et al., 2009; Rossignol et al., 2012) suggesting an increased vigilance in anxious states (Peschard et al., 2013). Given the results presented here, we can conclude that the P1 can be considered as an endophenotype of anxious disorders but also a biological marker useful for assessing treatment's efficacy.

We observed that the amplitude of the N2 can also be modulated by anxiety disorders (Hum et al., 2013a,b). Indeed, using a go/no-go task, Hum et al. (2013a) demonstrated larger N2 amplitudes in children who were confronted with emotional faces regardless of their emotional valence. These results suggest that anxious children allocate more neural resources to attentional control and inhibition. Furthermore, the lack of emotional specificity can be interpreted in two different ways: either anxious children consider every emotional face as threatening, or they feel anxious throughout the task and thus cannot distinguish different emotional patterns (Hum et al., 2013a). In their study, Hum et al. (2013a) highlighted that the neurophysiological data can be observed in the absence of behavioral effects. They confirmed the hypothesis of the attentional control theory developed by Eysenck et al. (2007). In their theory, Eysenck et al. (2007) differenciated the notions of efficiency and effectiveness, postulating that anxious individuals show similar behavioral performance as non-anxious individuals, although they recruit more attentional resources. In line with that, Hum et al. (2013b) also conducted a study in order to investigate the N2 before and after CBT intervention. They showed an enhancement of the N2 amplitude in children who had less anxious symptoms after therapy. This suggests that children who benefit more from CBT are those who recruit more cognitive resources while performing an attentional task. These results are also correspond the findings of other studies that showed an enhancement of prefrontal activity and of the N2 (Eldar and Bar-Haim, 2010; Maslowsky et al., 2010). However, it may seem counterintuitive that N2 enhancement can be interpreted as reflecting attentional control impairment in some studies, but improvement in others; thus, future studies are required for clarification, notably by controlling the experimental protocol and the level of conflict induced. High density recordings may allow detection of the neural source with more precision; it could be interesting to use combined fMRI and electro-encephalography (EEG) techniques (Campanella et al., 2013) to develop a precise model of the relationship between the occurrence of the N2 occurrence and the activity in the ACC and PFC.

Regarding the P3, studies have shown an enhancement of the P3 in children with anxiety disorders when they have to process and inhibit irrelevant stimuli that have a strong emotional valence (Éismont et al., 2009). These results concur

agree with the hypothesis of cortical immaturity. Indeed, the major generators of the P3 are located in the PFC which is implicated in affect mediation, cognition and behavior regulation (Halgren et al., 1998). The maturation of the PFC takes longer in childhood, explaining the difficulties of anxious children in consciously controlling attentional processing and regulating their emotions. Since we here focused on the inhibitory capability of anxious children, this review mainly considered about the P3 no-go component. Nevertheless, the P3-go may also be interesting in this context. Indeed, studies conducted in anxious adults have demonstrated an enhancement of RTs for the recognition of deviant faces in attentional oddball paradigms. This enhancement was accompanied by an enhancement of the P3 amplitude suggesting facilitated attentional processing of deviant stimuli (Rossignol et al., 2005; Moser et al., 2008; Righi et al., 2009). These results recall the distinction between the notions of efficacy and the effectiveness by Eysenck et al. (2007) since the increased electro-physiological responses reveal cognitive strategies used by anxious individuals in order to maintain attentional performances.

The LPP also presented some particularities in anxious children. Indeed, Kujawa et al. (2015) showed enhancement of LPP amplitudes in these children when they were confronted with angry or fearful faces. The results suggest sustained attentionnal processing in response to threatening faces (Bar-Haim et al., 2007; Richards et al., 2014). Furthermore, as highlighted by Dennis and Chen (2007), the LPP has an excellent temporal sensitivity and thus allows detection of similarities and differences between children suffering from different disorders, and also allows comparison of child and adult performance in an emotion regulation task. The LPP also appears to be a clinical measure for determining which children are at risk of developing psychopathological conditions due to difficulties with emotional regulation. Indeed, Kujawa et al. (2012) have demonstrated that the LPP can be considered as a vulnerability marker for depression.

Finally, studies conducted in children with anxiety disorders showed an enhancement of the ERN amplitude. This enhancement was also observed in children with depressive affects (Ladouceur et al., 2006). This may be due to a disorder of the maturation of the ACC which is the generator of this component. However, the literature shows that the ACC and the PFC are the generators of attentional control (Banich et al., 2000), particularly in conflict situations (Milham et al., 2001). A maturation disorder thus has an impact on attentional control, leading to attentional biases.

The results reviewed here confirm the notion that emotional biases in children with anxiety disorders can be indexed by electro-physiological component. Furthermore, these emotional biases highlight a deficit of attentional control in these children (Eysenck et al., 2007). The attentional control deficit leads to an imbalance between the automatic attentional subsystem and the strategic attentional subsystem, so that attentional biases could be observed at different stages of the attentional processing.

These biases can be attested by the study of the underlying electro-physiological components in children with anxiety disorders as shown in **Figure 1**.

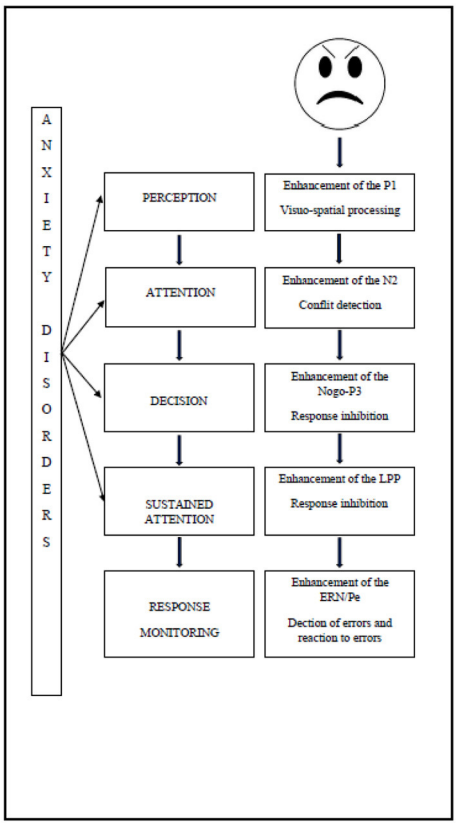

FIGURE 1 | Impact of anxiety disorder on attention processing of emotional stimuli.

The increased use of neural resources manifests immediately after the onset of the threatening stimulus. Firstly, studies have shown the impact of the attentional perception level, since the enhancement of P1 reflects visuo-spatial processing (Hum et al., 2013a). Secondly, the deficit of attentional control has an impact on conflict detection, manifested by an enhancement of the N2 (Hum et al., 2013a), and on response inhibition, manifested by enhancement of the P3 (Éismont et al., 2009). The attentional control deficit also has an impact on sustained attention, as manifested by an enhancement of the LPP amplitude in children (Kujawa et al., 2015). Finally, it has an impact during response monitoring, since studies have shown an enhancement of the ERN, thereby reflecting error detection and an enhancement of the Pe which is associated with error recognition (Ladouceur et al., 2006).

The results observed in anxious children are in line with those that had been observed in adults with the same psychopathological states (for review, see Bar-Haim et al., 2005). Furthermore, studies of the different components appear to be interesting in the early investigation of attentional biases in children who are at risk of developing a psychopathological disorder. Pollak and Tolley-Schell (2003) showed that hypervigilance to threatening faces in abused children manifested as an enhancement of the P1. The P3 was also enhanced when children were confronted with an angry expression from their

mother (Shackman et al., 2007). The N2 can be modulated by extreme shyness (Henderson, 2010). Behavioral inhibition also has an impact on ERN. Indeed, Lahat et al. (2014) have stated that enhancement of the ERN in these children suggests increased vigilance and a fear of negative evaluation, which could lead to the development of anxiety disorders. These results support the hypothesis that some electro-physiological components can be considered as endophenotypes or biological markers of anxiety disorders. Early investigation of these components could lead to the development of different types of innovative care for children at risk of developing psycho-pathological disorders. Indeed, the association between an attentional control deficit and anxious symptoms due to the development of attentional biases toward threat indicates that attentional training programs may be useful in the treatment and prevention of anxiety disorders (Bar-Haim, 2010; Bar-Haim et al., 2011; Eldar et al., 2012). This paper summarized the existing literature on attentional processing of emotional information and their electro-physiological correlates. Although the literature is emergent, consistent results have been demonstrated, although further replication and specification are required. Indeed, the disctinctions between the effects of various anxiety disorders may be difficult to establish, since most of studies have not distinguish between the different types of anxiety disorders. Furthermore, subsequent studies (e.g., those on P1) are needed to determine whether the effects observed in anxious children are specific to emotional stimuli or involve all types of stimuli. Such future studies could also indicate in which type of anxiety disorder the observed effects are the most consistent. Indeed, we should compare different types of anxiety disorders and investigate whether the observed electro-physiological effects are correlated to a specific dimension of anxiety (e.g., fear of being judged) or to a more general effect of arousal.

CONCLUSION

In conclusion, this review highlighted the fact that the study of electro-physiological components that underpin attentional processing of emotional stimuli in anxious children allow modeling of the impact of anxiety on cognition. Indeed, the results summarized here support the hypothesis of an attentional control deficit in anxious children, leading to attentional biases. We can observe these biases at different stages of the attentional process by studying the underpinning ERP components. However, further studies are needed in to obtain more information and provide a more comprehensive theoretical framework for this subject.

AUTHOR CONTRIBUTIONS

MR had the initial ideas; EW conducted literature searches and wrote the first draft of the manuscript; EW and MR revised the text and both authors have approved the final manuscript.

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The Effect of Affective Context on Visuocortical Processing of Neutral Faces in Social Anxiety

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It has been demonstrated that verbal context information alters the neural processing of ambiguous faces such as faces with no apparent facial expression. In social anxiety, neutral faces may be implicitly threatening for socially anxious individuals due to their ambiguous nature, but even more so if these neutral faces are put in self-referential negative contexts. Therefore, we measured event-related brain potentials (ERPs) in response to neutral faces which were preceded by affective verbal information (negative, neutral, positive). Participants with low social anxiety (LSA; $n = 23$) and high social anxiety (HSA; $n = 21$) were asked to watch and rate valence and arousal of the respective faces while continuous EEG was recorded. ERP analysis revealed that HSA showed elevated P100 amplitudes in response to faces, but reduced structural encoding of faces as indexed by reduced N170 amplitudes. In general, affective context led to an enhanced early posterior negativity (EPN) for negative compared to neutral facial expressions. Moreover, HSA compared to LSA showed enhanced late positive potentials (LPP) to negatively contextualized faces, whereas in LSA this effect was found for faces in positive contexts. Also, HSA rated faces in negative contexts as more negative compared to LSA. These results point at enhanced vigilance for neutral faces regardless of context in HSA, while structural encoding seems to be diminished (avoidance). Interestingly, later components of sustained processing (LPP) indicate that LSA show enhanced visuocortical processing for faces in positive contexts (happy bias), whereas this seems to be the case for negatively contextualized faces in HSA (threat bias). Finally, our results add further new evidence that top-down information in interaction with individual anxiety levels can influence early-stage aspects of visual perception.

Keywords: social anxiety, face processing, context effects, ERPs (Event-Related Potentials), EEG/ERP

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INTRODUCTION

Social anxiety disorder (SAD) is characterized by a "persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others," which leads to avoidance of, or intense anxiety or distress in these social situations (Diagnostic and Statistical Manual of Mental Disorders, DSM V; American Psychiatric Association, 2000). Cognitive models of SAD assume that cognitive biases in the processing of social information constitute important factors in the etiology and maintenance of this disorder

(Beck et al., 1985; Clark and Wells, 1995; Bögels and Mansell, 2004; Schultz and Heimberg, 2008; Cisler and Koster, 2010; Morrison and Heimberg, 2013). Biased information processing of unambiguous (i.e., threatening) or ambiguous signals of negative evaluation by others has been repeatedly shown across studies of attention, memory, and interpretation (Heinrichs and Hofman, 2001; Bögels and Mansell, 2004; Morrison and Heimberg, 2013). Particularly the misinterpretation of neutral or affiliative social signals as threatening is likely to deepen distress and contribute to the maintenance of SAD (e.g., Clark and Wells, 1995; Rapee and Heimberg, 1997; Gilbert, 2001; Alden and Taylor, 2004). Just recently, a meta-analysis including 24 studies on self-reported emotional reactions to facial expressions confirmed that socially anxious individuals show lower approachability to all types of expressions and higher arousal in response to neutral expressions (Kivity and Huppert, 2015).

Results of studies using event-related brain potentials (ERPs) in order to unfold the time course of face processing in social anxiety have been decidedly mixed (for an extensive review, see Schulz et al., 2013). To investigate electro-cortical response to faces and facial expressions, the following ERP components are of interest: As early ERP components which indicate visual processing the occipital P100 and the face-specific occipito-temporal N170. The P100 has been found to be modulated by facial expressions (e.g., Wieser et al., 2012b), presumably reflecting selective attention to emotional compared to neutral facial expressions, as also found in non-emotional attention research (e.g., Hillyard and Münte, 1984; Hillyard and Anllo-Vento, 1998). Furthermore, the N170 an index of structural encoding of faces (Bentin et al., 1996), is also modified by facial expressions (for reviews, see Eimer, 2011; Vuilleumier and Righart, 2011), although the empirical evidence for an emotional modulation of the N170 is mixed and remains an issue of debate. Most relevant for the current research questions are the subsequent emotion-sensitive components such as the early posterior negativity (EPN), and the late positive potential (LPP) (for a review, see Hajcak et al., 2012). Both of these are enhanced in response to emotional faces (e.g., Mühlberger et al., 2009; Wieser et al., 2012a,b), and index relatively early (EPN) and sustained (LPP) motivated attention to salient stimuli (Schupp et al., 2004; Wieser et al., 2010, 2012a,b). With regards to the face-specific N170 component of the ERP, some studies reported no effect of social anxiety on N170 responses to angry faces (Kolassa et al., 2007, 2009; Mühlberger et al., 2009), whereas other studies found that highly socially anxious participants exhibited larger N170 amplitudes to angry faces than low-anxiety participants over right temporo-parietal sites (Kolassa and Miltner, 2006). Interestingly, some studies report overall reduced N170 amplitudes (or M170, the MEG equivalent) in response to faces in general in socially anxious individuals, suggesting reduced encoding of faces (Mueller et al., 2009; Riwkes et al., 2015). Earlier effects on the P100 such as an amplitude enhancement, which is an index of selective attention (Hillyard and Münte, 1984), indicate an early attentional bias for social stimuli (hypervigilance), which may not be dependent on threat content (Schulz et al., 2013). Some studies found enhanced P100 amplitudes in response to faces in general (Kolassa et al., 2009; Rossignol et al., 2012, 2013) or selectively in response to threatening (angry) faces (Helfinstein et al., 2008; Mueller et al., 2009; Rossignol et al., 2012). Emotion-related ERP components such as the EPN and the LPP were also observed to be modulated by social anxiety. The EPN as an index for early, motivated attention was found to be larger for angry (and fearful) faces in trait and state social anxiety (Mühlberger et al., 2009; Wieser et al., 2010). Some studies reported greater LPPs for threatening but also neutral faces (Moser et al., 2008; Mühlberger et al., 2009; Kujawa et al., 2015), and positive correlations between social anxiety and the P3 amplitude for angry but not for happy faces (Sewell et al., 2008). However, other studies did not report modulation of late positive ERP during the processing of facial expressions by individuals suffering from social anxiety (Rossignol et al., 2007; van Peer et al., 2010).

The findings of enhanced LPPs to neutral faces in social anxiety point at the notion that ambiguous faces or neutral faces may be more threatening for socially anxious compared to healthy controls, so far from being neutral. This assumption is also supported by fMRI studies showing enhanced amygdala activations to neutral faces (Birbaumer et al., 1998; Straube et al., 2005; Cooney et al., 2006; Gentili et al., 2008). On a behavioral level, it has been demonstrated that social anxiety is also characterized by an interpretation bias such that socially anxious individuals more often interpret neutral faces as being negative (Yoon et al., 2007; Yoon and Zinbarg, 2008). Recently, it also has been demonstrated that social anxiety is associated with an expectancy bias for new neutrals faces such that HSA individuals lack a positive expectancy bias toward new social partners (Bielak and Moscovitch, 2012).

While it seems clear that perception and interpretation of emotional facial expressions is modulated by contexts in general (Barrett et al., 2011; Wieser and Brosch, 2012; Hassin et al., 2013; Hess and Hareli, 2015), particularly when processing ambiguous faces, individuals rely on contextual information to evaluate faces and form first impressions. This may especially be true when feeling anxious: When participants saw ambiguous facial expressions and simultaneously, positive or negative contextual information appeared on the screen, participants with high state anxiety showed greater use of contextual information in the interpretation of the facial expressions (Richards et al., 2007). Recently, several studies have shown that also verbal contextual information given beforehand alters processing of ambiguous faces such a neutral or surprised faces (Kim et al., 2004; Schwarz et al., 2013; Wieser et al., 2014; Klein et al., 2015). In an fMRI study showing neutral faces which were put into negative, positive, and neutral contexts by preceding sentences, enhanced amygdala activity was found for faces put in negative contexts (Kim et al., 2004).

Adapting this paradigm with neutral faces and self-reference as an additional contextual variable (i.e., the sentences were either self-related for the observer vs. other-related), it was demonstrated that contextual information is able to modify brain activity in response to neutral faces which did not differ on perceptual level (Schwarz et al., 2013). Specifically, it was found that two brain areas were especially responsive to faces put in a self-referential context: the medial prefrontal cortex (mPFC)

and the fusiform face area (FFA) in the fusiform gyrus. Whereas, mPFC is thought to play a role in processing of self-related information (e.g., Phan et al., 2004; Mitchell et al., 2005; Moran et al., 2006), activity in FFA is supposed to reflect face-specific activity and belongs to the core area of face processing (Haxby et al., 2000, 2002; Haxby and Gobbini, 2011). Rather intriguing, one has to bear in mind that the facial features for both categories are the same, which indicates a higher-order top-down influence of visual processing. In the same study, neutral faces put in a self-referential negative context were associated with enhanced activity in mPFC, which correlated with a measure of social anxiety (Schwarz et al., 2013). This is a first hint that contextual modulation of face processing may interact with individual levels of social anxiety, particularly so when the context is negatively framed. Recently, this paradigm was adapted to investigate ERP correlates of face processing (Wieser et al., 2014). Two important results emerged: (a) self-reference was found to modulate early and later stages of affective stimulus processing, namely the EPN and the LPP of the face-evoked ERP; and (b) affective valence of the context modulated early, but not later stages of affective face processing. These effects again occurred although faces *per se* did not differ perceptually. Affective ratings of the faces confirmed these findings. Altogether, these results demonstrate on both an electrocortical and behavioral level that contextual information modifies early visual perception in a top-down manner.

In the present study, we aimed at further examining how individual levels of social anxiety influence above-mentioned contextual modulation of neutral face processing. In addition to a replication of above-mentioned findings from behavioral studies, we sought to extend these findings to the neural level by using ERP methodology. As the fMRI results reported by Schwarz et al. (2013) suggest that the influence of social anxiety to be greatest for self-referential negative context information, we only investigated self-referential affective contexts (negative, positive, neutral) in this study. Based on previous findings showing biased processing of negative facial expressions (Staugaard, 2010; Gilboa-Schechtman and Shachar-Lavie, 2013), we assumed that individuals with high social anxiety would exhibit enhanced responding to negatively contextualized faces. This should be observable in affective ratings (higher arousal, more negative valence), and emotional components of the ERP (EPN, LPP). Based on previous findings, we also assumed that high social anxiety might show enhanced P100 amplitudes to faces in general as an index for hypervigilance. With regard to the face-selective N170 component, two alternative hypotheses were to be evaluated: N170 amplitudes could be enhanced in HSA selectively for negatively contextualized faces as previously observed for angry faces (e.g., Kolassa and Miltner, 2006), but also diminished as an index for perceptual avoidance or more superficial processing of faces (Mueller et al., 2009).

METHODS

Participants

Participants were undergraduate students at the University of Würzburg without any past or present psychiatric diagnosis (self-report), who were paid or received course credit for participation. Over 700 students filled in a pre-screening questionnaire consisting of five items (Supplementary Table 1) based on the DSM-IV criteria for social phobia (American Psychiatric Association, 2000), on a five-point Likert scale (0 = "Strongly disagree" to 4 = "Strongly agree"), such that a maximum of 20 points could be achieved. Based on the distribution of total scores, we aimed at inviting the upper 30% and the lower 10–40% to participate. Thus, participants scoring from 4 to 7 points were classified as low (LSA) and participants scoring above 12 points were classified as high socially anxious (HSA). Overall, 26 HSA and 24 LSA participants were invited to take part in the study. One LSA participant had to be excluded due to excessive artifacts in the EEG, and three HSA participants were excluded due to self-reported depression and/or abnormal BDI scores (>22), so that 47 participants (HSA: $n = 24$; LSA: $n = 23$) were included in the statistical analysis.

Mean questionnaire and age scores are given in **Table 1**. Groups did not differ in terms of age [$t_{(42)} = 1.61$, $p = 0.12$] and sex ratio [HSA: 19 women; LSA: 19 women; $\chi^2_{(1,\ N=44)} = 0.577$, $p = 0.38$]. To ensure that the screening was successful, participants completed the German version of the Social Phobia and Anxiety Inventory (SPAI; Turner et al., 1989; Fydrich, 2002). As expected, significant group differences were found in the total scores of the SPAI, $t_{(44)} = 7.09$, $p < 0.001$; HSA: $M = 100.54$, $SD = 23.90$; LSA: $M = 53.87$, $SD = 19.73$. Before the experimental task, participants also completed a socio-demographic questionnaire, the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970; Laux et al., 1981), the Beck Depression Inventory (BDI; Beck et al., 1961; Hautzinger et al., 2006), and the Positive and Negative Affect Scale (PANAS; Watson et al., 1988; Krohne et al., 1996). Groups did not differ in PANAS and state anxiety (STAI-S), but HSAs scored significantly higher on measures of trait anxiety (STAI-T) and depression (BDI), $t_{(42)} = 4.99$, $p < 0.001$, and $t_{(42)} = 2.45$, $p = 0.018$.

Experimental procedures were approved by the institutional review board of the University of Würzburg, and all participants provided informed consent. All participants of

TABLE 1 | Mean questionnaire and age scores for high socially anxious (HSA) and (LSA) participants.

Variable	HSA ($n = 21$)		LSA ($n = 23$)		t	p
	M	*SD*	*M*	*SD*		
Age	20.81	1.86	22.17	3.43	1.62	0.114
SPAI	100.54	23.90	53.87	19.74	7.09	**<0.001**
STAI State	40.38	7.24	36.09	7.24	2.57	0.070
STAI Trait	47.00	10.63	33.83	6.59	4.99	**<0.001**
BDI	8.05	5.55	4.70	3.35	2.45	**0.018**
PANAS_PA*	27.81	4.90	28.14	4.83	0.22	0.827
PANAS_NA*	13.04	4.14	13.10	3.52	0.37	0.971

*SPAI, Social Phobia and Anxiety Inventory; STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; PANAS, Positive and Negative Affect Scale (PA, positive affect; NA, negative affect). *n = 22 for the LSA group due to one participant missed filling in the PANAS questionnaire. Significant p-values are given in bold.*

the final sample were free of any neurological or psychiatric disorder (self-report) and had normal or corrected-to-normal vision.

Stimulus Materials

Thirty-six pictures (18 females) were selected from the Radboud Faces Database (Langner et al., 2010), all showing neutral facial expressions in frontal view. Pictures were selected based on normative ratings with regards to best percentage of agreement on emotion categorization and mean genuineness (Langner et al., 2010). Pictures were converted to gray-scale, and the contrast was approximated by calculating the variance, which was standardized across all the Radboud faces in order to minimize physical differences.

The paradigm was taken from a previous study from our lab (Wieser et al., 2014): For the context stimuli, 36 sentences were created, varying in terms of valence (positive, neutral, and negative), resulting in six sentences per category (for examples, see Wieser et al., 2014). In order to minimize grammatical differences or differences in word length between sentences, all sentences were of the same grammatical structure. Moreover, each sentence of each category contained six words. In contrast to the previous study, only self-referential sentences were used.

Procedure

Participants passively viewed sentences and neutral facial expressions according to the paradigm established by Wieser et al. (2014). For an example of an experimental trial see **Figure 1**.

Each sentence (positive, negative, neutral) was presented six times, three times with a male personal pronoun and three times with a female personal pronoun beginning the sentence. Consequently, each individual face was shown six times within a context category with different sentences. One set of three male and three female faces was assigned to positive sentences, another set of three male and three female faces was assigned to negative sentences, and the last set of three male and three female faces was assigned to neutral sentences. This assignment of picture sets to specific context valences was counterbalanced across participants to ensure that differences in the ERPs were not caused by intrinsic features of the faces. Overall, per session 72 trials per condition were presented (three male and three female faces repeated six times with the respective sentences) resulting in a total of 216 trials. In each trial, the sentence was presented for 2 s, after which with a gap of 500 ms a face was presented for 500 ms. After each trial, participants were asked to rate the respective face in terms of valence (-4 = very negative to $+4$ = very positive) and arousal (1 = not arousing at all to 9 = very arousing). The ratings scales were presented on the screen and the participants were asked to key in the respective number on a keyboard in front of them. Note that the valence scale -4 to $+4$ was stored as values ranging from 1 to 9. There was no time limit for the rating response. The ITI in which a fixation cross was presented, randomly varied between 2000 and 3000 ms. Presentation of the stimuli was controlled by presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA), the pictures were shown on a 21-inch CRT-monitor (60 Hz refresh rate) located ∼100 cm in front of the participant. Participants were instructed to keep their eyes comfortably focused on the center of the screen and to simply view the sentences and pictures, and rate the faces afterwards.

EEG Recording and Data Reduction

Brain and ocular scalp potentials were measured with a 128-channels geodesic sensor net (Electrical Geodesics, Inc., Eugene, OR, USA), on-line bandpass filtered from 0.1 to 100 Hz, and sampled at 250 Hz using Netstation acquisition software and EGI amplifiers. Electrode impedance was kept below 50 kΩ, as recommended for this type of high-impedance EEG amplifier. Data were recorded continuously with the vertex sensor as reference electrode. Continuous EEG data were low-pass filtered at 35 Hz using a zero-phase forward and reverse digital filter before stimulus-synchronized epochs were extracted from 200 ms pre-stimulus onset (face) to 800 ms post-stimulus onset and baseline-corrected (−100 ms). Preprocessing and artifact rejection were performed according to Junghöfer et al. (2000) using EMEGs software (Peyk et al., 2011). Off-line, data were re-referenced to an average reference. Afterwards, epochs were

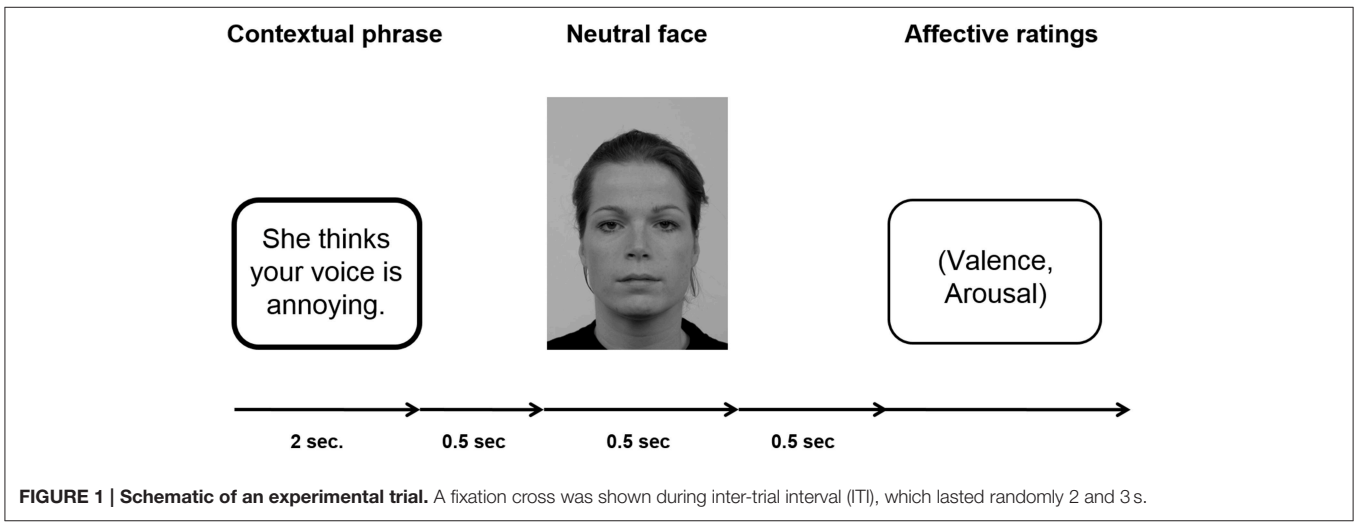

FIGURE 1 | Schematic of an experimental trial. A fixation cross was shown during inter-trial interval (ITI), which lasted randomly 2 and 3 s.

averaged for each participant and each experimental condition. ERP components were quantified on the basis of peak or mean amplitudes calculated over time windows defined on the basis of visual inspection and the literature (e.g., Wieser et al., 2010, 2014). The P100 component was analyzed as peak amplitude between 104 and 128 ms over right and left occipital electrode clusters including electrode O1 (EGI sensors 69, 70, 73, 74) and electrode O2 (EGI sensors 82, 83, 88, 89). For the N170 component, which reflects the early perceptual encoding stage of face processing, the peak amplitude was quantified between 152 and 182 ms after picture onset at lateral temporo-occipital clusters including electrodes P7 (EGI sensors 57, 58, 59, 63, 64, 65, 68, 69) and P8 (EGI sensors: 89, 90, 91, 94, 95, 96, 99, 100). The EPN was analyzed as an index of selective attention processes. It was scored as mean activity from 260 to 320 ms from a medial occipital cluster including Oz (EGI sensors 69, 70, 73, 74, 75, 81, 83, 88, 89). The LPP was analyzed (mean activity from 400 to 600 ms after face onset) as an index of sustained motivated attention across a central-parietal cluster (EGI sensors, 52, 53, 54, 55, 60, 61, 62, 67, 72, 77, 78, 79, 85, 86, 92) clusters.

Statistical Analysis

ERP measures as well as valence and arousal ratings were subjected to separate repeated-measures ANOVAs containing the within-subject factors Contextual Valence (negative vs. positive vs. neutral), and the between-subject factor Group (LSA vs. HSA). ANOVAs for lateralized ERPs (P100, N170) additionally contained the within-subjects factor hemisphere (left vs. right). If necessary, Greenhouse–Geisser correction of degrees of freedom (GG-ε) was applied. A significance level of 0.05 was used for all analyses. For all analyses, the uncorrected degrees of freedom, the corrected p-values, the GG-ε and the partial η^2 (η_p^2) are reported (Picton et al., 2000).

RESULTS

Event-related Brain Potentials (ERPs) in Response to Contextualized Faces

P100

The P100 of the face-evoked ERP did not show any effects of contextual valence. Also, no hemispheric differences were observed (**Figure 2**). However, a main effect of group was observed, $F_{(1,\ 42)} = 7.24$, $p = 0.010$, $\eta_p^2 = 0.147$, indicating larger P100 amplitudes in HSA ($M = 5.05\,\mu V$, $SD = 1.92$) compared to LSA ($M = 3.59\,\mu V$, $SD = 1.68$) in response to all faces, as expected from previous research.

N170

The N170 amplitudes of the face-evoked ERP were not modulated by contextual valence (**Figure 3**). Interestingly, N170 amplitudes were generally reduced in HSA ($M = -1.22\,\mu V$, $SD = 2.80$) compared to LSA ($M = -2.94\,\mu V$, $SD = 2.67$), $F_{(1,\ 42)} = 4.32$, $p = 0.044$, $\eta_p^2 = 0.093$ (**Figure 3**).

Early Posterior Negativity (EPN)

Cortical processing of neutral faces differed significantly in the EPN time window depending on verbal context presentation. For the mean EPN amplitudes (260–320 ms), a significant main effect of contextual valence was observed as expected, $F_{(2,\ 84)} = 3.48$,

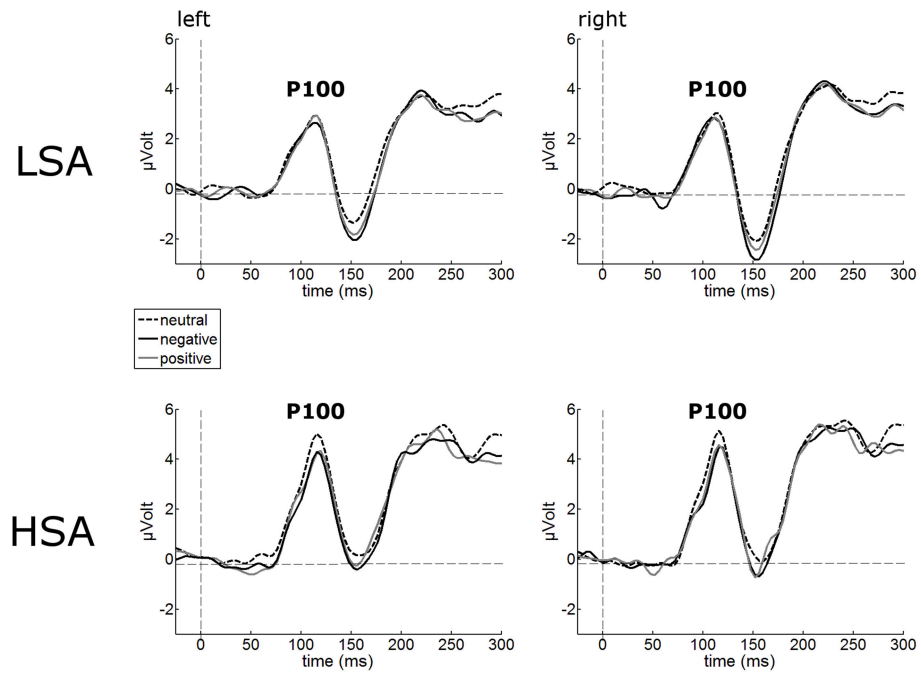

FIGURE 2 | Illustration of the P100 component averaged across left and right occipital electrode clusters per experimental group (HSA vs. LSA) for negatively, neutrally, and positively contextualized faces. Overall, P100 amplitudes are enhanced in HSA compared to LSA.

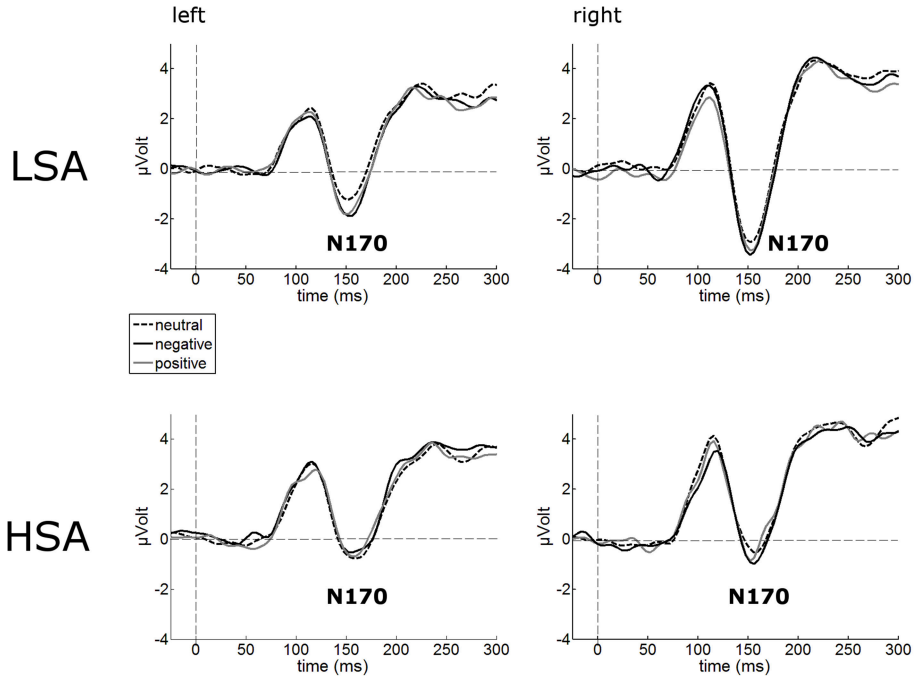

FIGURE 3 | Illustration of the N170 component averaged across left and right occipital electrode clusters per experimental group (HSA vs. LSA) for negatively, neutrally, and positively contextualized faces. Overall, N170 amplitudes are diminished in HSA compared to LSA.

$p = 0.043$, $\eta_p^2 = 0.077$. Faces put in a negative context elicited an increased relative negativity as compared to faces put in neutral contexts, $F_{(1, 42)} = 4.71$, $p = 0.036$, $\eta_p^2 = 0.10$ (**Figure 4**). The same effect was found for faces in positive compared to neutral contexts, $F_{(1, 42)} = 4.64$, $p = 0.037$, $\eta_p^2 = 0.10$. No other modulations were observed.

Late Positive Potential (LPP)

The waveform analyses revealed highly significant modulations of the LPP as a function of contextual valence and group, $F_{(2, 84)} = 3.32$, $p = 0.041$, $\eta_p^2 = 0.073$ (see **Figure 5**). *Post-hoc* simple *t*-tests performed for each group revealed that in LSA, faces in positive contexts elicited enhanced LPP amplitudes compared to faces put in negative or neutral contexts, $t_{(22)} = 2.53$, $p = 0.019$, and $t_{(22)} = 2.53$, $p = 0.019$. As expected, in HSA faces in negative contexts elicited larger LPP amplitudes compared to faces in neutral contexts, $t_{(20)} = 2.12$, $p = 0.046$ (**Figure 5**).

Affective Ratings of Faces

A highly significant main effect of contextual valence was observed for arousal ratings of faces, $F_{(2, 84)} = 7.74$, $p < 0.001$, GG-ε = 0.81, $\eta_p^2 = 0.16$. This modulation was slightly differentially expressed in both groups, $F_{(2, 84)} = 7.74$, $p = 0.053$, $\eta_p^2 = 0.07$. (**Figure 6A**), mostly due to a tendency for HSA compared to LSA participants to rate faces in negative contexts to be more arousing, $t_{(42)} = 1.98$, $p = 0.054$.

For valence ratings of faces, a highly significant main effect of contextual valence was observed, $F_{(2, 84)} = 27.48$, $p < 0.001$, GG-ε = 0.60, $\eta_p^2 = 0.40$. However, this affective modulation was differentially expressed in both groups as there was a significant Group x Contextual valence interaction effect, $F_{(2, 84)} = 3.78$, $p = 0.050$, $\eta_p^2 = 0.08$. *Post-hoc* comparisons between groups revealed that faces in a negative context were rated as more negative by HSA compared to LSA participants, $t_{(42)} = 2.04$, $p = 0.047$, whereas no differences emerged between groups for faces in positive or neutral contexts (**Figure 6B**).

Affective Ratings of Sentences

All the participants were asked to rate the sentences with regard to arousal and valence in a separate run after the main experiment (**Table 2**). Repeated-measures ANOVAs containing the within-subjects factor Contextual Valence (negative vs. neutral vs. positive) and the between-subjects factor Group were run on valence and arousal ratings separately. As expected, a significant main effect of contextual valence was observed for valence ratings, $F_{(2, 84)} = 426.58$, $p < 0.001$, $\eta_p^2 = 0.91$, with negative sentences being rated as more negative compared to neutral ones, $F_{(1, 42)} = 410.89$, $p < 0.001$, $\eta_p^2 = 0.91$, and positive sentences being rated as more positive compared to neutral ones, $F_{(1, 42)} = 337.16$, $p < 0.001$, $\eta_p^2 = 0.89$. A nearly significant Contextual Valence × Group interaction, $F_{(2, 84)} = 3.71$, $p = 0.055$, $\eta_p^2 = 0.81$, indicated that this effect was different in both groups. *Post-hoc* comparisons revealed that only for negative sentences, HSA showed significant more negative valence ratings compared to LSA, $t_{(42)} = 2.43$, $p = 0.019$.

For arousal ratings of the sentences, also a significant main effect of contextual valence was observed, $F_{(2, 82)} = 118.24$, $p < 0.001$, $\eta_p^2 = 0.74$, with negative and positive sentences being rated

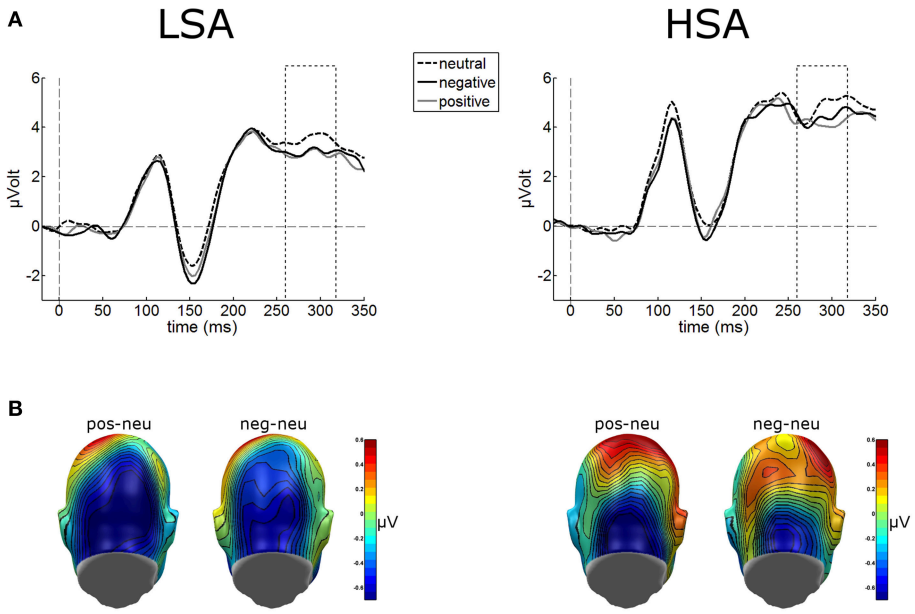

FIGURE 4 | (A) Illustration of the EPN component (260–320 ms, see hatched box) averaged across medial occipital electrode cluster for both groups. **(B)** On a back view of the model head the scalp potential map of the difference waves "negative-neutral" and "positive-neutral" are given. No group differences emerged, but enhanced EPN was observed for negative and positive contextualized faces.

as more arousing compared to neutral ones, $F_{(1,\ 42)} = 127.02$, $p < 0.001$, $\eta_p^2 = 0.75$, and $F_{(1,\ 42)} = 142.46$, $p < 0.001$, $\eta_p^2 = 0.77$, respectively. Here, the interaction of group and contextual valence was highly significant, $F_{(2,\ 84)} = 4.92$, $p = 0.01$, GG-$\varepsilon = 0.68$, $\eta_p^2 = 0.11$. *Post-hoc* comparisons showed that HSA selectively rated negative sentences as more negative than LSA participants did, $t_{(42)} = 2.16$, $p = 0.036$, corroborating the findings in the valence ratings.

DISCUSSION

How does trait social anxiety influence the contextual modulation of neutral face processing? The present study investigated the possible association of social anxiety and the influence of affective context features on the evaluation and electrocortical processing of neutral human faces. To this end, participants high and low in social anxiety (HSA vs. LSA) viewed neutral facial expressions, which were preceded by phrases conveying contextual information about affective valence. Meanwhile, event-related brain potentials (ERPs) in response to the neutral face stimuli were recorded and affective ratings of these faces were obtained.

Results revealed main effects of contextual valence on early as well as later stages of electro-cortical affective stimulus processing (as indexed by EPN and LPP), which is in line with our previous findings where negative affective context was associated with enhanced early preferential processing as indexed by an emotional modulation of the EPN (Wieser et al., 2014). Interestingly, this modulation of face processing was differentially expressed in HSA compared to LSA at later stages of face processing (LPP). At this later stage, HSA showed enhanced processing of negatively contextualized compared to neutral faces, whereas for LSA highest LPP amplitudes were observed for positively contextualized faces. Affective ratings support these ERP findings, with higher arousal ratings for negative and positive compared to neutral contextualized faces. Selectively, HSA rated negatively contextualized faces as more arousing and more negative. At earlier stages of visuocortical face processing, two main effects of social anxiety were observed: HSA show hypervigilance for faces in general (enhanced P100 amplitudes), but reduced structural encoding of faces (diminished N170 amplitudes).

The enhanced P100 in HSA in response to faces is consistent with a plethora of studies in which HSA or patients with SAD showed increased amplitudes of the face-evoked P100 component (Kolassa et al., 2009; Mueller et al., 2009; Rossignol et al., 2012, 2013; Peschard et al., 2013). This effect was also observed when social anxiety was induced by a fear-of-public-speaking task (Wieser et al., 2010). As the P100 indexes selective attention (Hillyard and Anllo-Vento, 1998; Hillyard et al., 1998) and P100 enhancements were also found to threat-stimuli (Pourtois et al., 2005) and have therefore been assumed to indicate increased attention to threat (Vuilleumier and Pourtois, 2007), our findings again support the notion that social anxiety is characterized by initial hypervigilance to social stimuli and may indicate an early automatic attentional bias for social cues (Schulz et al., 2013).

Notwithstanding this early enhancement of face processing, HSA individuals in our study showed decreased N170 amplitudes in response to all face stimuli. This finding is also in line with some earlier studies, in which a decreased N170 (or its MEG equivalent, the M170) in response to faces was reported (Mueller

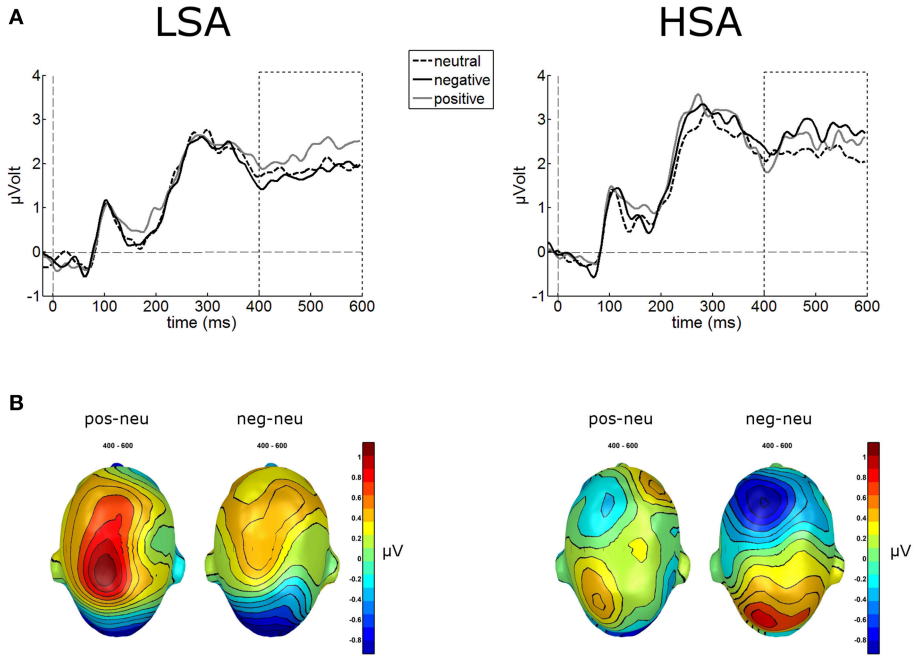

FIGURE 5 | Illustration of the LPP component averaged across medial-central sensor cluster for the three contextual conditions per group. **(A)** Enhanced LPP amplitudes were observed for positively contextualized compared to neutrally contextualized faces in LSA, but for negatively contextualized faces in HSA. **(B)** Scalp potential maps of the difference waves "negative-neutral" and "positive-neutral" for the LPP component are given on a top view of the model head.

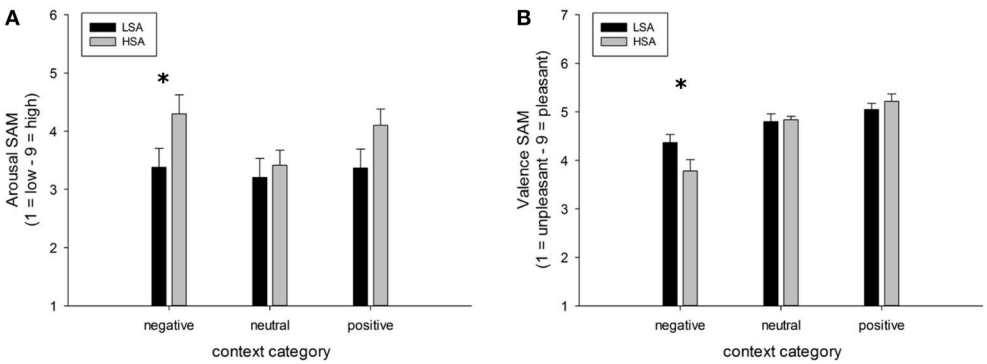

FIGURE 6 | Mean ratings (+SEM) of arousal (A) and valence (B) for faces in negative, neutral, and positive contexts, separated per group. Group differences emerged for the negatively contextualized faces, only. *Indicates p-values < 0.05.

et al., 2009; Riwkes et al., 2015). The N170/M170 face-selective component (Bentin et al., 1996) indexes structural encoding of faces, which includes a configurational analysis of whole faces. A reduced N170 in HSA might thus support the notion that an in-depth face analysis is avoided (Chen et al., 2002) or disrupted (Horley et al., 2003, 2004) in SAD. It has to be noted that others studies however report enhanced N170 amplitudes at least to some facial expressions such as anger (Kolassa and Miltner, 2006; Mühlberger et al., 2009). Most likely, these inconsistencies are a result of the different tasks employed in these studies (emotions were task relevant) or different types of facial stimuli (artificial vs. natural faces). Overall, our results are in line with earlier findings of studies indicating an attenuation of early neural components during face processing of individuals with high trait anxiety (e.g., Frenkel and Bar-Haim, 2011; Walentowska and Wronka, 2012). An interesting alternative explanation for the reduced N170 has been proposed by Riwkes et al. (2015). They assume that HSA use low-spatial frequency (LSF) information contained in faces differently such that they rely more on LSF information (connected to amygdala activation, see for example Vuilleumier et al., 2003) compared to high spatial frequency (HSF) information (connected to fusiform activation, see for example Vuilleumier et al., 2003), resulting in a reduced N/M170.

TABLE 2 | Mean affective ratings + SD (valence and arousal) of sentences with contexts (negative, neutral, positive) in both groups (HSA, LSA).

Contextual valence	HSA ($n = 21$)		LSA ($n = 23$)	
	Valence	Arousal	Valence	Arousal
Negative	2.35 (0.58)	5.96 (1.69)	2.88 (0.82)	4.72 (2.08)
Neutral	5.22 (0.31)	2.02 (1.26)	5.07 (0.28)	2.23 (1.39)
Positive	7.41 (0.86)	5.63 (1.67)	7.12 (0.77)	4.87 (2.19)

While no differences between groups were found at the ERP correlate of early emotional discrimination (EPN), HSA showed largest LPP amplitudes in response to negatively contextualized faces, whereas LSA showed a positivity bias in this ERP component. Thus, although it seems that contextual information may not influence early stages of face processing, HSA show sustained processing of especially negatively contextualized faces. This is in line with previous findings of elevated LPP amplitudes in response to negative faces in SAD (Moser et al., 2008; Mühlberger et al., 2009; Kujawa et al., 2015), which point at sustained attentional capture by negative facial expressions, a result also supported by recent flicker paradigms employing steady-state visual evoked potentials (ssVEP) technique (McTeague et al., 2011; Wieser et al., 2011, 2012c). However, one has to bear in mind that in the former studies the face stimuli were inherently negative (i.e., they contained negative facial expressions such as fear, anger, etc.), whereas, in our study the perceptual information in the faces was the same, namely void of any emotion. This shows that even contextual information, which is not present anymore during face processing, influences visual processing in a top-down manner depending on individual levels of social anxiety. The latter findings also corroborate the results from affective ratings in our study, where HSA tended to rate negatively contextualized faces as more arousing and more negative compared to LSA. Overall, these effects support for the first time on a cortical level the findings of HSAs to perceive self-relevant social contexts as being more threatening (see Moscovitch, 2009), so this provides an account of some of the neural mechanisms that may be involved in negative interpretation biases of ambiguous stimuli (see also Moscovitch and Hofmann, 2007).

As a limitation of the present study, we have to acknowledge that only a sub-clinical sample and not individuals clinically diagnosed with SAD were investigated. We assume that observed effects would be more pronounced in a clinical sample or there might be additional effects, e.g., it has to be clarified whether individuals with SAD show differences in the processing of contextualized neutral faces at earlier stages of face processing already. Furthermore, the use of individually tailored affective sentences containing the respective individual phobic cues would be necessary to identify how much these effects depend on the individual content of fear (Pergamin-Hight et al., 2015). Another potential issue relates to the fact that the differences observed in later stages of face processing might not only be driven by higher anxiety or arousal levels in HSA, but also by other features of social anxiety such as potential differences in hostility/aggression toward others and social situations (Kashdan and McKnight, 2010) or fear of positive or negative evaluation (Weeks and Howell, 2014).

Altogether, the present study shows that social anxiety may be characterized by two main biases in face processing even when the face itself does not carry affective information: *(a) a general attentional bias (hypervigilance), but reduced configural processing of faces; and (b) a selective enhancement of processing negatively contextualized faces, which is also reflected in subjective ratings.* Overall, the present findings together with previous results (Schwarz et al., 2013; Wieser et al., 2014; Klein et al., 2015) support the notion that face processing is highly context-dependent (Wieser and Brosch, 2012), and this may even be more relevant and pronounced with elevated levels of social anxiety. Further research may clarify to what extent HSA individuals rely on context information when they encounter emotional facial expressions and whether they could be trained to reappraise contextual information as a useful strategy for modifying attentional biases in social perception similar to attentional bias modification training (Beard et al., 2012) or re-appraisal of emotional stimuli (Moscovitch et al., 2012). Clearly, new research also needs to take into account other non-verbal social cues as potential contextual modulators of face processing in social anxiety (Bielak and Moscovitch, 2013; Gilboa-Schechtman and Shachar-Lavie, 2013).

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SUPPLEMENTARY MATERIAL

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Unexpected Acceptance? Patients with Social Anxiety Disorder Manifest their Social Expectancy in ERPs During Social Feedback Processing

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Previous studies on social anxiety have demonstrated negative-expectancy bias in social contexts. In this study, we used a paradigm that employed self-relevant positive or negative social feedback, in order to test whether this negative expectancy manifests in event-related potentials (ERPs) during social evaluation among socially anxious individuals. Behavioral data revealed that individuals with social anxiety disorder (SAD) showed more negative expectancy of peer acceptance both in the experiment and in daily life than did the healthy control participants. Regarding ERP results, we found a overally larger P2 for positive social feedback and also a group main effect, such that the P2 was smaller in SAD group. SAD participants demonstrated a larger feedback-related negativity (FRN) to positive feedback than to negative feedback. In addition, SAD participants showed a more positive ΔFRN (ΔFRN = negative – positive). Furthermore, acceptance expectancy in daily life correlated negatively with ΔFRN amplitude, while the Interaction Anxiousness Scale (IAS) score correlated positively with the ΔFRN amplitude. Finally, the acceptance expectancy in daily life fully mediated the relationship between the IAS and ΔFRN. These results indicated that both groups could differentiate between positive and negative social feedback in the early stage of social feedback processing (reflected on the P2). However, the SAD group exhibited a larger FRN to positive social feedback than to negative social feedback, demonstrating their dysfunction in the late stage of social feedback processing. In our opinion, such dysfunction is due to their greater negative social feedback expectancy.

Keywords: feedback-related negativity (FRN), P2, outcome evaluation, social anxiety disorder, social rejection

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INTRODUCTION

Social anxiety disorder (SAD) is characterized by fear of negative evaluation from others in social contexts according to the Diagnostic and Statistical Manual of Mental Disorders IV (American Psychiatric Association, 2000). Such intense fear of social evaluation is associated with a negative cognitive bias (i.e., negative-expectancy bias), which in turn impairs social ability in daily life. The cognitive-behavioral model of social anxiety proposes that socially anxious individuals assume that other people are inherently critical (Rapee and Heimberg, 1997) and have a negative-expectancy bias, i.e., severely socially anxious individuals hold a generalized belief that other people

tend to evaluate them more negatively and underestimate their social performance (Leary et al., 1988; Alden and Wallace, 1995; Spence et al., 1999). For instance, socially anxious participants rated interviewers as having more negative opinions about them (Pozo et al., 1991). The existence of such a negative-expectancy bias was also confirmed in a recent study, which indicated that highly socially anxious individuals showed lower expectancy of positive social feedback in a two-visit task (Caouette et al., 2015). In a word, converging evidences have suggested that socially anxious individuals and patients with SAD demonstrate a negative bias in their expectancy for, and interpretation of, social evaluation (Amin et al., 1998; Messenger et al., 2004; Franklin et al., 2005; Creswell et al., 2014).

According to the cognitive-behavioral models of social anxiety, the relationship between cognitive processes (negative beliefs in social contexts) and social behaviors (perpetuated avoidance and withdrawal) is the core mechanism that comprises and maintains social anxiety (Heimberg et al., 2010). The negative-expectancy bias is one of the key cognitive aspects of SAD and plays a important role in the core mechanism of social anxiety. First, it leads to withdrawal or avoidance behavior among socially anxious individuals (Bogels and Mansell, 2004; Stirling et al., 2006), which results in poor social performance. Furthermore, negative evaluation of their performance may further lower their level of self-esteem and reinforce their negative belief (Leary, 1990; Stopa and Clark, 2000; de Jong, 2002; Amir et al., 2005; Laposa et al., 2010).

However, to our knowledge, there has been no direct evidence of the neural correlates of social feedback processing in SAD, which could demonstrate the relationship between social evaluation expectancy and outcome evaluation. The primary aim of the present study, therefore, was to examine the social evaluation expectancy bias and social outcome processing in individuals with SAD using a neuroscience approach.

As a brain area closely related to conflict monitoring (Botvinick et al., 2004) and pain (Eisenberger and Lieberman, 2004), the anterior cingulate cortex (ACC) has been suggested to be activated by social feedback (Somerville et al., 2006, 2010; Gunther Moor et al., 2010). For instance, a study using a Chat Room task showed that positive feedback evoked stronger activations in the ACC, as compared with negative feedback (Guyer et al., 2012). This task has also shown individual differences in ACC activity during social feedback processing (Bolling et al., 2011; Masten et al., 2011). For example, functional magnetic resonance imaging (fMRI) results have indicated that individuals with low self-esteem showed increased ACC activity in response to social rejection than those with high self-esteem (Onoda et al., 2010). One key event-related potential (ERP) component identified to be sensitive to outcome feedback is the feedback-related negativity (FRN), which is considered to be associated with the reward prediction-error mechanism located in the ACC (Holroyd and Coles, 2002; Yeung and Sanfey, 2004; Holroyd et al., 2006). This component is considered as an important biomarker in a large body of work on outcome evaluation (Gehring and Willoughby, 2002; Holroyd et al., 2004; Nieuwenhuis et al., 2004; Yeung et al., 2005; Wu and Zhou, 2009; Pedroni et al., 2011; Osinsky et al., 2014). Numerous studies have shown that the FRN is sensitive to outcome expectation (e.g., Hajcak et al., 2007), supporting the concept that the ACC is involved in predicting and signaling unexpected outcomes, regardless of their valence (Ferdinand et al., 2012). A recent study combining expectation and social feedback showed that the FRN is sensitive to both social prediction error and social rejection (Sun and Yu, 2014). Specifically, a more negative FRN waveform was observed when people were socially rejected and their explicit expectancy was violated. We thus predict that the relatively less optimistic expectancy being prevalent in individuals with SAD may lead to a larger FRN in response to positive social feedback.

Indeed, several previous ERP studies on social feedback processing have reported the effect of social anxiety on ERPs (Van der Molen et al., 2013; Kujawa et al., 2014). For example, an ERP study in young individuals using an "Island Getaway task" found a more negative FRN in response to negative than to positive feedback (Kujawa et al., 2014). More interestingly, their results also showed the influence of social anxiety on the FRN, such that a higher level of social anxiety was related to greater rejection − acceptance differentiation (ΔFRN). Besides the FRN, the significances of the P2 and P3 component for feedback processing have also been reported (Hajcak et al., 2005; Leng and Zhou, 2010; Lange et al., 2012; Schuermann et al., 2012; Flores et al., 2015). Although it remains controversial as to whether P3 can differentiate good from bad outcome, several studies have shown such a differentiation effect (Hajcak et al., 2005, 2007; Wu and Zhou, 2009). Frontal P2 is associated with the early stage of attention processing (Van der Molen et al., 2013). A number of studies have indicated that the P2 is also modulated by motivational relevance and affective significance (Cuthbert et al., 2000; Carretie et al., 2001, 2004). Moreover, a recent study reported that a strongly psychopathic group showed increased P2 and decreased P3 following reward delivering (Salim et al., 2015). In the current study, we expected to observe group differences in P2 amplitude, since individuals with higher rejection sensitivity have been reported to show a larger P2 in a modified face dot-probe task (Ehrlich et al., 2015).

To elicit the FRN in social feedback, we used the "Island Getaway task," which is similar to the paradigm used by Kujawa et al. (2014). The primary goal of the current study was to investigate whether SAD individuals would exhibit more pessimistic expectancy in a social evaluation situation. The second aim was to examine whether the expectancy difference between a SAD and non-SAD group would manifest in the FRN amplitude during social feedback processing, particularly positive feedback. We expected that the negative expectancy in SAD would lead to a larger FRN to positive social feedback. Following the ΔFRN findings by Kujawa et al. (2014), we also expected to observe between-group differences and the influence of expectancy on ΔFRN. Specifically, we expected a larger ΔFRN for SAD group for their lower acceptance expectancy. Additionally, given that the high social rejection sensitivity was associated with larger P2 to faces (Ehrlich et al., 2015), we expected a smaller P2 for SAD group after the feedback onset due to their earlier elevated attention on faces. Considering that P3 is

a classic outcome evaluation component, we also measured and analyzed this component.

MATERIALS AND METHODS

Participants

The study was carried out in accordance with the Declaration of Helsinki and the experimental protocols were approved by the institutional review board (IRB) of Harbin Medical University. All participants provided written informed consent for the experiment.

The participants were recruited in two stages: the screen and the diagnostic interview. Two psychologists collected data in the screening stage. Additionally, two psychiatrists were in charge of the diagnostic interview in the follow-up stage of this study.

Screening Stage

We selected 1836 students by stratified randomized sampling; this group covered a wide range of socio-demographic status of all students attending Harbin Medical University (Da Qing Campus). These sampled students completed the Interaction Anxiousness Scale (IAS) questionnaire (Leary and Kowalski, 1993); based on a rule of thumb, after ranking the scores of the IAS, the top 27% and bottom 27% of students were classified as the high-score group and the low-score group respectively, and the remaining students were classified as the intermediate-score group (Wiersma and Jurs, 1985).

Follow-up Stage

All students in the high-score group were checked by the validated Chinese translation of the Structured Clinical Interview for DSM-IV (SCID-IV; Ruying et al., 1997), as the gold standard for assessing SAD; the results revealed that 102 students met the criteria for SAD. In the current study, we recruited 21 of these SAD students who agreed to participate in the electroencephalography (EEG) experiment, together with 21 matched non-socially anxious students [healthy controls (HCs)]. Due to EEG artifacts that affected data quality, the final sample consisted of 40 participants (20 SAD and 20 HC).

Procedure

Three to five days before the formal experiment, participants were asked to upload their profiles with their photos, study majors, personal interests, and so on. Participants were told that they would be evaluated by another 120 peer participants (half of whom were females) based on the impression created by their profiles. To ensure the plausibility of this cover story, all participants were asked to evaluate the profiles of 10 fake participants and to vote on whether this person could remain in the group. This approach was consistent with the "Island Getaway task" in which individuals need to vote whether the presented people may remain on the island, given the limited resources (Kujawa et al., 2014). Thereafter, the formal procedure presented 60 faces of pseudo-participants with positive social feedback (i.e., social acceptance), and another 60 faces with negative social feedback (i.e., social rejection). All 120 faces were presented twice, resulting in 240 trials in total. The procedure is illustrated in **Figure 1**.

During the feedback-processing task, the face of the pseudo-participant, indicating the one who would evaluate the participant in this trial, was presented for 2000−2500 ms. Thereafter, social feedback was presented for 1000−1500 ms. An inter-trial interval was randomized from 1000 to 1500 ms, which appeared at the end of each trial (see **Figure 1**). The probability of the appearance of positive/negative social feedback was set as equal for each trial.

In the formal procedure, all instructions were presented with Microsoft PowerPoint (2013) software (Microsoft, Inc., Redmond, WA, USA). All aforementioned procedures were conducted using E-Prime software (Version 2.0, Psychology Software Tools, Inc., Pittsburgh, PA, USA).

Expectation Rating

After the EEG procedure, participants were instructed to assess to what extent they expected their peers to accept them in real life on a scale from 0 to 100, with 0 = "Not at all" and 100 = "Very much." Given that the number of evaluation faces used in the experiment was large ($n = 120$ in total), participants were also asked to rate how many peers they expected would accept them prior to the experiment (60 was the midpoint in this case); we also asked participants to rate their expectation after the experiment. Thus, the former rating measured real-life expectancy, while the latter measured the expectancy in the experiment.

Electroencephalographic (EEG) Recording and Preprocessing

During the EEG recording, participants sat comfortably in an electrically shielded room approximately 80 cm from a computer screen. The EEG data was recorded using a 64-channel NeuroScan system (Neuroscan, Inc, Herndon, VA, USA). Raw EEG data were sampled at 1000 Hz/channel, referenced to the nose on-line, with impedances lower than 5 kΩ. Vertical electrooculograms (VEOGs) were recorded supra- and infra-orbitally for the left eye. Horizontal EOGs (HEOG) were recorded by electrodes at the left and right orbital rims. The online continuous data were digitized with a band-pass of 0.05−100 Hz.

Electroencephalography were re-referenced to the average of the left and right mastoids and filtered with a low pass of 20 Hz (24 dB/oct) off-line (Ferdinand et al., 2012). Epochs were feedback-locked, beginning 100 ms before feedback onset to 500 ms afterward. Ocular artifacts were removed from the EEGs using a regression procedure implemented in the Neuroscan software (Scan 4.5, NeuroScan, Inc., Herndon, VA, USA). Trials exceeding the threshold of ±80 μV were excluded from further analysis. Trials of two conditions (acceptance and rejection) were averaged, and a −100 to 0 ms baseline was used to perform a baseline correction.

ERP Analysis

We were interested in the between-group difference on ERPs in both the positive and the negative feedback conditions.

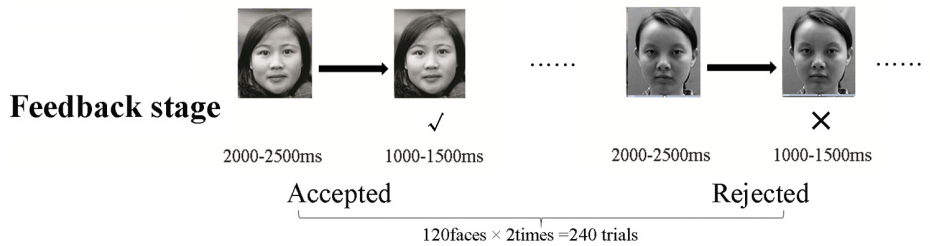

FIGURE 1 | A sample trial in the social feedback stage. The face of the evaluator was first presented for 2000−2500 ms; then, feedback of acceptance (√) or rejection (×) was presented below the face for 1000−1500 ms.

Therefore, we directly measured the FRN in grand-averaged waveforms rather than the difference waves between positive and negative trials. The grand-averaged ERPs at FCz and Pz and the corresponding topography map are presented in **Figure 2**. The P2 component was detected as a peak amplitude at C1, Cz, and C2 at 220−280 ms, since P2 then reached its maximum over these electrodes (see **Figure 2**). The P3 component was detected at three parietal electrodes (CP1, CPz, and CP2). The FRN was detected at three fronto-central electrodes (FC1, FCz, and FC2), which are usually used for FRN detection (Zottoli and Grose-Fifer, 2012; Luo et al., 2014). Visual observation of the topography map supported the above selections (see **Figure 2**). The original FRN amplitude was measured for each participant as the peak amplitude within the 280–340 ms window. However, considering that the P2 was also sensitive to negative vs. positive difference and group difference in our study, we used a peak-to-peak measurement here to eliminate the potential influence of P2 on the FRN (Ferdinand et al., 2012). Therefore, the reported FRN results are based on the difference of the FRN and P2 amplitudes. The P3 was identified as the average amplitude within the 340−450 ms window. To directly compare with the finding of Kujawa et al. (2014), we also analyzed the negative minus the positive amplitude difference (ΔFRN), in which more negative values reflect heightened reactivity to negative vs. positive feedback. The averaged P2, P3, and FRN amplitudes were entered into a 2 (feedback valence: positive vs. negative) × 2 (group: SAD vs. HC) analysis of variance (ANOVA). In addition, the ΔFRN was incorporated into a two-sample *t*-test with group as the between-subject variable. The reported degrees of freedom of the F-ratio were corrected by using the Greenhouse–Geisser method when the sphericity assumption was violated.

RESULTS

Patient Demographics

The basic information of the participants is provided in **Table 1**. An independent-samples *t*-test revealed that the two groups differed significantly in anxiety scores, but not in age or gender ratio. All participants had normal vision (with correction), and were right-handed.

Feedback Expectancy Results

The expectancy probabilities of peer acceptance in both real life and in the experiment were analyzed. The two sample *t*-test showed that the SAD participants ($M = 58.5\%$, $SD = 13.96$) showed significantly lower peer-acceptance expectancy in real life than did the HCs ($M = 78.95\%$, $SD = 15.09$; $t_{38} = 4.614$, $p < 0.001$). Similarly, SAD participants ($M = 43.5\%$, $SD = 13.89$) also had significantly more negative-acceptance expectancy in the experiment than did HC participants ($M = 58.62\%$, $SD = 11.13$; $t_{38} = 3.847$, $p < 0.001$).

The two types of expectancy probability were positively correlated ($r = 0.492$, $p < 0.001$). Moreover, the IAS score was negatively correlated with both social acceptance expectancy in real life ($r = -0.663$, $p < 0.001$) and acceptance expectancy in the experiment ($r = -0.421$, $p < 0.01$).

ERP Results

Figure 2 shows the ERPs elicited by the two types of feedback at the midline electrodes (FCz, Cz, CPz, and Pz).

The P2 Component

Analysis of variance on P2 amplitudes revealed a significant main effect of feedback valence ($F_{1,38} = 16.09$, $p < 0.001$, $\eta_p^2 = 0.297$), such that positive social feedback ($M = 4.60$ μV, $SE = 0.43$) evoked a larger P2 than did negative social feedback ($M = 3.53$ μV, $SE = 0.41$). Furthermore, the P2 amplitude also indicated a significant main effect of group ($F_{1,38} = 8.63$, $p < 0.01$, $\eta_p^2 = 0.185$), such that the SAD group ($M = 2.91$ μV, $SE = 0.56$) had a smaller P2 than did the HC group regardless of feedback valence ($M = 5.23$ μV, $SE = 0.56$).

The FRN

For the peak-peak FRN amplitudes, ANOVA indicated a significant main effect of feedback valence ($F_{1,38} = 7.84$, $p < 0.01$, $\eta_p^2 = 0.171$), showing that the FRN of positive social feedback ($M = -3.14$ μV, $SE = 0.33$) was larger than that of negative social feedback ($M = -2.41$ μV, $SE = 0.31$). Furthermore, the feedback valence × group interaction effect ($F_{1,38} = 5.79$, $p < 0.05$, $\eta_p^2 = 0.132$) indicated that only SAD participants showed such a positive vs. negative FRN effect (positive: $M = -3.40$ μV, $SE = 0.47$, negative: $M = -2.04$ μV, $SE = 0.43$), whereas HC

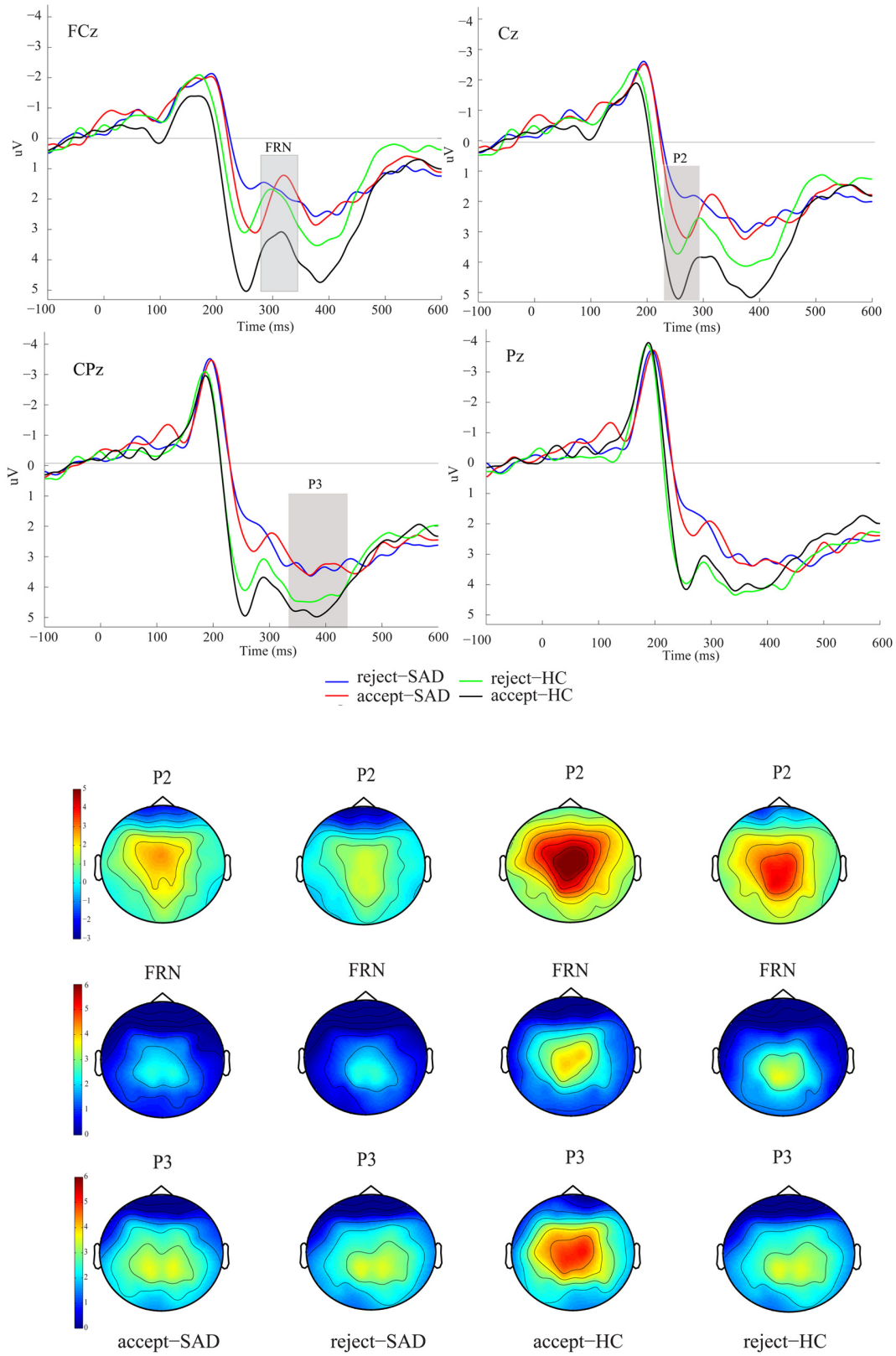

FIGURE 2 | Grand averaged event-related potentials (ERPs) and topographic maps of the two feedback types for the social anxiety disorder (SAD) and healthy control (HC) groups over midline electrodes (FCz, Cz, CPz, and Pz).

TABLE 1 | Characteristics and self-reported measures of participant groups.

	SAD group ($n = 20$)	Healthy controls ($n = 20$)	t-test ($df = 38$)
Age in years *(SD)*	20 (1.11)	20.42 (0.74)	1.476
Gender (% females)	63.6%	61.9%	χ^2 test, $p = 0.74$
IAS *(SD)*	51.05 (11.36)	30.29 (5.60)	−7.337***
STAI			
Trait anxiety *(SD)*	49.64 (13.75)	33.67 (7.60)	−4.317***
State anxiety *(SD)*	47.68 (14.44)	30.38 (7.36)	−4.539***
SES *(SD)*	24.41 (6.31)	32.71 (2.68)	5.229***

*SAD, social anxiety disorder; IAS, Interaction Anxiousness Scale; SES, self-esteem scale; STAI, Chinese version of Spielberger's trait anxiety inventory (STAI); ***$p < 0.001$.*

participants did not (positive: $M = -2.90\,\mu V$, $SE = 0.45$, negative: $M = -2.77\,\mu V$, $SE = 0.46$, $p = 0.72$).

Furthermore, the ΔFRN (rejection – acceptance) analysis showed that SAD participants had a more positive ΔFRN ($M = 1.36\,\mu V$, $SD = 1.60$) than did HCs ($M = 0.10\,\mu V$, $SD = 1.69$; $t_{38} = -2.41$, $p < 0.05$).

The P3 Component

Analysis of variance on P3 failed to find any social feedback effect or group-related effect (Fs < 1.30, ps > 0.27).

Correlations between Behavioral and ERP Results

A bivariate correlation analysis showed that the peer-acceptance expectancy in real life correlated negatively with the ΔFRN ($r = -0.469$, $p < 0.01$). Interestingly, the IAS score correlated positively with the ΔFRN ($r = 0.342$, $p < 0.05$). No other significant correlation was detected.

Mediation Analysis Results

We conducted a mediation analysis to assess whether the acceptance expectancy in real life lays in the causal path between the IAS score and the FRN amplitude, using a bootstrapping number of 5000 (Preacher and Hayes, 2008). In the analysis model, ΔFRN was set as the outcome variable, acceptation expectancy in real life served as the mediator, and the IAS score was entered as the predictor (see **Figure 3**), and the analysis was performed as described by (Preacher and Hayes, 2004). First, we found that the direct effect in the model with acceptance expectancy was not significant (B = 0.56, $SE = 0.19$, $p > 0.77$). Second, a significant indirect effect of social anxiety through acceptance expectancy was confirmed (B = 0.287, $SE = 1.34$, $p = 0.025$) at a 95% bias-corrected confidence interval (95%, CI: 0.0105−0.5624), establishing that acceptance expectancy was in the causal path between social anxiety and ΔFRN.

DISCUSSION

The primary aim of the present study was to investigate whether people with SAD exhibit less positive expectancy in social situations than healthy people, and to what extent this kind of expectancy bias manifests in the ERPs. By using a social feedback task, we found that SAD participants had less positive social acceptance expectancy in both real life and experimental social situations than did HCs. The ERP findings of FRN showed a more negative FRN in response to positive feedback than to negative feedback in SAD individuals. We interpret this finding as indicating that lower expectation is associated with a larger FRN. Thus, this result reflects the cognitive negative bias in SAD. Moreover, the correlation between acceptance expectancy, IAS and ΔFRN amplitude further confirms that highly socially anxious participants showed a larger positive vs. negative differentiation, since this was mediated by acceptance expectancy.

Larger FRN for Positive Social Feedback vs. Negative Feedback in SAD

Previous studies on anxious participants have reported individual differences in the FRN, such that larger FRN amplitudes are associated with lower levels of anxiety (Gu et al., 2010a,b; Simons, 2010; Takács et al., 2015). In the current study, the SAD group showed more negative FRN values for positive than for negative social feedback. We suggest that this result may indicate the negative expectancy in SAD participants. Indeed, behavioral measures showed that their expectancy rate of being accepted was 43.5% in the experiment situation, which was significantly lower than the random level (50%, $p < 0.05$). Such an inference effect was consistent with the prediction of the response-outcome theory (Alexander and Brown, 2010, 2011) that FRN is related to subjective expectancy, regardless of feedback valence.

An alternative interpretation of the larger FRN to positive feedback in SAD individuals is the blunting of the FRN after negative feedback in SAD (see **Figure 2**). That is, considering that the FRN is also related to performance monitoring (see review Ullsperger et al., 2014), a dysfunction in the social performance monitoring processes of anxious participants may result in weaker sensitivity to negative feedback. In parallel with this hypothesis, previous studies in depression (Foti and Hajcak, 2009) have also shown a blunted FRN on non-reward feedback. A recent study on problematic internet use (PIU; Yau et al., 2015) also indicated overall decreased sensitivity to feedback in individuals with PIU, which manifested as a reduced FRN. For the purpose of social adaptation, negative feedback is of great significance for adjusting social behavior to be more favorable (Ruff and Fehr, 2014). Individuals with SAD may have impaired negative social feedback processing, which is reflected by blunted neural responses to negative feedback.

The absence of differences in FRN between negative and positive feedback in HCs is consistent with some previous studies that did not report an FRN differentiation effect (Bolling et al., 2011; Leitner et al., 2014; Dekkers et al., 2015). For example, with a similar social feedback paradigm, Leitner et al. (2014) did not find any feedback effect on the FRN. However, the absent positive vs. negative feedback effect seems inconsistent with previous studies which showed that the FRN is sensitive to the valence of

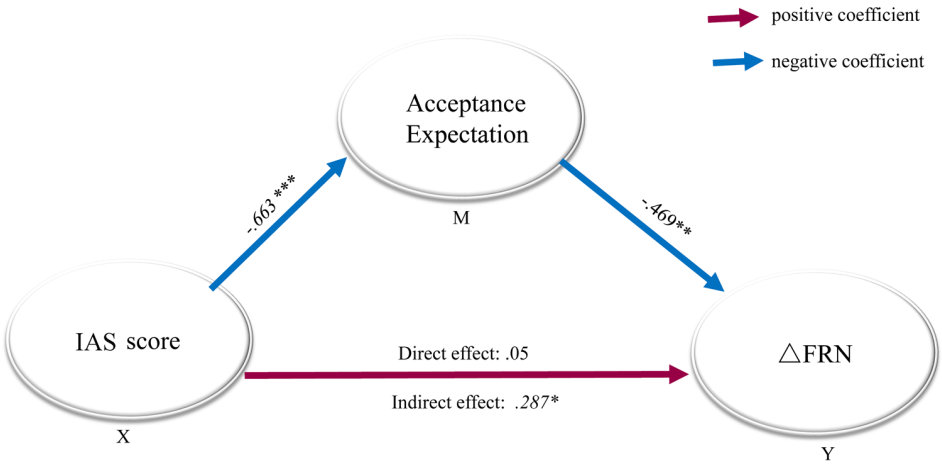

FIGURE 3 | Mediation model with standardized regression coefficients for the relationship between social anxiety and ΔFRN. Mediation model with standardized regression coefficients showing the relationship between social anxiety and ΔFRN as mediated by acceptance expectancy. The standardized regression coefficient between the Interaction Anxiousness Scale (IAS) score and ΔFRN, controlling for acceptance expectancy, was 0.05. Social anxiety (IAS score) predicted the acceptance expectancy (B = −0.663), which in turn predicted ΔFRN (B = −0.469). The direct effect of IAS on ΔFRN (when expectancy bias was included in the model) was not significant, $p = 0.77$, while the indirect effect was significant, indicating that acceptance expectancy fully mediated the relationship between IAS and ΔFRN. X: predictor, Y: outcome variable, M: mediate variable, $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

social feedback, and is more negative in response to rejection than to being accepted (Kujawa et al., 2014; Sun and Yu, 2014). We posit that the paradigm used, or the ERP measurement itself, may contribute to such inconsistent findings. Regarding the paradigm, in Sun and Yu's (2014) study, Somerville's task was used, which presented the expectation and feedback simultaneously, was used, while only the feedback from the peer was presented in our task. Regarding the measurement, the FRN effect is strongly dependent on how the FRN is quantified. In Kujawa et al.'s (2014) work, the FRN was scored as the original FRN mean amplitude, but not as the peak-to-peak amplitude. In contrast, we reported peak-to-peak amplitude results due to the potential P2 influence. When using the same measurement in the original research of Kujawa et al. (2014), the main effect of feedback, i.e., that negative feedback evoked more negative FRN, was also observed.[1] The current study was unable to determine whether either or both of the above factors contribute to the absence of positive vs. negative effect. Further research is required to clarify this issue.

Relationship between Expectation, Social Anxiety, and ΔFRN

ΔFRN is an index of the level of differentiation between negative and positive feedback, which was found to be sensitive to individual differences in social anxiety in a previous study (Kujawa et al., 2014). In the current study, we further established the link between expectancy, social anxiety and ΔFRN. First, SAD participants showed a larger ΔFRN (negative – positive) than did HCs. Moreover, this index was correlated with acceptance expectancy in real life as well as with the IAS score. More specifically, individuals with high acceptance expectancy in real life exhibited a smaller ΔFRN, and individuals with high social anxiety exhibited a larger ΔFRN in response to social feedback. Finally, mediation analysis confirmed that the acceptance expectancy in real life fully mediated the correlation between social anxiety and ΔFRN.

In line with the cognitive-behavior model of social anxiety (Rapee and Heimberg, 1997), it is conceivable that social expectancy mediated the FRN effect in social feedback processing. That is, an increase in social interaction anxiety predicted a decline in social acceptance expectancy in real life, which in turn predicted the FRN difference between the response to social positive vs. negative feedback. For SAD individuals, negative beliefs about social situations lead to their negative expectancy of future social evaluation (Caouette et al., 2015). Such negative expectancy also influences social evaluation processing, which is reflected by a more negative FRN to positive social feedback and a more negative ΔFRN (negative – positive). The dysfunction in social evaluation differentiation (indicated by a larger ΔFRN) may further reinforce SAD individuals' cognitive symptoms or negative beliefs during social life. In line with the existing studies that proposed the FRN as a biomarker in psychopathology (Olvet and Hajcak, 2008; Proudfit, 2015), we suggest that the ΔFRN in response to social feedback may serve as a potential biomarker of SAD.

The Social Feedback Valence Effect and Group Effect on P2

Although there have been many ERP studies on social rejection, few studies have reported the P2 effect (Sreekrishnan et al., 2014).

[1]When we analyzed the original FRN mean amplitude, the ANOVA indicated a significant main effect of feedback valence ($F_{1,38} = 5.737$, $p < 0.05$, $\eta_p^2 = 0.131$), indicating more negative FRN in response to negative feedback.

Our results showed a smaller P2 for social rejection, which is consistent with a previous study on autism spectrum disorder subjects that also showed a smaller P2 for rejection, regardless of the group difference (McPartland et al., 2011).

In the current study, there was a between-group difference in P2: the HC group showed a larger P2 to social feedback than did the SAD group. A smaller P2 in anxious participants than in non-anxious participants has also been observed in a study using fear stimuli (Frenkel and Bar-Haim, 2011), in which non-anxious participants showed overall larger ERPs (P1, P2, early posterior negativity). The anxiety-related attenuation of early P2 was also found in social distance processing (Perry et al., 2013). Given these findings, we consider that the reduced P2 associated with social rejection in the SAD group reflects reduced engagement of attentional resources during the early stage of social feedback processing (McPartland et al., 2011). Such a smaller P2 for SAD individuals may reflect a critical social avoidance; i.e., smaller P2 amplitudes in SAD indicates an early avoidance response after the face of the evaluator was presented, since socially anxious individuals tend to avoid social contact (Amir et al., 1998; Heuer et al., 2007; Lange et al., 2008; Heitmann et al., 2014).

CONCLUSION

To sum up, both groups showed an positive vs. negative differentiation effect on the P2, which also showed a between-group difference. This result might reflect a shared early social evaluation sensitivity mechanism for both socially anxious and non-anxious individuals, although it might also sensitive to the level of social anxiety. Furthermore, SAD participants exhibited a larger FRN to positive social feedback and a blunted FRN to negative social feedback, demonstrating their dysfunction in feedback processing. Combining the ERP findings, and the correlation and the mediation effect for ΔFRN, our results indicated that ΔFRN is a potential biomarker for SAD.

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REVIEW
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Just Swap Out of Negative Vibes? Rumination and Inhibition Deficits in Major Depressive Disorder: Data from Event-Related Potentials Studies

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Major depression is a serious disorder of impaired emotion regulation. Emotion hyperactivity leads to excessive negative ruminations that daily hijack the patient's mental life, impacting their mood. Evidence from past researches suggest that depressive patients present several cognitive impairments in attention and working memory, leading to a more acute selective attention for negative stimuli and a greater accessibility of negative memories. Recently, is has been proposed that impaired inhibitory functioning with regard to emotional information processing might be one of the mechanisms of ruminations linking memory, attention and depression. It seems that inhibition deficit is present at both *the input level* (i.e., the ability to reduce the interference from emotional distracters) and *the higher level* (i.e., the ability to direct the attention away from emotional material that has already been processed) of emotional information processing. Event-related potentials (ERP) have widely been used to study inhibition in adults suffering from various psychopathological states. In particular, depressive disorder has been linked to ERPs modulations, at early as well as at latter stages of the information-processing stream, when processing affective material. For instance, deficits in inhibiting negative information have been indexed by changes in the parameters (amplitudes and latencies) of early P2, P1 and N1 components while other ERP studies have shown an ability to differentiate depressed patients from normal controls based upon response inhibition difficulties in go-nogo tasks, indexed by later NoGo P3 differences. In this review, we will focus on results of ERP studies investigating inhibition and its interaction with emotional related cue processing in depressive populations. Implications for future research and theoretical perspectives will be discussed within the framework of current models of depressive disorder, based upon the hypothesis that negative ruminations are at the center of depression processes.

Keywords: Major Depressive Disorder, MDD, inhibition, rumination, event-related potentials, emotion-regulation strategy

NEGATIVE VIBES: DISTURBANCES IN EMOTIONAL PROCESSING

Depressed patients seem to daily experience sustained negative affect and a persistent reduction in positive affect that impact their thoughts, behavior, mood and physical health. Importantly, those ones cannot just swap out of negative vibes. Current pharmacological and psychological treatments are quite effective in reducing depressive symptoms at short term, but relapse rates remain very high (Kessler et al., 2005). Considering that Major Depressive Disorder (MDD) affects 350 million people and is the leading cause of disability worldwide (World Health Organization [WHO], 2015), an important research challenge should be the identification of contributing factors to the development, the maintenance and the recurrence of the disease. A disrupted emotional processing has been found in depressive patients that may constitute a causal factor in the development or maintenance of clinical depression (Demenescu et al., 2010). In point of fact, healthy emotional processing has been associated with good health, relationships, academic success and work performances (John and Gross, 2004), whereas emotional dysfunctions has been related to poor social outcomes and is considered as a main causal factor in various pathological conditions such as aggressiveness, addiction, risk-taking behaviors, anxiety and depression (Davidson, 2000). It's then worthwhile to delineate bias at the level of emotional processing in Major Depression.

Impaired Emotional Processing in Major Depression

Major Depressive Disorder is a serious disorder of impaired emotional functioning. Behavioral studies investigating the emotional processing stream – which, ranges from an interpretation of the stimulus to the preparation of an appropriate behavioral response (Green and Leitman, 2008) – have shown that depressed patients display difficulties in the perception, the recognition and/or the regulation of emotions. In other words, compared to healthy controls, depressive individuals exhibit a disrupted emotional processing, indexed by lower performance and/or delayed response latencies (Delle-Vigne et al., 2015). For instance, emotion perception and recognition abilities have often been studied through the recognition of emotional facial expressions (EFEs) (Delle-Vigne et al., 2015). Intensity judgment task in which participants have to identify either regular EFE stimuli, either morphed stimuli, have widely been used in order to assess the ability to recognize, judge and categorize emotions. In tasks using morphed EFE stimuli, controls and depressed participants have been confronted to faces, appearing on a screen and slowly evolving from neutral to full emotional intensity. Patients were required to freeze an exhibited face and to select the best fitted emotion in a list. Such studies have shown that, compared to healthy individuals, depressed patients were less accurate in decoding anger (Mendlewicz et al., 2005), required greater intensity of emotion in order to correctly identify happy faces, but required less intensity of emotion in order to correctly identify sad and angry faces (Joorman and Gotlib, 2006), displayed longer reaction times to correctly identify sad faces than happy ones (Gollan et al., 2008), and were performing better in recognizing sad faces than in recognizing any other emotions or subtle emotional intensity (Gollan et al., 2010).

However, perception and recognition are not the only impaired faculties in the emotional functioning in depressed individuals. A deficit in emotion regulation - the processes that influence when and how emotions are experienced (Gross and Thompson, 2007; cited in Hajcak et al., 2010) – has widely been cited as a central causal factor in major depression. Indeed, it has been suggested that the possible primary dysfunction in depression not only resides in the low mood state itself, but in the brain's inability to appropriately regulate that state (Holtzheimer and Mayberg, 2011). In point of fact, people daily experience negative events without encountering prolonged negative affect (Teasdale, 1988). Yet, something is certainly happening differently for depression-vulnerable people compared to non-vulnerable people as MDD patients are much more affected by negative experiences and are to some extend "looking on the dark side" (Hertel et al., 2014). Apparently, the difference could lie in the use of specific emotion regulation strategies not allowing patients to repair their mood once they have experienced sadness or other negative emotions (Teasdale, 1988). Indeed, some findings suggest that more frequent use of certain strategies (e.g., expressive suppressions, thought suppression, rumination, catastrophizing) and less frequent use of other strategies (e.g., reappraisal, self-disclosure) are related to levels of depression (Gross and John, 2003; Campbell-Sills et al., 2006; Garnefski and Kraaij, 2006, 2007). Most studies investigating emotion-regulation strategies in MDD have focused on rumination, which is, up to now, considered as a main causal factor of relapse in the disease (Spasojević and Alloy, 2001).

Moreover, brain imaging studies, such as functional magnetic resonance imaging (fMRI) researches, have been conducted in order to highlight the defective brain circuitry in depression that further support the idea of an impaired emotional processing in Major Depressive Disorder. Various neuropathological and neurochemical abnormalities have been found in depressive patients within the neural systems that modulate emotional behavior (Drevets et al., 2008). A particularly modified functional activity in regions involved in depression's symptoms was widely observed. Commonly, MDD patients disclose a hyper-activated amygdala region, mainly due to a hypo-activation of prefrontal region (Dannlowski et al., 2005).

Importantly, researchers have begun to explore the neural correlates of emotion regulation strategies (Ochsner and Gross, 2005). They observed that processes, aiming to regulate an emotional state, seem to rely on a similar network of neural activation indicating a diminished emotional reactivity related to a diminished activation of the amygdala, and an increased cognitive control related to an increased activation in areas of the prefrontal cortex (Hajcak et al., 2010). For example, reappraisal has been related to an increased activation in areas of the lateral and medial prefrontal cortex and decreased activation of the amygdala (Oschner et al., 2002). When these regions miscommunicate, a hampering of the cognitive processing of

emotions has been observed (Mériau et al., 2006), and it has especially been suggested that it might subtend excessive elaboration and/or rumination on negative information (Koster et al., 2011).

Rumination in Major Depression

Rumination – a style of information processing defined by the process of recurrent thoughts and ideas (Nolen-Hoeksema, 1991) – is a prevalent trait in MDD. Indeed, depressive patients regularly engage themselves in vicious cycles of ruminative thinking focused on their symptoms, their causes and implications (Nolen-Hoeksema, 1991). Two subtypes of this process have been identified. On the one hand, reflective pondering or reappraisal, which is a solution-focused and depression-alleviating behavior. On the other hand, brooding, which consists in harmful negative interpretations and self-criticism (Treynor et al., 2003). MDD patients would mainly use the brooding subtype of rumination process that theorists consider as a particularly detrimental emotion-regulation strategy mainly increasing the hallmarks symptoms of depression (i.e., sustained negative affect and a persistent reduction in positive affect) (for a meta-analysis, see Aldao et al., 2010). Besides, it has been shown to delay recovery from negative mood and has been associated to a heightened vulnerability for the development and maintenance of depression, to higher levels of depressive symptoms, to longer and more severe episodes and might even be a mediator for the gender difference in depressive symptoms (Nolen-Hoeksema et al., 1999, 2007, 2008; Spasojević and Alloy, 2001). Indeed, approximately twice as many women as men are diagnosed with MDD (Weismann and Klerman, 1977; Kuehner, 2003) and studies using self-reported scales have shown that women had higher levels of depressed mood than men (Jorm, 1987; Nolen-Hoeksema, 1987; Kessler, 2006; cited by Leach et al., 2008). Previous studies have shown that women are more likely than men to ruminate about negative experiences or thought processes, resulting in higher levels and longer episodes of depression (Nolen-Hoeksema, 1987; Butler and Nolen-Hoeksema, 1994).

A COGNITIVE PERSPECTIVE FOR EMOTION REGULATION DEFICITS AND RUMINATION IN DEPRESSION

It's likely that there are a number of factors that affect emotion regulation in depression. Notably, cognitive models suggest that cognitions play a crucial role in emotion regulation processing (for a review, see Mathews and MacLeod, 2005). Actually, if former theoretical models of cognitive vulnerability for depression have focused on investigating the negative content of depressogenic cognitions (for a review, see Abramson et al., 2002), recent studies have highlighted the importance of underlying cognitive processes potentially related to the sustained negative affect and impaired emotion-regulation that characterizes MDD (Joormann and D'Avanzato, 2010). Bias across several stages of emotional information-processing stream have been found to influence the etiology and maintenance of depression (for a review, see Mathews and MacLeod, 2005) and investigators have established causal connections from the cognitive impairments to features of emotional disorders (for a review, see Hertel and Mathews, 2011). It has especially been proposed that deficits in attention and working memory make negative content more accessible to depressed individuals. Indeed, negative mood has been found to be more frequently related to negative attention bias toward emotional information (Koster et al., 2005; De Raedt and Koster, 2010) and to greater accessibility of negative memories (Taylor and John, 2004; for a review, see Matt et al., 1992).

In this vein, some specific cognitive deficits have been identified as potentially leading depressed people to engage themselves in ruminative processes (Nolen-Hoeksema et al., 2008). Recent data suggests that emotional regulation processes depend on a variety of top–down strategies that includes cognitive control. For example, researchers have explored the neurophysiological correlates of various emotion regulation strategies (cfr. below for the usefulness of neurophysiological/ERPs measurements of cognitive processes), and have pointed out that emotion regulation combines both automatic and more controlled cognitive processes (Hajcak et al., 2010). Indeed, they explored the effects of various emotion regulation strategies on automatic and on later and more controlled event-related potentials (ERPs) components, such as P300 and Late Positive Potential (LPP), and found quantitative differences on the LPP's parameters (amplitude and latencies) (Hajcak and Nieuwenhuis, 2006; Moser et al., 2006; MacNamara et al., 2009). For instance, Foti and Hajcak (2008) showed that the LPP to unpleasant pictures is reduced when a more neutral interpretation of the picture is given. They suggested that the reduced LPP might therefore reflect reduced emotional responses due to emotion regulation instructions, probably resulting from shifts in meaning and/or from the recruitment of prefrontal cortical resources associated with effective cognitive control (Ochsner and Gross, 2005).

Thus, cognitive control seems to play a major role in the use of emotion regulation strategies. Importantly, deficits in cognitive control such as inhibition, working memory updating and set shifting (Whitmer and Gotlib, 2013), and in perseverative behavior and thinking have widely been observed in ruminators samples. Among them, impaired inhibition has been identified as a potentially main causal factor in rumination (Linville, 1996; Hertel, 2004; Joormann, 2004; Cohen et al., 2014), which could provide an important link between memory and attention deficits, and depression (Joormann et al., 2007).

INHIBITION DEFICITS IN MAJOR DEPRESSION

Impaired Cognitive Inhibition as a Main Mechanism of Rumination

Inhibition – pivot of cognitive control – is not a unitary construct but instead, involves several components such as response inhibition, cognitive inhibition and neural inhibition.

Among them, cognitive inhibition refers to an active process that tempers unwanted external and/or internal stimuli that compete for processing resources in the context of limited capacity system (Hasher and Zacks, 1988). Dealing with negative emotional situations and negative mood states then requires effective cognitive inhibition. That is, it allows people to stop the processing of an activated negative material in working memory and to reorient their attention to other aspects of the situation (Joormann, 2010). Basically, inhibition operates at different levels of the information-processing stream (Hasher and Zacks, 1988) as it can both allow people to reduce the interference from emotional distracters (input level) and to direct attention away from emotional material that has already been processed and needs to be removed from working memory (higher level).

Exploring the Inhibiting Brain Through Behavioral and ERPs Studies

Inhibition of emotional content may be explored through several approaches. To date, it looks like they have been more behavioral researches on inhibition in depressed samples than cerebral mechanisms studies.

In order to assess inhibitory functioning, either at the input level or at the higher level of emotional processing stream, cognitive psychologists have investigated distracter inhibition, interference inhibition and inhibition of return (IOR) in behavioral tasks that required participants to ignore emotional (positive or negative) material to response to a target stimulus such as the emotional Stroop Task (i.e., interference inhibition; Yovel and Mineka, 2005), the negative affective priming task (NAP) (i.e., distracter inhibition; Joormann, 2004; Goeleven et al., 2006), the cue-target task (i.e., inhibition of return; Dai and Feng, 2009) and the Go-NoGo task (Erickson et al., 2005). Meanwhile, neuroscience has completed behavioral measures by elucidating neural correlates associated with impaired information processing in various psychiatric diseases. Especially, the development of brain imaging techniques, such as fMRI, provided the possibility to explore brain regions involved in emotional processes and how they fail to interact in depression (Dannlowski et al., 2005; Mériau et al., 2006; Kerestes et al., 2012). For example, recent neuroimaging data, with a good spatial resolution, has allowed researchers to observe impairments at the neural level and to further support previous behavioral results (Rogers et al., 2004). The idea of exploring the neural correlates associated with depression-related impaired inhibition over emotional stimuli is then encouraging. However, fMRI suffers from poor temporal resolution. Cognitive functions, such as inhibition, require various steps and cognitive stages (serially or in parallel) to give rise to a normal performance. The origin of a behavioral impairment may thus arise from the alteration of a particular cognitive stage differently situated along the information-processing stream. The possibility to access dynamic temporal information should then be promoted and techniques effective enough to explore real time brain activity in the range of milliseconds should be used. A possible way to obtain a complete overview of the information processing across time is to use ERPs as they reflect changes in brain activity at early and late latencies. Actually, ERPs consist in several components, each one characterized by two main parameters: amplitude and latency. It's believed that the amplitude represents the degree of brain activation during a cognitive task, reflecting the attentional resources occupied during the task, and the latency represents the speed at which the stimulus is perceived, reflecting the time needed to discriminate the stimuli (Olofsson et al., 2008). Changes in the parameters (amplitudes and latencies) of some ERP's components, considered as an electrophysiological index of cognitive functioning (Miller, 1996), may so index particular cognitive impairments (Rugg and Coles, 1995).

Paradigms

The Emotional Stroop Task

In the emotional Stroop task, participants are confronted to emotional words written in different colors (see **Figure 1** below for an illustration). They are required to name colors of positive, neutral and/or negative words. Researchers then examine time responses for each emotional condition, reflecting different mechanisms of interference, which include interference inhibition. Note that this task, traditionally used in neuropsychological studies on inhibition, does not allow distinguishing between active selection of task relevant material and active inhibition of task-irrelevant (emotional) material (Hasher and Zacks, 1988).

The Negative Affective Priming Task

In classic NAP tasks, subjects are simultaneously confronted with two emotional stimuli (e.g., emotional words and/or emotional faces) (see **Figure 2** below for an illustration). One of those stimuli consists in a probe trial, and the other consists in a prime trial. Subjects have to specify the valence of the probe trial as fast as possible. Accordingly, the time necessary to respond depends on the prime trial. Indeed, the probe trial is processed faster when the prime is valence-congruent, while slower when the prime is valence-incongruent. On the following trial, the previous prime may become the new probe trial (or not). In this special case, priming occurs because the prime triggers other information of the same valence (Fazio et al., 1986). The power of cognitive inhibition on the first trial is indexed by the response latency for the new probe trial (Kircanski et al., 2012). A modified version of the negative priming paradigm (Joormann, 2004) allows examining both the possibility of enhanced facilitation and impaired inhibition at the input level in a single design.

FIGURE 1 | Illustration of an Emotional Stroop Task. Participants are asked to name the ink color as fast as possible for each presented words.

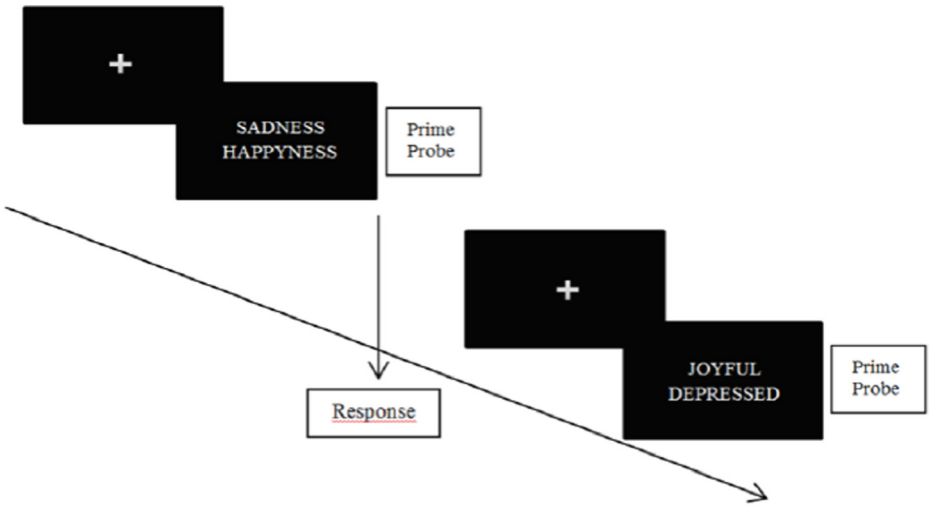

FIGURE 2 | Illustration of NAP task. Participants are asked to specify the valence of the probe stimulus as fast as possible.

The Cue-Target Task:

In a classical cue-target task, participants are required to response to the location of a target appearing after a cue (see **Figure 3** below for an illustration). Two conditions can occur: (1) a valid cue condition in which the target appears at the same location as the cue, and (2) an invalid cue condition in which the target appears at a different location as the cue. Cue validity is inferred if the reaction times (RTs) in the valid cue condition are significantly shorter than those in the invalid cue condition. On the contrary, an IOR effect is obtained if the RTs in the valid cue condition are not significantly shorter than those in the invalid cue condition.

The Go-NoGo Task:

During a classic Go-NoGo task, participants have to respond as fast as possible to one stimulus ("Go" stimulus), which set up a prepotent response tendency and not to another one ("NoGo" stimulus), which require that prepotent response tendency to be inhibited (see **Figure 4** below for an illustration). In an affective Go-NoGo task, subjects are required to respond to stimuli of one valence while inhibiting responses to stimuli of the opposite valence (Erickson et al., 2005; Bermpohl et al., 2006).

ERPs Components Reflecting Inhibition

Event-related potentials have widely been used to study neuronal processing related to inhibition in adults suffering from various psychopathological states. With regard to MDD, ERPs measured during cognitive inhibition tasks, such as the previously cited ones, revealed some modulation at early as well as at latter stages of the information-processing stream when processing affective material. Indeed, tasks looking for neurophysiological indices for impaired inhibition have respectively focused on several relevant ERPs components thought to index cognitive processes involved in inhibition. Early (P1, P2, N1 and N2) and late (P3, No-Go P3, N450, LPC) components have been explored depending on the tasks used to assess cognitive inhibition. That is, neuronal processing related to cognitive inhibition can be examined with electroencephalography (EEG) when combined with particular paradigms from used in cognitive psychology studies.

Early P1, P2, N1, N2

Firstly, detected around 60–140 milliseconds (ms) after stimuli onset, the P1 component consists in a positive deflection, which is thought to index the low-level features of stimuli and initial encoding for sensory information (Pierson et al., 1996; cited by Yang et al., 2011). Secondly, detected around 100–200 ms after stimuli onset, the N1 component consists in a negative deflection thought to index the attentional focus on target and a discrimination process within the focus of attention (Dai et al., 2011). Thirdly, detected around 160–210 ms after stimuli onset, the P2 component consists in a positive deflection, which is thought to index the detection of visual aspects at perceptual stages of information processing (Luck and Hillyard, 1994; cited by Yang et al., 2011). Above all, P2 with an anterior distribution on the scalp is also thought to reflect the initial difference of task-relevant stimuli from task-irrelevant stimuli. (Lindholm and Koriath, 1985; Hegerl and Juckel, 1993; cited by Yang et al., 2011). Finally, detected around 250–430 ms after stimuli onset, the N2 component consists in a negative deflection thought to index further evaluation of targets (Ritter et al., 1979; cited by Yang et al., 2011). Above all, N2 is also thought to reflect cognitive control, mismatch detection and affective experiences (Deldin et al., 2000; Folstein and Van Petten, 2008; cited by Yang et al., 2011).

Late P3, No-Go P3, LPC, N450

Firstly, detected around 300–600 ms after stimuli onset, the P3 component consists in a positive deflection thought to index late evaluation stage of processing and updating in working memory (Donchin and Coles, 1988; cited by Yang et al., 2011). Evaluated in Go-NoGo tasks, NoGo-P3 is thought to index cognitive inhibition function (Smith et al., 2013). Secondly, detected around 400–500 ms after stimuli onset, the N450 component

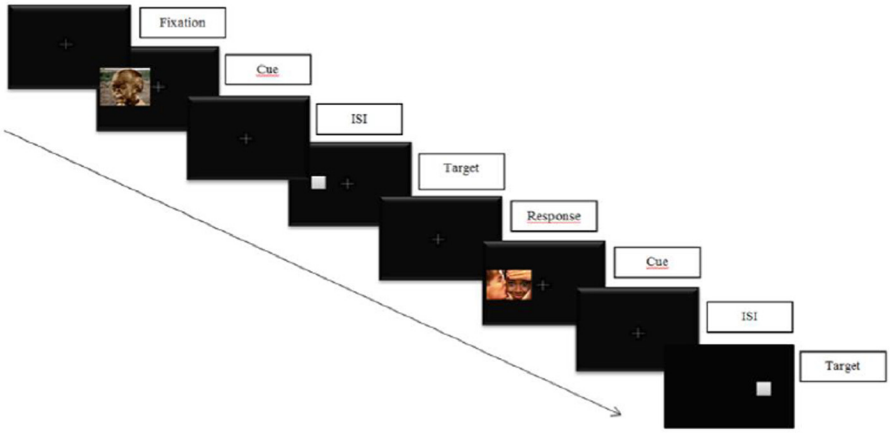

FIGURE 3 | Illustration of an emotional cue-target task. Participants are required to respond to the target location while inhibiting informations on cue's location.

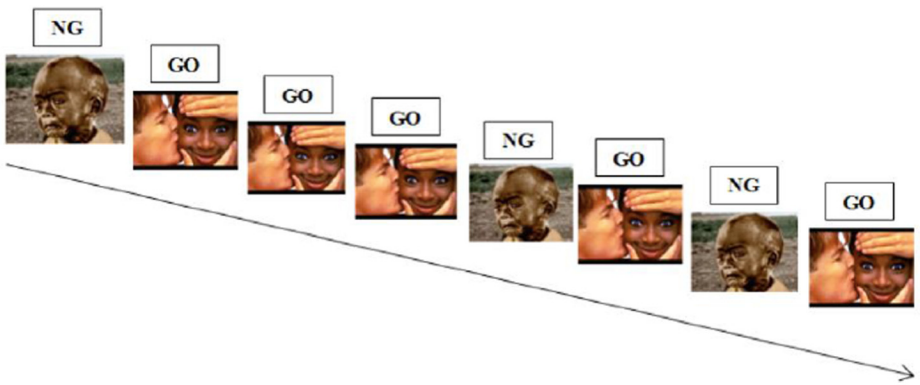

FIGURE 4 | Illustration of an emotional Go-NoGo task. Participants are required to respond to positive stimuli while inhibiting responses to negative stimuli.

consists in a negative deflection thought to index conflict processing. Importantly, it has been correlated to cognitive inhibition in the standard Stroop Task (McNeely et al., 2008). Finally, detected around 400–800 ms after stimuli onset, the Late Positive Component (LPC) consists in a positive deflection thought to index working memory updating at late evaluation stage of processing (Donchin and Coles, 1988; cited by Yao et al., 2010).

Inhibition Disturbances in Depression

Behavioral Studies

From now on, behavioral studies investigating cognitive inhibition deficits in MDD, through the used of inhibitory tasks described above, have found consistent impairments both in the processing of neutral material (Moritz et al., 2002; Erickson et al., 2005; Stordal et al., 2005; Markela-Lerenc et al., 2006; Gohier et al., 2009), and in the processing of emotional information (Joormann, 2004, 2010; Goeleven et al., 2006; Frings et al., 2007; Joorman and Gotlib, 2008; Dai and Feng, 2009; Yao et al., 2010; Dai and Feng, 2011; Dai et al., 2011). In this case, they have observed that depression is associated with impaired inhibition both at the input level (i.e., the ability to reduce the interference from emotional distracters) and the higher level (i.e., the ability to direct the attention away from emotional material that has already been processed) of the emotional information processing stream (Joormann, 2004; Goeleven et al., 2006; Joorman and Gotlib, 2008). Importantly, those studies have observed diminished inhibition ability in response to negative stimuli in depressed patients compared to control samples. For example, behavioral data obtained through NAP tasks suggested that, compared with control participants, MDD patients had enhanced negative priming and less inhibition of sad faces. For example, using a NAP task, Joormann (2004) have observed an altered inhibition toward negative words in depressive patients (MDD) and in remitted depressed patients (RMD). In another NAP study using facial emotions, Goeleven et al. (2006) observed a less effective inhibition specifically toward negative information in MDD individuals compared to never depressed patients (NC) and RMD subjects. Interestingly enough, mixed results have been found considering eventual inhibition impairments in RMD patients (Joormann, 2004; Goeleven et al., 2006). Indeed, while Joormann (2004) have observed a specific impaired

inhibition for negative material in formerly depressed patients as in currently depressed patients, Goeleven et al. (2006) have observed that formerly depressed individuals demonstrated impaired inhibition of both negative and positive information.

Importantly, most of those studies have suggested that the valence-specific (negative) inhibition impairment observed in MDD play a crucial role in rumination (Joormann, 2004; Joorman and Gotlib, 2006; Frings et al., 2007; De Lissnyder et al., 2010; Joormann and Gotlib, 2010; Zetsche and Joormann, 2011; Cohen et al., 2012, 2014, 2015; Daches and Mor, 2014). That is, when inhibition process malfunction, it might set the stage for ruminative responses to negative events and negative mood states due to a prolonged processing of negative, goal-irrelevant information (Koster et al., 2011). In other words, inhibitory dysfunction might reduce the control of access of negative cognitions into working memory. Given the capacity limitations of this system, it could lead to difficulties in attending to new information and reorient the attention to other aspects of the situation (Joormann and Gotlib, 2010), thereby hampering recovery from negative mood and leading to increased levels of negative affect Inhibition deficits might then link attention (Koster et al., 2005; De Raedt and Koster, 2010; Koster et al., 2011), memory (Hascher et al., 1999; cited by Lyubomirsky et al., 1998; Gohier et al., 2009) and rumination in MDD patients (Joormann, 2010). For instance, Koster et al. (2011) suggested that inefficient inhibitory functioning might be at the heart of difficulty to disengage attention away from irrelevant negative information, which contributes to rumination. Therefore, a major challenge of up-to-date research is to assess inhibitory functioning in MDD population.

Event-Related Potentials Studies

Only recently, studies have begun to explore the neural correlates associated with depression-related impaired inhibition over emotional stimuli with electroencephalography (EEG) during particular tasks in which participants have to inhibit some task-irrelevant information. Mounting ERP evidence indicates that depressive individuals display inhibitory dysfunction at the input and the higher level of the information processing-stream. We summarized here ERPs studies investigating inhibition in MDD.

Dai et al. (2011), interested in exploring the neural correlates of distracter inhibition ability for emotional faces in MDD patients, have used a modified emotional NAP task combined with ERPs. They have applied the task in control individuals who had never suffered from depression (NC), remitted depressed patients (RMD), and major depressive disorder patients (MDD). Their behavioral results suggested that MDD patients, compared to controls, had enhanced positive priming and less inhibition of sad faces, and those RMD patients, compared to controls, had general inhibitory deficits for all emotions faces and facilitation for sad faces. Accordingly, their neurophysiological results revealed that MDD patients displayed larger P1 and P3 amplitude for sad faces in the positive priming condition compared to both NC and RMD groups; and smaller P3 amplitude for sad faces in the negative priming condition. Those results suggest a deficient distracter inhibition and an excessive facilitation for negative stimuli in MDD patients. Interestingly, a deficient inhibition and an excessive facilitation for both positive and negative information were found in RMD patients.

In another study, Yao et al. (2010) have used a similar experimental design as they combined an affective NAP task while recording early P2 and later LPC components. At a behavioral level, they found a less effective inhibition for negative material. At a neurophysiological level, they observed an overall diminution in P2 amplitude for negative trials, and an overall diminution in LPC amplitude for both negative and positive trials. Specifically, their results also suggest that MDD patients have decreased central-parietal P2 amplitude and decreased LPC amplitude for negative material compared to controls.

Furthermore, interested in exploring the neural correlates of interference inhibition ability for emotional words in MDD patients, Dai and Feng (2011) have used a modified emotional Stroop task combined with ERPs. Comparing control individuals who had never suffered from depression (NC), subclinically depressed patients (RMD), and major depressive disorder patients (MDD), they found that MDD patients are characterized by behavioral (e.g., MDD patients have a higher interference effect for negative words than NC and RMD groups) and neurophysiological indices (e.g., diminished N1 amplitude for negative words and a diminished P1 amplitude for positive words in MDD patients compared to the other groups) for impaired attentional inhibition for negative information. Interestingly, impaired attentional inhibition for negative words was only observable in terms of neurophysiological responses in RMD patients (both RMD and MDD groups displayed enhanced N450 amplitude over the parietal regions for negative words compared to controls).

Another research has used a cue-target task to investigate the phenomenon of inhibition of return (IOR) in depressed individuals. In this study, Dai and Feng (2009) using emotional faces as cues, have applied their paradigm, combined with ERPs, on three groups: control individuals who had never suffered from depression (NC), remitted depressed patients (RMD), and major depressive disorder patients (MDD). They found that depressed patients had cue validity and a deficient IOR for negative stimuli that makes them enable to eliminate the interference of negative stimuli and might causes the development and the maintenance of depression (Dai and Feng, 2009). Interestingly, RMD participants had cue validity and a deficient IOR for both positive and negative stimuli, which, according to the authors, makes them enable to maintain emotional balance. Indeed, they observed in MDD patients larger P1 amplitude for sad cue compared to the others groups, larger P3 amplitude for sad cue than for other faces cues, smaller P3 amplitude for sad faces in the invalid cue-condition compared with the NC group, and smaller P3 amplitude for happy faces in the valid cue condition compared with the other groups.

In summary, behavioral studies have shown that MDD patients present inhibition dysfunction for negative material. Importantly, those results are mirrored in ERPs data, which shows that it modulates the earlier attention allocation stage as well as the later evaluation stage.

TOWARD A BETTER KNOWLEDGE OF INHIBITION DEFICITS THROUGH ERPs'

Depressed patients seem to daily experience sustained negative affect and a persistent reduction in positive affect. Several questions remain to find out why depressed patients cannot just swap out of negative vibes. Therefore a major research challenge is to identify contributing factors to the development, the maintenance and the recurrence of Major Depressive Disorder. It has been shown that the system that filters emotionally relevant information from irrelevant one is impaired in patients with Major Depressive Disorder and that this could underlie rumination by linking depression, attention and memory deficits observed in the disease. We reported here behavioral and ERPs results related to inhibition. Importantly, ERPs data mirror behavioral results showing that MDD patients present inhibition dysfunction for negative material, which modulates the earlier attention allocation stage as well as the later evaluation stage. Several theoretical and clinical implications for future developments arise from this.

Indeed, better theoretical knowledge of Major Depressive Disorder and its underlying cognitive deficits are needed. ERPs, with its good temporal resolution, seem to be a preferred technique to study cognitive impairments at a neural level. Moreover, ERPs could allow us to further deep into inhibitory processes. For instance, recent studies have suggested that diminished inhibitory control in response to a negative stimulus might in fact stem from a breakdown in both reactive and proactive cognitive control (Braver, 2012; Vanderhasselt et al., 2012, 2014). That is, Braver (2012) in the Dual Mechanisms of Control framework (DMC), states that cognitive inhibitory control consists of two complementary mechanisms in response to an imperative stimulus (e.g., conflict) that operate at different moments during conflict monitoring. On the one hand, proactive control appears early and refers to anticipatory or preparatory processes (i.e., activating and maintaining online goal-relevant information). On the other hand, reactive control appears later during conflict monitoring and acts as a correction mechanism that is activated when an ambiguous or conflict stimulus occurs (Jacoby et al., 1999). In recent studies, researchers have precisely resorted to ERPs to assess the amount of proactive and reactive control in depressed samples (Vanderhasselt et al., 2012, 2014). Furthermore, Major Depression Disorder is a heterogeneous mental illness (e.g., symptomatology, course, and treatments) (Downar et al., 2014). Subtypes of depression have been identified such as melancholia and non-melancholia and ERPs have already shown their discrimination power with regard to depression subtypes (Kemp et al., 2010). ERPs could then be considered as tools for parsing the heterogeneity of depression in ways that are intrinsically relevant for treatment selection.

In this vein, using ERPs could be of major relevance for clinicians. Firstly, future diagnosis and treatment procedures could be facilitated by the use of ERPs as they have shown in previous studies their ability to discriminate between currently depressed patients remitted patients and never depressed controls (Dai and Feng, 2009, 2011; Kemp et al., 2009; Dai et al., 2011; Delle-Vigne et al., 2015). Secondly, if traditional psychiatry has focused on behavioral symptoms rather than neurophysiological criteria to study mental disorders, their pathology, and orient their treatments, recent studies have demonstrated the possibility of using ERPs data as a potential state biomarker of various psychiatric disorders such as alcoholism (Petit et al., 2014) and depression (Kemp et al., 2009). Indeed, ERPs could be sensitive to some behaviorally invisible vulnerability. By indexing which stage of the inhibition process is impaired and revealing some behaviorally invisible vulnerabilities, ERPs could influence the choice of treatment for clinicians and therapists.

An interesting question would be whether boosting inhibition in MDD patients could lead to less rumination. For instance, cognitive training (Ditye et al., 2012) and neuromodulation techniques, such as repetitive Transcranial Magnetic Stimulation (rTMS) or transcranial Direct Current Stimulation (tDCS) (Hsu et al., 2011; Ditye et al., 2012; Juan and Muggleton, 2012; Campanella et al., 2016), have already been used to boost inhibitory functioning in normal controls and other psychopathological states. Indeed, cognitive training is an effective tool to improve a variety of cognitive functions. Regarding tDCS, it has previously been demonstrated that stimulation over the right inferior frontal gyrus (rIFG) facilitates behavioral inhibition performance and modulates its neurophysiological correlates (Campanella et al., 2016). Recently, researchers have begun to combine cognitive training and brain stimulation in order to assess the enhancing/synergic effect of those techniques. For instance, the study of Ditye et al. (2012) aimed to investigate the behavioral facilitation in the context of a learning paradigm by giving tDCS over the rIFG repetitively (i.e., 1.5 mA during 15 min) over four consecutive days of training on a behavioral inhibition task [stop signal task (SST)]. Their findings suggest that tDCS combined with cognitive training is effective for improving inhibitory functioning. In this view, the next step might be to investigate whether combining different techniques in order to boost inhibitory functioning could be of some relevance in clinical population in order to improve their pathological state.

With their potential to measure the evolution of resistance to distracting interferences, ERPs could be used as a way to assess inhibitory control, when patients are processing negative emotional stimuli, from baseline to one of those treatments's endpoint. Furthermore, in the aim to individualize treatment based on the personal characteristics of each patient, ERPs could help to predict which patient could benefit from those treatments. That is, patients who don't display inhibition deficits, when viewing negative emotional stimuli at baseline, should presumably not benefit from inhibition improvement treatments. Therefore ERPs combined to an inhibition task at baseline of treatment could have predictive value and be useful in the selection of patients who could benefit from it. However, further investigations are needed for neurophysiological biomarkers being regularly used in clinical psychiatry, which requires multi-guidelines to be developed for ERPs recording (Campanella and Colin, 2014).

CONCLUSION

Major Depressive Disorder patients cannot just swap out of negative vibes. Based upon the hypothesis that negative ruminations are at the center of depression processes and are probably underlined by impaired cognitive inhibition, we would preconize a multi-disciplinary treatment approach of the disease including social, psychological and medical support/treatment. Among them, neuromodulation techniques, such as transcranial Direct Current Stimulation (tDCS), Mindfulness and cognitive inhibition training could enhance depressed patients' abilities to inhibit negative ruminations. ERPs, given their high sensitivity for cognitive impairments, could play a crucial role by highlighting which impaired cognitive process should be trained in order to improve the patient's clinical state.

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All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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Prediction of Treatment Outcome in Patients with Obsessive-Compulsive Disorder with Low-Resolution Brain Electromagnetic Tomography: A Prospective EEG Study

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The issue of predicting treatment response and identifying, in advance, which patient will profit from treating obsessive-compulsive disorder (OCD) seems to be an elusive goal. This prospective study investigated brain electric activity [using Low-Resolution Brain Electromagnetic Tomography (LORETA)] for the purpose of predicting response to treatment. Forty-one unmedicated patients with a DSM-IV diagnosis of OCD were included. A resting 32-channel EEG was obtained from each participant before and after 10 weeks of standardized treatment with sertraline and behavioral therapy. LORETA was used to localize the sources of brain electrical activity. At week 10, patients were divided into responders and non-responders (according to a reduction of symptom severity >50% on the Y-BOCS). LORETA analysis revealed that at baseline responders showed compared to non-responders a significantly lower brain electric activity within the beta 1 ($t = 2.86$, $p < 0.05$), 2 ($t = 2.81$, $p < 0.05$), and 3 ($t = 2.76$, $p < 0.05$) frequency bands and ROI analysis confirmed a reduced activity in alpha 2 ($t = 2.06$, $p < 0.05$) in the anterior cingulate cortex (ACC). When baseline LORETA data were compared to follow-up data, the analysis showed in the responder group a significantly lower brain electrical resting activity in the beta 1 ($t = 3.17$. $p < 0.05$) and beta 3 ($t = 3.11$. $p < 0.05$) frequency bands and equally for the ROI analysis of the orbitofrontal cortex (OFC) in the alpha 2 ($t = 2.15$. $p < 0.05$) frequency band. In the group of non-responders the opposite results were found. In addition, a positive correlation between frequency alpha 2 (rho = 0.40, $p = 0.010$), beta 3 (rho = 0.42, $p = 0.006$), delta (rho = 0.33, $p = 0.038$), theta (rho = 0.34, $p = 0.031$), alpha 1 (rho = 0.38, $p = 0.015$), and beta1 (rho = 0.34, $p = 0.028$) of the OFC and the bands delta (rho = 0.33, $p = 0.035$), alpha 1 (rho = 0.36, $p = 0.019$), alpha 2 (rho = 0.34, $p = 0.031$), and beta 3 (rho = 0.38, $p = 0.015$) of the ACC with a reduction of the Y-BOCS scores was identified. Our results suggest that measuring brain activity with LORETA could be an efficient and applicable technique to prospectively identify treatment responders in OCD.

Keywords: treatment prediction, obsessive–compulsive disorder, LORETA, anterior cingulate cortex, EEG

INTRODUCTION

Obsessive-compulsive disorder (OCD) has a life-time prevalence of 0.8–2% and is characterized by the presence of obsessions and/or compulsions (Baldwin et al., 2005). Patients suffering from this disorder are best treated with a combination therapy consisting of a selective serotonin reuptake inhibitor (SSRI) and cognitive behavioral therapy (CBT), using exposure and response prevention techniques. However, not all patients profit from this treatment. Up to 30% of OCD patients treated with this combination therapy show no or poor improvement after this standard treatment (Ferguson, 2001). Differences of treatment response suggest the existence of biological differences among groups of OCD patients. Therefore, it would be desirable to distinguish responders and non-responders before initiation of the treatment course. The non-responder group could possibly profit from early on augmentation treatment strategies and a closer clinical monitoring. To date some studies have tried to identify helpful tool for predicting therapy response in OCD patients. One genome-wide association study indicated suggestive roles of genes in the glutamatergic neurotransmission and the serotonergic system as genetic predictors of treatment response in the OCD patient cohort (Qin et al., 2015). Also, longer duration of illness was found to be a significant predictor of remission (Eisen et al., 2013). One PET imaging study showed that a reduced regional cerebral blood flow in the orbitofrontal cortex (OFC) and higher values in the posterior cingulate cortex predicted better treatment response to fluvoxamine (Rauch et al., 2002). However, studies investigating prognostic biomarkers that are widely available and can be measured before treatment are rare. One pilot study examined the possibility of predicting treatment response in OCD patients with low-resolution electromagnetic tomography and investigated therefore 17 drug-free OCD patients. Over the course of a 12 week treatment with antidepressants (clomipramine, fluoxetine, sertraline, paroxetine, imipramine, nortiptyline, venlafaxine, and mirtazapine), LORETA values were calculated twice. The 17 patients were classified as responders and non-responders according to a reduction of at least 35% in the YBOCS score. The authors found that responders exhibited significantly lower activities in the beta band in the rostral anterior cingulate and the medial frontal gyrus (Fontenelle et al., 2006). Though the results have to been seen as preliminary as the sample size was rather small and OCD patients did not have a standardized treatment. In addition, functional imaging studies have revealed an abnormally increased activity in the OFC, the basal ganglia and the anterior cingulate cortex (ACC) in patients with OCD (Alptekin et al., 2001; Lacerda et al., 2003), whereas successful pharmacological or psychotherapeutic treatment of OCD patients was associated with a reduction of aberrant activity in the OFC area (Aouizerate et al., 2004).

The present study is based on the previously above mentioned results mainly the findings from Fontenelle et al. and aimed to further investigate whether Low-Resolution Brain Electromagnetic Tomography (LORETA; Pascual-Marqui et al., 1994), a three-dimensional EEG source localization technique, could be a helpful tool to identify whether OCD patients that show a clinical improvement over the course of treatment compared to those patients who do not respond show differences in LORETA values before and/or after standardized treatment. In addition, the correlation between clinical treatment effects and the electromagnetic tomography data was evaluated.

MATERIALS AND METHODS

Subjects

In total, forty-one patients with OCD (18 women, 23 men; average age 34.5 years, SD: 9.8; mean duration of illness: 12.8 years, SD 9.3) participated in the study. All patients were diagnosed according to DSM-IV and ICD-10. Symptom severity was assessed using the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS; Goodman et al., 1989), where a score of at least 18 was required for inclusion. In addition, the Maudsley Obsessive–Compulsive Scale (MOCI; Hodgson and Rachman, 1977) for the assessment of OCD symptoms and the Hamilton Depression Scale (HAMD-17; Hamilton, 1960) as well as the Beck Depression Inventory (BDI; Beck et al., 1961) for the assessment of comorbid depressive symptomatology were applied. Moreover, the State-Trait Anxiety Inventory (STAI; Laux et al., 1981) was used in order to assess state and trait anxiety in patients. Subjects had to be free of comorbid psychiatric, neurological or severe somatic diagnoses. All patients were either unmedicated or had undergone a wash-out period of at least 2 weeks. The study was reviewed and approved by the local ethics committee of the Ludwig–Maximilians University and was carried out in accordance with the Declaration of Helsinki. All subjects gave written informed consent for participation in this study, after design and procedures had been fully explained.

Study Design

A neurophysiological baseline recording of resting EEG was performed in all patients. After this initial examination, patients received for 10 weeks a combination therapy consisting of an antidepressant and psychotherapy. All patients received the selective serotonin reuptake inhibitor (SSRI) sertraline. The initial dose was 50 mg/d for 4 weeks unchanged. Patients that showed a reduction of <10% in the Y-BOCS score after 4 weeks on treatment received a dose augmentation to 100 mg/d sertraline and after 7 weeks an increase to 150 mg/d was possible. In addition, all patients received semi-structured CBT (with flooding, family and couple therapy) as an inpatient at the Psychosomatic clinic Roseneck. At the end of the 10 week treatment phase, a second EEG was performed in all study participants. Treatment response was defined as a 50% or more decrease in the Y-BOCS score after 10 weeks treatment with sertraline and behavior therapy. The 50% reduction criterion was chosen according to reports by Tolin et al. (2005) who demonstrated that a Y-BOCS reduction of 40–50% may be optimal for predicting mild illness or better at posttreatment (CGI 3), and Lewin et al. (2011) who showed that a 35% Y-BOCS reduction may be sufficient for clinical use, but for research 45% or even 55% may be more efficient.

EEG Data Acquisition and Loreta Analysis

For EEG recording, patients were seated in a sound-attenuated, electrically shielded room in a reclining chair with eyes closed (wakeful-resting condition). Electrodes were placed via electrocaps (Electro-Cap International, Inc., Eaton, USA) according to the 10/20 system with Cz as reference and Fpz as ground electrode. Additional electrodes (above the left eye and at the left ocular canthis) were used to record the electrooculogram (EOG) simultaneously. Electrode skin impedance was $<5\,k\Omega$ throughout the session. Data were collected with a sampling rate of 250 Hz and an analogous bandpass filter (0.16–50 Hz). All EEG recordings lasted 40 min. Before analysis, artifact detection was visually performed and additionally, the EEG was analyzed four times independently by two experienced neurophysiologists. When artifact detection was finished, segments with 2048 ms (512 data points) were chosen for further processing. A priori it was determined that only subjects with at least 40 artifact-free epochs would be included. The analyses of the frequency and localization were performed with the LORETA (low resolution brain electromagnetic tomography) software package (Pascual-Marqui et al., 1999). The following (standard definitions) frequency bands of LORETA cross spectrum analysis were identified for: delta (1.5–6.0 Hz), theta (6.5–8.0 Hz, alpha1 (8.5–10.0 Hz), alpha2 (10.5–12.0 Hz), beta1 (12.5–18.0 Hz), beta2 (18.5–21.0 Hz), and beta3 (21.5–30.0 Hz). The method LORETA assumes that the smoothest of all activity distributions is most plausible ("smoothness assumption") and therefore, a particular current density distribution is found. This fundamental assumption of LORETA directly relies on the neurophysiological observation of coherent firing of neighboring cortical neurons during stimulus processing (Pascual-Marqui et al., 1994) and therefore can be seen as a physiologically based constraint. However, this coherent firing has been described on

TABLE 1 | Descriptive socio-demographic data of responders and non-responders.

Comparison of responders ($n = 20$) and non-responders ($n = 21$)			
	Responder	**Non-responder**	**Significance**
Age in years	35.0 (±8.8)	34.0 (±10.7)	$p = 0.758$ $t = 0.311$
Age of disease onset	22.3 (±10.5)	21.2 (±8.3)	$p = 0.716$ $t = 0.367$
Duration of illness	12.7 (±9.7)	12.8 (±9.0)	$p = 0.963$ $t = 0.047$
Dose of sertraline (mg)	63.2 (±36.7)	61.9 (±21.8)	$p = 0.334$ $\chi^2 = 2.191$
Smoking status	5 smoker; 15 non-smoker	5 smoker; 16 non-smoker	$p = 0.929$ $\chi^2 = 0.008$
Gender	9 female; 11 male	9 female; 12 male	$p = 0.890$ $\chi^2 = 0.190$

TABLE 3 | Differences of responders and non-responders at baseline and follow-up.

Comparison of responders ($n = 20$) and non-responders ($n = 21$)			
	Responder	**Non-responder**	
BASELINE			
Y-BOCS total score	25.15 (±6.21)	25.43 (±5.49)	$p = 0.880$ $t = 0.15$
Y-BOCS compulsions	11.80 (±4.20)	11.86 (±3.47)	$p = 0.962$ $t = 0.05$
Y-BOCS obsessive thoughts	13.35 (±2.96)	13.57 (±2.64)	$p = 0.802$ $t = 0.25$
HAMD-17	13.90 (±6.55)	11.65 (±5.53)	$p = 0.248$ $t = 1.18$
MOCI	12.61 (±4.63)	13.83 (±3.92)	$p = 0.399$ $t = 0.86$
BDI	15.21 (±8.31)	19.44 (±8.73)	$p = 0.140$ $t = 1.51$
AFTER 10 WEEKS TREATMENT			
Y-BOCS total score	8.30 (±4.04)	20.29 (±6.09)	$p = 0.000$ $t = 7.39$
Y-BOCS compulsions	3.90 (±2.17)	9.43 (±3.71)	$p = 0.000$ $t = 5.86$
Y-BOCS obsessive thoughts	4.40 (±2.44)	10.86 (±2.94)	$p = 0.000$ $t = 7.64$
HAMD-17	8.30 (±7.40)	10.00 (±6.85)	$p = 0.456$ $t = 0.75$
MOCI	7.06 (±5.18)	11.18 (±6.17)	$p = 0.043$ $t = 2.11$
BDI	10.11 (±12.37)	17.78 (±12.17)	$p = 0.069$ $t = 1.88$
DIFFERENCE BASELINE—WEEK 10			
Y-BOCS total score	16.85 (±5.82)	5.14 (±4.91)	$p = 0.000$ $t = 6.97$
Y-BOCS compulsions	7.90 (±3.60)	2.43 (±3.14)	$p = 0.000$ $t = 5.20$
Y-BOCS obsessive thoughts	8.95 (±3.52)	2.71 (±2.76)	$p = 0.000$ $t = 6.33$
HAMD-17	5.60 (±5.69)	1.47 (±7.53)	$p = 0.063$ $t = 1.92$
MOCI	5.93 (±5.42)	2.87 (±2.75)	$p = 0.064$ $t = 1.96$
BDI	5.71 (±11.37)	2.65 (±8.62)	$p = 0.384$ $t = 0.88$

TABLE 2 | Descriptive psychopathology of the patients at baseline and follow-up.

Patients with OCD ($n = 41$)				
	Baseline mean (*sd*)	**After 10 weeks treatment mean (*sd*)**	**Delta (sd)**	**Significance**
Y-BOCS total score	25.29 (±5.78)	14.44 (±7.94)	10.85 (±7.96)	$p = 0.000$ $t = 8.74$
Y-BOCS sub score (compulsions)	11.83 (±3.79)	6.73 (±4.12)	5.10 (±4.33)	$p = 0.000$ $t = 7.54$
Y-BOCS sub score (obsessive thoughts)	13.46 (±2.77)	7.71 (±4.22)	5.76 (±4.43)	$p = 0.000$ $t = 8.32$
HAMD-17	12.78 (±6.08)	9.15 (±7.09)	3.59 (±6.89)	$p = 0.002$ $t = 3.26$
BDI	17.27 (±8.67)	13.94 (±12.70)	4.18 (±10.06)	$p = 0.002$ $t = 2.42$
MOCI	13.20 (±4.16)	8.80 (±5.56)	4.40 (±4.50)	$p = 0.000$ $t = 5.36$

the level of cortical columns, which have a much smaller diameter than the voxels used in the LORETA software; the empirical basis for coherent firing in the millimeter range is not strong enough to fully accept this constraint as a physiological one, even if it might help to produce useful results. While for typical scalp-potentials, coherent firing might be observed in brain volumes as large as or even larger than LORETA voxels. Therefore, the resulting solution is characterized by its relatively low spatial resolution, which is a direct consequence of the smoothness constraint. Taken this together, the solution produces a "blurred-localized" image of a point source, conserving the location of maximal activity, but with a certain degree of dispersion. In the present study, the version of LORETA used is the digitized Talairach atlas available as digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute, estimating the current source density (microAmperes/mm2) distribution for either single time points or epochs of brain electric activity on a dense grid of 2394 voxels at 7 mm spatial resolution (Pascual-Marqui et al., 1999). The solution space (the three-dimensional space where the inverse EEG problem is solved) was restricted to the gray matter and hippocampus in the Talairach atlas (anatomically based constraint). Localization with regard to spherical and realistic head geometry was done using EEG electrode coordinates reported by Towle et al. (1993).

Statistical Analyses

EEG frequency bands included in the analyses of delta (1.5–6.0 Hz), theta (6.5–8.0 Hz), alpha 1 (8.5–10 Hz), alpha 2 (10.5–12.0 Hz), beta 1 (12.5–18.0 Hz), beta 2 (18.5–21.0 Hz), and beta 3 (21.5–30.0 Hz). For the assessment of treatment effects in OCD patients, a region of interest (ROI) approach was defined as follows: 1. ACC: anterior cingular cortex and 2. OFC: orbito-frontal cortex. These regions were chosen because these have been previously identified with altered activity and response to antidepressant treatment (Fontenelle et al., 2006; Mulert et al., 2007; Schiepek et al., 2007). The first ROI ACC consisted of 25 voxel from the Brodmann areas 24, 25, and 32 and also the Talairach from x = −10 to 11, from y = 3 to 45 and from z = −6 to 8. The second ROI OFC consists of 298 voxel from the Brodmann areas 10, 11, 25, and 47 and also the Talairach from x = −45 to 52, from y = 9 to 65 and from z = −25 to 24.

In order to evaluate group differences between responders and non-responders in regard to age, age of disease onset, gender and data about the psychopathology unpaired *t*-test for independent samples was used. Spearman's correlation coefficients were calculated to relate the measured LORETA current density changes in the defined ROIs vs. the reduction of Y-BOCS scores. In addition, linear as well as robust regression techniques were used to assess the association between density changes and the reduction of Y-BOCS. Huber type M-estimation (Huber and Ronchetti, 1981) as implemented in the R package MASS (Venables and Ripley, 2002; function rlm) was used to down-weight observations with extreme density changes. As further robust technique, which also takes outliers in Y-BOCS scores and leverage points into account, we used MM-estimation (Yohai et al., 1991; Marazzi, 1993; function rlm) which combines M-estimation with the resistance of high breakdown estimators. Approximate *p*-values based on the assumption that the t statistics [estimate/SE(estimate)] are approximately normally distributed were obtained for M-estimators and MM-estimators. Given the exploratory character of the study, statistical significance levels were set to $p < 0.05$ and $p < 0.10$ (statistical trend) and not additionally corrected for multiple comparisons. Statistical analyses were performed using the SPSS software (IBM SPSS, Version 23.0), the statistical software R (version 3.0.1; Team, 2013) or with the implemented LORETA analysis tool that includes a correction for multiple comparisons and does not require any assumption of Gaussianity (Diener et al., 2010). The localization of the differences in activity between the groups of responders and non-responders was assessed by voxel-by-voxel non-paired *t*-test of the LORETA images, based on the power of estimated electric current density, which results in *t* statistic three dimensional images (Mientus et al., 2002). In these images, cortical voxels of statistically significant differences were identified by a non-parametric approach (maximum t-statistic) using randomization strategy that determined the critical probability threshold values for actually observed statistic with corrections for multiple testing (Holmes et al., 1996).

RESULTS

All OCD Patients Compared at Baseline and Follow-Up

Descriptive Clinical Data

Sociodemographic data was compared between the groups of responders and non-responders and no statistical differences were identified. Data concerning the psychopathology of the patients showed a significant reduction over the course of the therapy in all rating scales. After 10 weeks of treatment, 20 of 41 patients fulfilled the criteria for treatment response, defined as a decrease in the Y-BOCS score by at least 50%, see also **Tables 1–3** for detailed results.

EEG Data

The distribution of EEG frequency bands is shown in **Tables 4–7** and **Figure 1** for baseline and follow-up and also the comparison of the responders and non-responders (OFC and ACC region) are displayed.

Responders Compared at Baseline and Follow-Up

When the time points at baseline and follow-up were compared, responders exhibited significantly lower brain electrical resting activity in the LORETA analyses in the beta 1 (12.5–18.0 Hz; $t = 3.17$. $p < 0.05$) and beta 3 (21.5–30.0 Hz; $t = 3.11$. $p < 0.05$) frequency band, especially in the pre- and postcentral gyri of the frontal and parietal lobe. This indicates an increase in activity over the course of treatment. Results are shown in **Table 8** and **Figures 2A,B**.

Within the ROI analysis of the brain area OFC responders exhibited a significantly lower brain electrical resting activity in the alpha 2 (10.5–12.0 Hz; $t = 2.15$. $p < 0.05$) frequency band

TABLE 4 | Frequency bands of the ACC.

Frequency bands (in 10^{-3} μV^2)		alpha1 T0	alpha1 T1	alpha2 T0	alpha2 T1	beta1 T0	beta1 T1	beta2 T0	beta2 T1	beta3 T0	beta3 T1	delta T0	delta T1	theta T0	theta T1
Non-responder	Mean	0.049	0.043	0.107	0.099	0.060	0.061	0.177	0.220	1.306	1.218	0.738	0.526	0.079	0.068
	n	21	21	21	21	21	21	21	21	21	21	21	21	21	21
	sd	0.0412	0.0363	0.0755	0.0921	0.0522	0.0769	0.1481	0.3323	0.8993	1.0182	0.6295	0.3232	0.0664	0.0574
	Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.3	0.2	0.2	0.0	0.0
	Maximum	0.2	0.1	0.3	0.4	0.2	0.3	0.6	1.6	3.5	4.9	2.6	1.4	0.2	0.2
Responder	Mean	0.049	0.068	0.067	0.091	0.034	0.042	0.101	0.122	0.980	2.032	0.552	1.633	0.088	0.087
	n	20	20	20	20	20	20	20	20	20	20	20	20	20	20
	sd	0.0543	0.0816	0.0459	0.0599	0.0217	0.0248	0.0840	0.0765	0.6675	3.5464	0.4261	3.2201	0.0908	0.0716
	Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.1	0.2	0.0	0.0
	Maximum	0.2	0.3	0.2	0.3	0.1	0.1	0.4	0.3	3.0	16.0	1.6	014.5	0.4	0.3
All patients	Mean	0.049	0.055	0.087	0.095	0.047	0.051	0.140	0.172	1.147	1.615	0.647	1.066	0.083	0.077
	n	41	41	41	41	41	41	41	41	41	41	41	41	41	41
	sd	0.0474	0.0631	0.0653	0.0773	0.0419	0.0579	0.1257	0.2460	0.8020	2.5810	0.5415	2.3002	0.0783	0.0647
	Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.1	0.2	0.0	0.0
	Maximum	0.2	0.3	0.3	0.4	0.2	0.3	0.6	1.6	3.5	16.0	2.6	0.4.5	0.4	0.3

Descriptive data about the frequency bands of the ACC region. T0 are baseline values and T1 are values after 10 weeks of treatment in μV^2. n, number of patients; sd, standard deviation.

TABLE 5 | Frequency bands of the OFC.

Frequency bands (in 10^{-3} μV^2)		alpha1 T0	alpha1 T1	alpha2 T0	alpha2 T1	beta1 T0	beta1 T1	beta2 T0	beta2 T1	beta3 T0	beta3 T1	delta T0	delta T1	theta T0	theta T1
Non-responder	Mean	0.052	0.044	0.130	0.111	0.074	0.073	0.214	0.243	1.275	1073	0.641	0.476	0.076	0.057
	n	21	21	21	21	21	21	21	21	21	21	21	21	21	21
	sd	0.0510	0.0464	0.1035	0.1073	0.0725	0.1059	0.2016	0.3661	1.1111	0.9726	0.8012	0.3530	0.0787	0.0518
	Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.2	0.1	0.1	0.0	0.0
	Maximum	0.2	0.2	0.4	0.4	0.3	0.5	0.9	1.7	5.1	4.7	3.9	1.4	0.3	0.2
Responder	Mean	0.042	0.059	0.062	0.099	0.033	0.047	0.098	0.140	0.826	1.974	0.452	1.453	0.068	0.073
	n	20	20	20	20	20	20	20	20	20	20	20	20	20	20
	sd	0.0453	0.0576	0.0406	0.0737	0.0204	0.0317	0.0765	0.0999	0.5289	3.3293	0.3307	3.0294	0.0672	0.0588
	Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.4	0.2	0.2	0.0	0.0
	Maximum	0.2	0.2	0.2	0.3	0.1	0.1	0.3	0.4	2.4	14.3	1.3	12.9	0.3	0.2
All patients	Mean	0.047	0.051	0.097	0.105	0.054	0.060	0.157	0.193	1.056	1.513	0.549	0.953	0.072	0.065
	n	41	41	41	41	41	41	41	41	41	41	41	41	41	41
	sd	0.0480	0.0520	0.0856	0.0915	0.0571	0.0792	0.1631	0.2728	0.8955	2.4384	0.6182	2.1600	0.0725	0.0553
	Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.2	0.1	0.1	0.0	0.0
	Maximum	0.2	0.2	0.4	0.4	0.3	0.5	0.9	1.7	5.1	14.3	3.9	12.9	0.3	0.2

Descriptive data about the frequency bands of the OFC region. T0 are baseline values and T1 are values after 10 weeks of treatment in μV^2. n, number of patients; sd, standard deviation.

where time points before and after treatment were compared. For the frequency bands alpha 1 (8.5–10.0 Hz; $t = 2.05$. $p < 0.10$) and beta 1 (12.5–18.0 Hz; $t = 1.80$. $p < 0.10$) a trend toward a reduced activity was evaluated. In addition, ROI analysis of the area ACC revealed a trend toward a reduced activity in the frequency band alpha 1 (8.5–10.0 Hz; $t = 1.77$. $p < 0.10$) when baseline was compared to follow-up.

Non-Responders Compared at Baseline and Follow-Up

For the patient group of the non-responders a significantly higher brain electrical resting activity according to the LORETA analysis could be shown in the beta 1 (12.5–18.0 Hz; $t = 3.11$. $p < 0.05$) frequency band when baseline was compared to follow-up, indicating that brain activity decreased over the course of treatment. A similar trend toward a higher activity in the

TABLE 6 | Changes of the frequency bands of the ACC.

Changes in the frequency bands (in 10^{-3} μV^2)		alpha1 T1–T0	alpha 2 T1–T0	beta 1 T1–T0	beta 2 T1–T0	beta 3 T1–T0	delta T1–T0	theta T1–T0
Non-responder	Mean	−0.006	−0.064	0.001	0.044	−0.087	−0.211	0.000
	n	21	21	21	21	21	21	21
	sd	0.0270	0.0624	0.0581	0.2835	0.9188	0.7525	0.0400
	Minimum	−0.1	−0.2	−0.1	−0.2	−2.3	−2.0	0.0
	Maximum	0.1	0.0	0.2	1.2	2.8	1.0	0.0
Responder	Mean	0.019	0.001	0.007	0.021	1.052	1.080	0.000
	n	20	20	20	20	20	20	20
	sd	0.0475	0.0688	0.0280	0.1024	3.3387	3.2735	0.0800
	Minimum	−0.1	−0.1	0.0	−0.2	−0.2	−0.7	0.0
	Maximum	0.2	0.2	0.1	0.2	0.2	14.2	0.0
All patients	Mean	0.006	−0.032	0.004	0.033	0.469	0.419	0.000
	n	41	41	41	41	41	41	41
	sd	0.0399	0.0725	0.0455	0.2128	2.4596	2.4086	0.06
	Minimum	−0.1	−0.2	−0.1	−0.2	−2.3	−2.0	0.0
	Maximum	0.2	0.2	0.2	1.2	14.0	14.2	0.0

TABLE 7 | Changes of the frequency bands of the OFC.

Changes in the frequency bands (in 10^{-3} μV^2)		alpha1 T1–T0	alpha 2 T1–T0	beta 1 T1–T0	beta 2 T1–T0	beta 3 T1–T0	delta T1–T0	theta T1–T0
Non-responder	Mean	–0.007	–0.019	0.001	0.000	–0.202	–0.165	–0.019
	n	21	21	21	21	21	21	21
	sd	0.0450	0.0928	0.0965	0.3400	1.1531	0.7782	0.0724
	Minimum	–0.1	–0.2	–0.1	0.0	–3.9	–3.3	–0.3
	Maximum	0.1	0.3	0.4	0.0	2.9	0.7	0.1
Responder	Mean	0.017	0.037	0.013	0.000	1.148	1.001	0.005
	n	20	20	20	20	20	20	20
	sd	0.0393	0.0776	0.0342	0.1200	3.1715	3.0062	0.0626
	Minimum	0.0	–0.1	0.0	0.0	–1.4	–0.7	–0.2
	Maximum	0.1	0.2	0.1	0.0	12.5	12.2	0.1
All patients	Mean	0.005	0.008	0.006	0.000	0.456	0.404	0.007
	n	41	41	41	41	41	41	41
	sd	0.0436	0.0893	0.0726	2.4309	2.4309	2.2235	0.0681
	Minimum	–0.1	–0.2	–0.1	0.0	–3.9	–3.3	–0.3
	Maximum	0.1	0.3	0.4	0.0	12.5	12.2	0.1

non-responder group was detected for the frequency bands alpha 1 (8.5–10.0 Hz; $t = 2.90$. $p < 0.10$), alpha 2 (10.5–12.0 Hz; $t = 2.92$. $p < 0.10$) and beta 2 (18.5–21.0 Hz; $t = 2.73$. $p < 0.10$). Over the course of treatment the activity diminished. In the ROI analysis no significant differences were found for the non-responder group. **Table 9** shows the significant results and **Figures 3A,B** displays the current density of the LORETA analysis for beta 1.

Responders vs. Non-Responders at Baseline

Responders were compared to non-responders before therapy at baseline, where a significant hypoactivity for responders was found in the LORETA analyses in the frequency bands beta 1 (12.5–18.0 Hz; $t = 2.86$, $p < 0.05$), beta 2 (18.5–21.0 Hz; $t = 2.81$, $p < 0.05$) and beta 3 (21.5–30.0 Hz; $t = 2.76$, $p < 0.05$). Precisely, the brain regions that were affected by the hypoactivity were for beta 1 the medial/superior frontal gyrus (12 voxels, BA 9/10, $p < 0.05$, *t*-values between −2.90 and −3.31) and the inferior frontal gyrus, precentral gyrus (5 voxels, BA 44, $p < 0.05$, $t = -3.31$). For beta 2 the medial/superior frontal gyrus (9 voxels, BA 10, $p < 0.05$, t-values between −2.88 and 3.03) and medial/inferior temporal gyrus (4 voxels, BA 20, 21, $p < 0.05$, $t = 3.01$) and precentral gyrus (3 voxels, BA 6, $p < 0.05$, $t = 3.29$). And for beta 3 the medial/superior frontal gyrus (BA 10, $p < 0.05$, 13 voxels, *t*-values between 2.80 and −3.04)

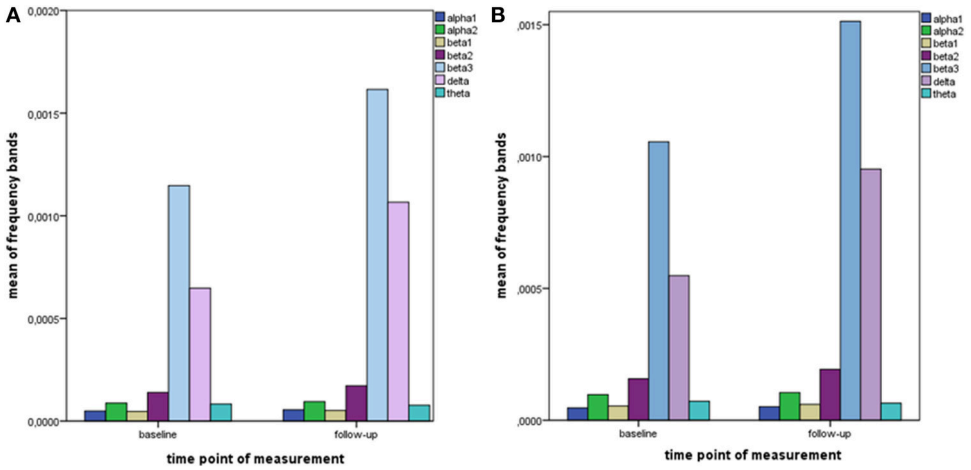

FIGURE 1 | Descriptive data of EEG frequency bands. Mean values of all measured EEG frequency bands (in μAmpere/mm^2) are shown at baseline and at follow-up. **(A)** brain region ACC; **(B)** brain region OFC.

TABLE 8 | Characteristics of LORETA current density differences for responders at baseline and follow-up.

Frequency band	Talairach coordinates X Y Z			*t*-value (significance)	Anatomy
beta 1	−45	24	22	3.40 ($p < 0.05$)	BA 46 (medial frontal gyrus)
	−52	24	29	3.40 ($p < 0.05$)	BA 46 (medial frontal gyrus)
	−45	24	29	3.40 ($p < 0.05$)	BA 46 (medial frontal gyrus)
	−24	45	29	3.18 ($p < 0.05$)	BA 10 (superior frontal gyrus)
	−31	52	29	3.18 ($p < 0.05$)	BA 10 (superior frontal gyrus)
beta 3	−31	−18	−34	3.22 ($p < 0.05$)	BA 20 (uncus. Limbic cortices)
	−31	−11	−27	3.22 ($p < 0.05$)	BA 20 (uncus. Limbic cortices)
	−31	−18	−27	3.22 ($p < 0.05$)	BA 36 (parahippocampal gyrus)

BA, Brodmann area.

and fusiform gyrus (BA 20/37, 21 voxels, $p < 0.05$, *t*-values between −2.97 and −4.06) and parahippocampal gyrus (5 voxels, $p < 0.05$, *t*-values between −2.97 and −4.33) and medial/inferior temporal gyrus (BA 37, 6 voxels, $p < 0.05$, *t*-values between −3.00 and −4.06) were identified. **Figures 4A,B** summarize the results.

The ROI analysis revealed that the area ACC shows a significantly reduced activity of the responders in comparison to non-responders in the frequency band alpha 2 (10.5–12.0 Hz; $t = 2.06$, $p < 0.05$) at baseline. Additionally, a trend toward a reduced activity was found for beta 1 (12.5–18.0 Hz; $t = 2.06$, $p = 0.05$) and beta 2 (18.5–21.0 Hz; $t = 2.04$, $p = 0.05$). The other investigated area OFC had also a reduced activity for the group of responders compared to non-responders in the frequency bands alpha 2 (10.5–12.0 Hz; $t = 2.81$, $p < 0.01$), beta 1 (12.5–18.0 Hz; $t = 2.50$, $p < 0.05$) and beta 2 (18.5–21.0 Hz; $t = 2.50$, $p < 0.05$) at baseline.

Responders vs. Non-Responders at Follow-Up

The two groups of responders and non-responders did not show significant differences with regard to LORETA and ROI analyses after 10 weeks at follow-up.

Correlation of the Psychopathology with Electrophysiological Data

The psychopathology of the OCD patients measured with the aid of Y-BOCS was correlated with the brain activity of the ROI areas OFC and ACC at baseline and follow-up. The activity change was defined as: brain activity after 10 weeks of treatment minus activity at baseline. Using Spearman's correlation coefficient a positive correlation between the brain activity change in the area ROI OFC and the reduction of the Y-BOCS scores was identified for the frequency bands alpha 2 (rho = 0.40, $p = 0.010$), beta 3 (rho = 0.42, $p = 0.006$), delta (rho = 0.33, $p = 0.038$), theta (rho = 0.34, $p = 0.031$), alpha 1 (rho = 0.38, $p = 0.015$), and beta1 (rho = 0.34, $p = 0.028$).

Since the data contains many outliers, linear regression was not appropriate and robust regression techniques were applied. **Figure 5** shows the regression lines obtained by Huber-type M-estimation (dotted line) and MM-estimation (dashed line). In addition, the regression line of the classical least squares fit is shown (solid line) to assess the influence of outlying observations. For five of six frequency bands the slope of the least squares regression line is larger than that of the robust techniques, indicating that the outlying observations induce a larger correlation between psychopathology and electrophysiological data. The approximate *p*-values for testing the regression coefficients obtained through M-estimation or MM-estimation are very small (**Table 10**), indicating that there is an association even after taking outliers and influential points into account.

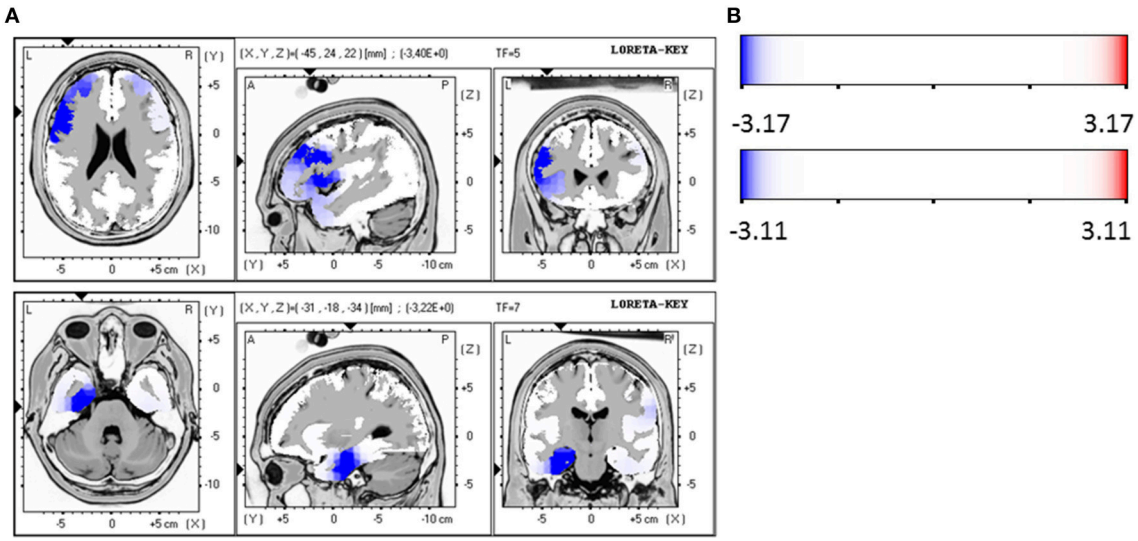

FIGURE 2 | (A) LORETA images for responders at baseline and follow-up: Images on top show voxel-wise current density differences in the frequency band beta 1 for responders at baseline compared to follow-up. In the bottom line the same is shown for the frequency band beta 3. The blue color indicates a statistical significant effect (images in the top line: $t_{max} = -3.40$, xyz = −45, 24, 22, $p < 0.05$ and bottom line: $t_{max} = -3.22$, xyz = −31, −18, −34) of reduced current density in the MNI-MRI-standard space. **(B)** Corresponding color bar.

TABLE 9 | Characteristics of LORETA current density differences for non-responders.

Frequency band	Talairach coordinates X Y Z	*t*-value (significance)	Anatomy
beta 1	39 10 −6	3.20 ($p < 0.05$)	BA 13 (sub-lobar)

BA, Brodmann area.

Furthermore, the brain activity of the other region ACC was correlated with the psychopathology of the OCD patients measured with Y-BOCS at baseline and follow-up. Again, the activity change was as explained above, and a positive correlation between the brain activity in the ROI ACC and the reduction of Y-BOCS scores was identified using Spearman's correlation coefficient. The frequency bands delta (rho = 0.33, $p = 0.035$), alpha 1 (rho = 0.36, $p = 0.019$), alpha 2 (rho = 0.34, $p = 0.031$), and beta 3 (rho = 0.38, $p = 0.015$) are shown in **Figure 6**. Also shown are the regression lines for the least squares fit and the robust regression methods. The findings are very similar to those for the ROI area OFC: outlying observations induce a larger correlation between psychopathology and electrophysiological data since the robust regression methods yield less steep regression lines. Approximate *p*-values are shown in **Table 11**.

DISCUSSION

The present study aimed to identify possible predictors of treatment response in patients suffering from OCD. We found that treatment responders exhibited already at baseline significantly lower brain electrical activity in higher frequency bands compared to non-responders and these findings were confirmed with ROI analyses that also revealed a significantly lower brain electrical resting activity in the ACC of responders. Over a 10 week course of treatment, the responder group had an increase in brain electric activity from baseline to follow-up, confirmed by LORETA analyses showing significantly lower brain electrical activity in the beta frequency bands, the same was true for the ROI analysis of the OFC brain area of responders. In addition, the group of non-responders exhibited the opposite findings: These OCD patients had a significantly higher brain electrical resting activity in the beta frequency band when baseline was compared to follow-up. The presented data clearly indicate that the brain activity increases in responders, whereas in non-responders brain activity decreases over the course of treatment. Therefore, the collection of electromagnetic tomography data might eventually help to distinguish between OCD patients who will respond to treatment and those who do not respond already before the onset of therapy.

Regarding lower electrical activity in responders to OCD treatment our results are consistent with those of previous studies: In particular, one pilot study found that lower pretreatment activity in the beta band within the rostral anterior cingulate and the medial frontal gyrus was associated with a better therapeutic response (Fontenelle et al., 2006). Based on these preliminary data, our group has replicated these findings on a larger OCD patient sample with stricter response criteria: We chose a reduction of at least 50% of the YBOCS score instead of 35%. In addition a standardized treatment with only one antidepressant (sertraline) was determined, and further investigations of electrical resting activity at different time points as well as correlations of the psychopathology with these data were added.

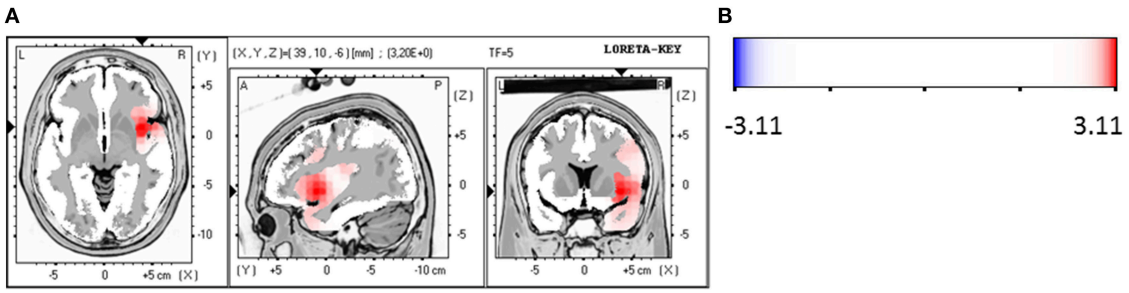

FIGURE 3 | (A) LORETA images for non-responders at baseline compared to follow-up: voxel-wise current density differences in the frequency band beta 1 for non-responders. Red areas represent brain regions showing significantly higher activity at baseline compared to follow-up. The red color indicates a statistical significant effect ($t_{max} = 3.20$, xyz = 39, 10, −6 $p < 0.05$) of reduced current density in the MNI-MRI-standard space. **(B)** Corresponding color bar.

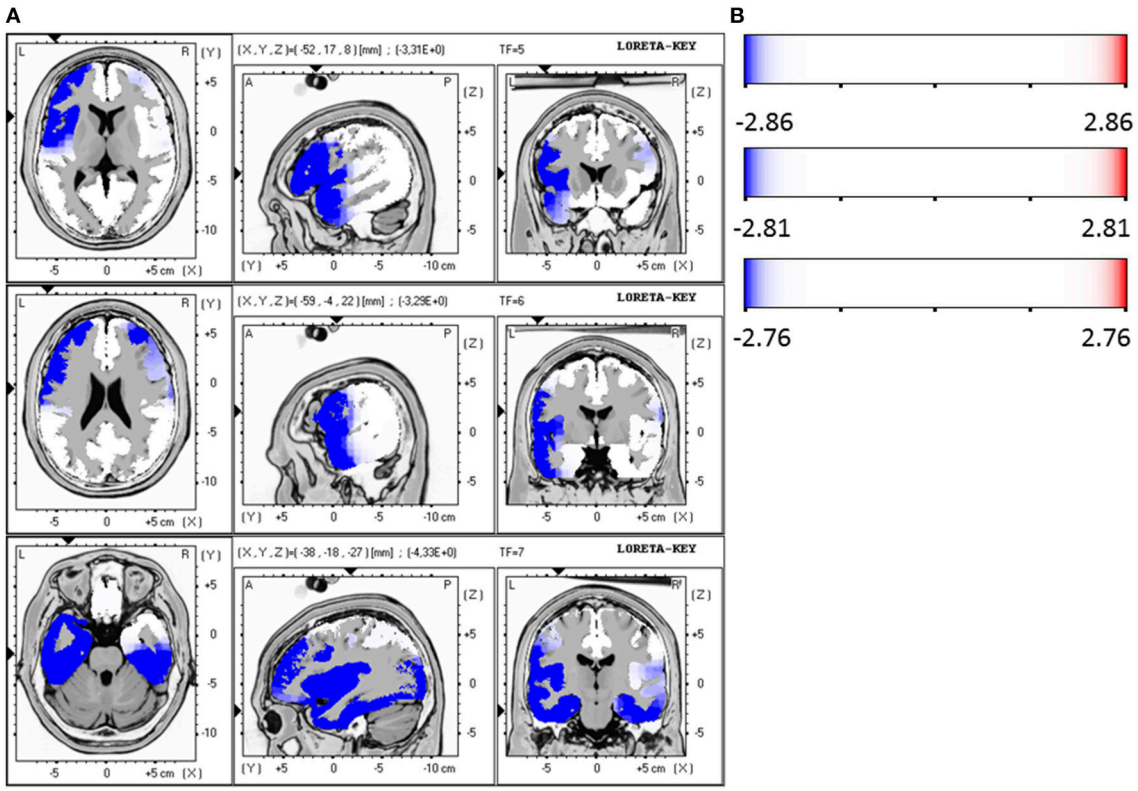

FIGURE 4 | (A) LORETA images for responders vs. non-responders at baseline: Images on top show voxel-wise current density differences in the frequency band beta 1 at baseline. The middle line contains the frequency band beta 2, in the bottom line the same is shown for the frequency band beta 3. Blue areas represent brain regions showing significantly lower LORETA values at baseline. The blue color indicates a statistical significant effect (images in the top line: $t_{max} = -3.31$, xyz = −52, 17, 8 $p < 0.05$; middle line: $t_{max} = -3.29$, xyz = −59, −4, 22 and bottom line: $t_{max} = -4.33$, xyz = −38, −18, −27) of reduced current density in the MNI-MRI-standard space. **(B)** Corresponding color bar.

In order to address the question whether psychopathology of OCD was associated with brain activity, OCD symptom severity—assessed with the aid of Y-BOCS—was correlated with ROI analyses. A positive correlation between frequency bands of both brain areas, the ROI OFC and the ROI ACC, with a reduction of Y-BOCS scores was identified. These findings indicate that an improvement of OCD symptoms is associated with an altered brain activity. In a previous study our research group has already identified evidence for symptom-related electrophysiological alterations in unmedicated patients with OCD. It has been shown that patients presenting with high levels of obsessions had higher absolute EEG power measures, especially for the faster frequencies, whereas patients with high compulsion scores were likely to have lower absolute EEG power, especially of slower frequencies (Andreou et al., 2013).

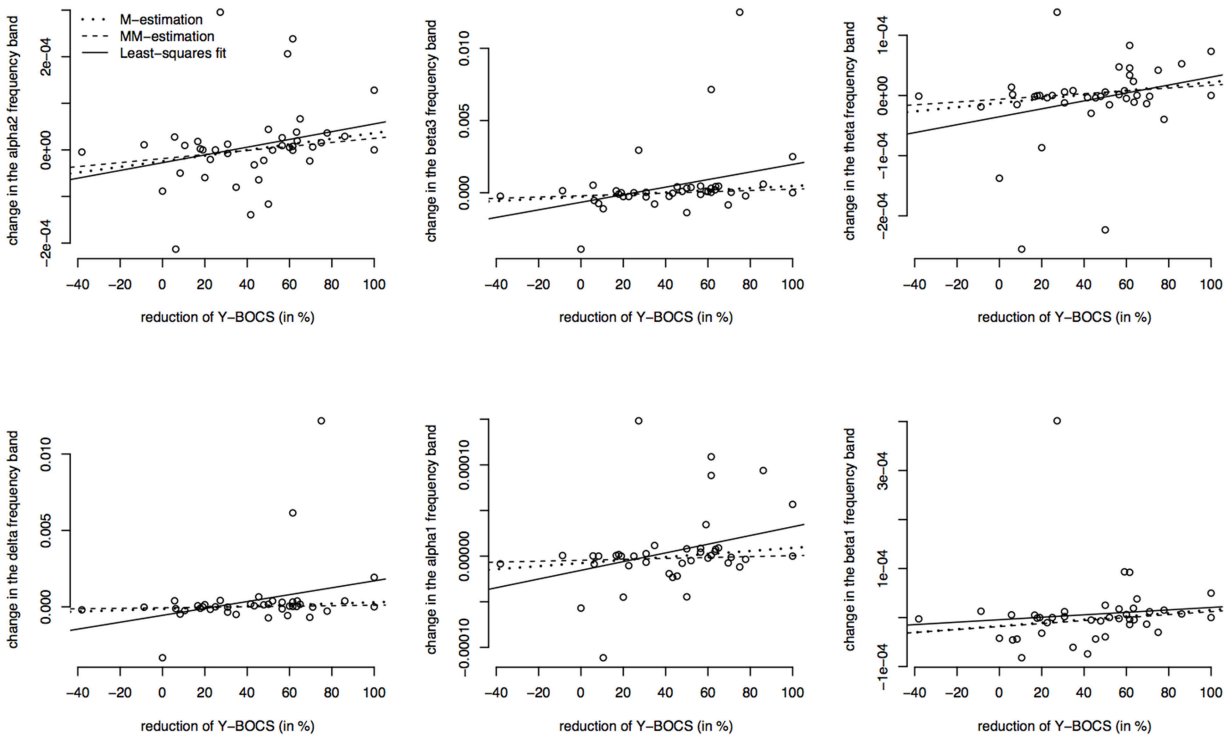

FIGURE 5 | Correlations between the psychopathology [reductions of Y-BOCS scores (%)] and the change in frequency bands (time point 10 weeks minus baseline) in the OFC. Frequency band alpha 2, beta3, theta, delta, alpha 1, and beta 1 are shown (in μAmpere/mm^2) and regression lines obtained through M-estimation, MM-estimation and the least squares method.

TABLE 10 | Estimated regression coefficients from robust regression (M-estimation and MM-estimation), corresponding *t*-values and approximate *p*-values for OFC.

	Regression coefficient M-estimation in 10^{-7}	Regression coefficient MM-estimation in 10^{-7}	*t*-value (*p*-value) M-estimation	*t*-value (*p*-value) MM-estimation
alpha 2	6.05	4.33	2.18 ($p = 0.0357$)	1.88 ($p = 0.0683$)
beta 3	74.10	45.00	2.76 ($p = 0.0088$)	1.93 ($p = 0.0603$)
theta	3.46	2.32	2.19 ($p = 0.0344$)	1.73 ($p = 0.0912$)
delta	43.10	16.70	2.18 ($p = 0.0351$)	0.92 ($p = 0.3607$)
alpha 1	1.67	0.505	1.94 ($p = 0.0592$)	0.73 ($p = 0.4717$)
beta 1	3.27	3.04	1.99 ($p = 0.0539$)	1.81 ($p = 0.0784$)

T-values are computed as t = estimate/SE(estimate) and p-values are obtained using the Wald test.frequency band.

Also, a previous PET study investigated the correlation between symptomatology of OCD and brain activity and showed that in medicated OCD patients, the decrease in right orbitofrontal metabolism was directly correlated with two measures of OCD improvement (Swedo et al., 1992), indicating that brain activity and OCD psychopathology are mutually dependent parameters.

In our study, the investigated brain areas ACC and OFC had already been linked to an abnormal activity in OCD patients and were therefore proposed to play a role in the pathophysiology of the disease. However, other brain regions like the dorsolateral prefontal cortex and the inferior frontal gyrus that have previously shown abnormalities in OCD patients (Goncalves et al., 2015; Tang et al., 2015) have not been investigated in our study. Andreou et al. have examined brain activity distribution with LORETA and reported an increased P300-related activity predominantly in the left OFC, but also in left prefrontal, parietal and temporal areas in OCD patients compared to controls (Andreou et al., 2013). Moreover, especially the beta frequency bands have already been shown to have a lower power also in the frontal brain regions (Kuskowski et al., 1993). For the other investigated region ACC, LORETA analyses revealed an excess current source density in the beta frequencies in the cingulate gyrus in OCD patients compared to controls (Sherlin and Congedo, 2005). Also fMRI studies strengthen the evidence for ACC dysfunction in OCD (Brennan et al., 2015). In addition, another LORETA study in OCD patients has shown that there are differences in the frequency

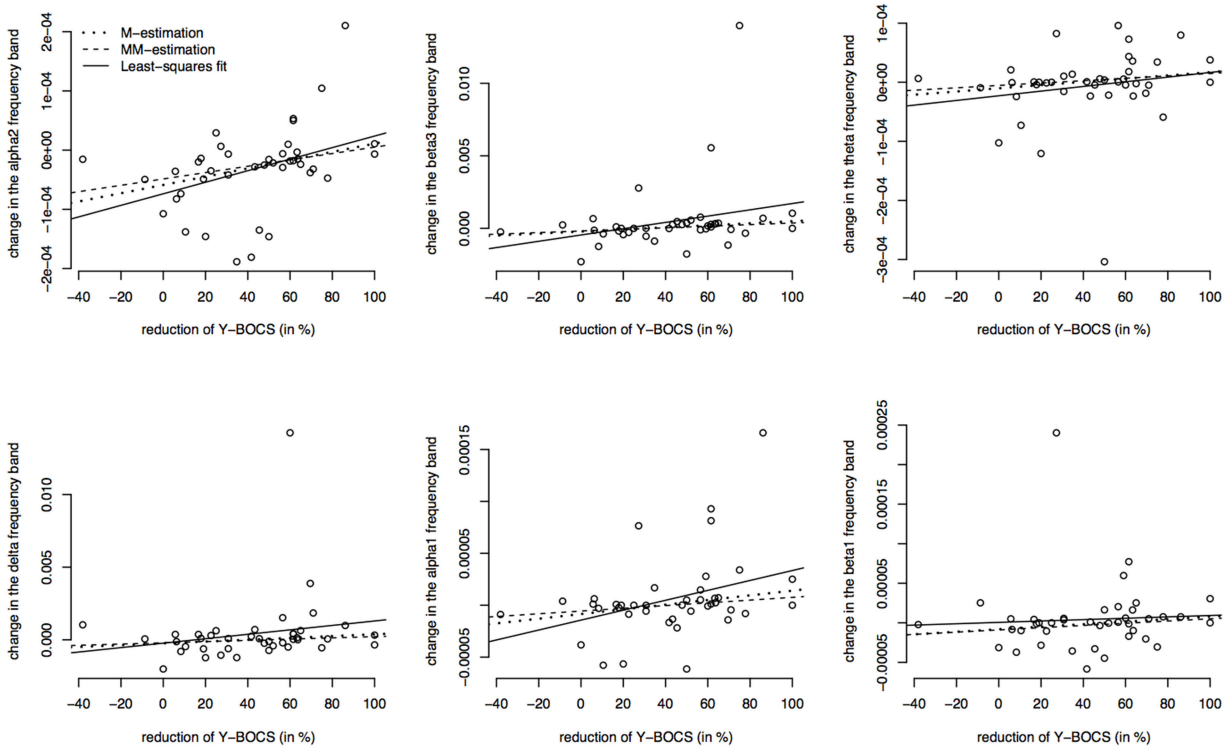

FIGURE 6 | Correlations between the psychopathology [reduction of Y-BOCS scores (%)] and the change in frequency bands (time point 10 weeks minus baseline) in the ACC. Frequency bands alpha 2, beta3, theta, delta, alpha 1, and beta 1 are shown (in μAmpere/mm^2) and regression lines obtained through M-estimation, MM-estimation and the least squares method.

TABLE 11 | Estimated regression coefficients from robust regression (M-estimation and MM-estimation), corresponding *t*-values and approximate *p*-values for ACC.

	Regression coefficient M-estimation in 10^{-7}	Regression coefficient MM-estimation in 10^{-7}	*t*-value (*p*-value) M-estimation	*t*-value (*p*-value) MM-estimation
alpha 2	6.98	5.37	2.56 ($p = 0.0144$)	2.11 ($p = 0.0410$)
beta 3	70.60	54.80	2.49 ($p = 0.0173$)	2.05 ($p = 0.0473$)
theta	2.72	2.02	1.73 ($p = 0.0910$)	1.25 ($p = 0.2205$)
delta	62.206	42.50	1.48 ($p = 0.1460$)	1.06 ($p = 0.2945$)
alpha 1	2.25	1.32	2.09 ($p = 0.0435$)	1.64 ($p = 0.1098$)
beta 1	1.59	1.40	1.36 ($p = 0.1812$)	1.15 ($p = 0.2574$)

T-values are computed as t = estimate/SE(estimate) and p-values are obtained using the Wald test.frequency band.

bands between patients and controls. The authors found that OCD patients had an increased current density for beta in the frontal, parietal and limbic lobes (Velikova et al., 2010). However, our data are difficult to compare to studies investigating OCD patients in comparison to healthy controls, since we looked only at OCD patients. Still, our findings that patients who are going to be treatment responders have lower activation levels in relevant brain areas may point toward a rather normal brain activity level, possibly making them more likely to respond to treatment.

The present study has several strengths and limitations. Regarding its strength our study has a comparatively large patient sample with a homogenous standardized treatment for all OCD patients. With the criteria of response chosen at the level of at least 50% reduction in the Y-BOCS, these rather strict response criteria identified only responders who really had a clinically significant improvement of their OCD symptoms. In terms of limitations, all our patients were only unmedicated and not drug naïve. Furthermore, in this study no testing for multiple comparisons was done due to the exploratory character of the study. Therefore, based on the findings by Fontenelle et al. (2006) our results can only be seen as the next step toward the clinical applicability of predictive electromagnetical markers in OCD patients. However, the final clinical implementation of EEG markers in OCD cannot yet be reached with the present results.

Some authors have suggested that an increase in brain activity is due to an improvement of depressive symptoms (Kennedy et al., 2001). However, our sample of OCD patients did not distinguish between groups of responders and non-responders with regard to depressive symptoms. Study participants had a mean HAMD-17 score of 12.78 indicating only mild depressive symptoms (cut-off HAMD-17; Zimmerman et al., 2013) before treatment, and a score of 9.15 after treatment. Responders and non-responders did not show a significant difference regarding HAMD-17 or BDI scores for depressive symptoms. Therefore, a contamination of our results caused by the influence of depressive symptoms seems unlikely in our investigated sample.

It would also be of interest to link our data to research on brain connectivity in order to broaden the picture of OCD psychopathology. Consistent with neurobiological models of OCD, OFC, and basal ganglia have been identified to be hyperconnected in unmedicated patients, and antidepressant medication may reduce connectivity within corticobasal ganglia-thalamo-cortical circuits in OCD (Beucke et al., 2013). Also, an altered global brain connectivity in dorsal and ventral striatum of OCD patients has been shown, as well as complex disturbances in PFC networks which could contribute to disrupted cortical-striatal-cerebellar circuits in OCD (Anticevic et al., 2014).

Altogether, our results suggest that measuring brain activity with LORETA could eventually be an efficient and simple technique in order to identify OCD patients likely to respond to treatment. We hope that future studies will continue to rigorously examine whether the biomarkers we have shown in the present study might qualify as an effective predictor of treatment response in OCD patients. More generally, our findings illustrate the potential utility of resting EEG and LORETA analyses for identifying biomarkers of treatment response, thereby facilitating a personalized clinical approach to treating patients suffering from OCD.

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New Perspectives in the Exploration of Korsakoff's Syndrome: The Usefulness of Neurophysiological Markers

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This perspective aims at underlining the usefulness of event-related potentials (ERP) to better understand the brain correlates of Korsakoff's syndrome (KS), a neuropsychiatric disease characterized by severe memory impairment and most frequently resulting as a neurological complication of alcohol-dependence (AD). While ERP have been broadly used in AD, it has up to now been very little applied in KS or in the comparison of KS and AD. Within the framework of dual-process models, an influential theory postulating that addictive states result from an imbalance between under-activated reflective system and over-activated automatic-affective one, this paper proposes: (1) a brief synthesis of the main results of ERP studies in AD and KS, and (2) new research avenues using ERP to identify the electrophysiological correlates of cognitive and emotional dysfunction in KS. These experimental perspectives aim at exploring the continuity hypothesis, which postulates a gradient of impairments from AD to KS. We conclude on the possibility of developing neuropsychological strategies with electrophysiological follow-up to ensure KS diagnosis and test the efficacy of patient's neurocognitive rehabilitation.

Keywords: Korsakoff's syndrome, alcohol-dependence, electroencephalography, event-related potentials, dual-process models, emotion, cognition

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INTRODUCTION

Korsakoff's syndrome (KS), a frequent neurological complication of alcohol-dependence (AD), is mainly caused by the combined effect of thiamine deficiency and alcohol neurotoxicity. KS is classically associated with disorientation, confabulation, and amnesia (Victor et al., 1971), severe anterograde and retrograde memory deficits constituting the key symptom of KS (Butters and Cermak, 1980; Fama et al., 2012). Several studies found that KS' brain damages and cognitive impairments are more severe than those reported in AD patients (e.g., Brokate et al., 2003; Brand, 2007; Pitel et al., 2008, 2012; Sullivan and Pfefferbaum, 2009). This has notably led to the continuity hypothesis (see Pitel et al., 2014 for a recent review; Ryback, 1971), which assumes a gradual worsening of memory deficits between "uncomplicated" AD and KS. Beyond memory impairments, recent studies have also emphasized executive (Van Oort and Kessels, 2009; Maharasingam et al., 2013) and emotional (Montagne et al., 2006; Labudda et al., 2008) dysfunctions in KS, but the continuity hypothesis has been little explored for these impairments. It has recently been proposed (Brion et al., 2015) that a dual-process perspective, which represents

a well-validated conception in the addiction field (Bechara, 2005; Bechara and Damasio, 2005; Mukherjee, 2010; Noël et al., 2010), might constitute a reliable theoretical background to address this shortcoming. The dual-process models assume that every adapted human behavior (e.g., a decision-making) mobilizes the interaction between two systems: (1) the "reflective system" (mostly relying on prefrontal areas), a controlled and inhibitory process, relying on memory and executive functions to initiate controlled-deliberate responses (response-consequences link), and (2) the "automatic-affective system" (mostly relying on limbic areas), an appetitive system triggering impulsive responses based on associative learning (stimulus–response link). Actually, the automatic-affective system can be divided into an affective subcomponent associated with the core affect decoding (e.g., facial expression or prosody) and an automatic subcomponent related to the attribution of a pleasant or aversive value to environmental stimuli through conditioning (Bechara, 2005; Bechara and Damasio, 2005). According to these models, AD is characterized by a combination of weak executive functioning related to the reflective system (e.g., reduced ability to refrain drinking behavior) and inadequate automatic-affective processing (e.g., strong appetitive drive toward alcohol, emotion perception impairments, Field et al., 2010; Noël et al., 2010). As KS exploration has up to now been focused on the reflective system, it appears necessary to go beyond this classical exploration of cognitive functions to assess emotional abilities as well as emotion-cognition interactions and revisit the classical picture/description of cognitive function in KS.

An interesting way to conduct these cognitive-emotional explorations in KS is the event-related potentials (ERP) technique. Indeed, this non-invasive tool, which allows measuring brain electrical activity associated with cognitive functioning, constitutes a method of choice to assess cognitive deficits in pathological populations and has notably proven its usefulness among several psychiatric disorders (Pogarell et al., 2007; McLoughlin et al., 2014). In particular, ERP present the advantage (as compared to other neuroimaging tools like Magnetic Resonance Imaging) to have a high temporal resolution, enabling the detailed investigation of successive steps associated with stimulus processing (i.e., perceptual, attentional, and decisional stages) as well as performance and feedback monitoring [see **Figure 1** illustrating the sequence of main ERP components during (visual) information processing; Rugg and Coles, 1995; Falkenstein et al., 2000; San Martin, 2012; Walsh and Anderson, 2012; Kamarajan and Porjesz, 2015]. This method enables identifying the component related to the onset of dysfunctions, and then inferring the associated impaired processing stage (Rugg and Coles, 1995). While ERP have been fruitfully used for decades to explore brain correlates of AD, some authors highlighting the potential utility of P3 as an endophenotype of AD (Campanella et al., 2014; Kamarajan et al., 2015), only very few ERP studies have been conducted on KS. This analysis is quite surprising, considering also that ERP technique is well-suited to experimentation with patients with severe deficits like KS.

Accordingly, the aim of the present paper is twofold. First, we report the results of the few ERP studies in KS.

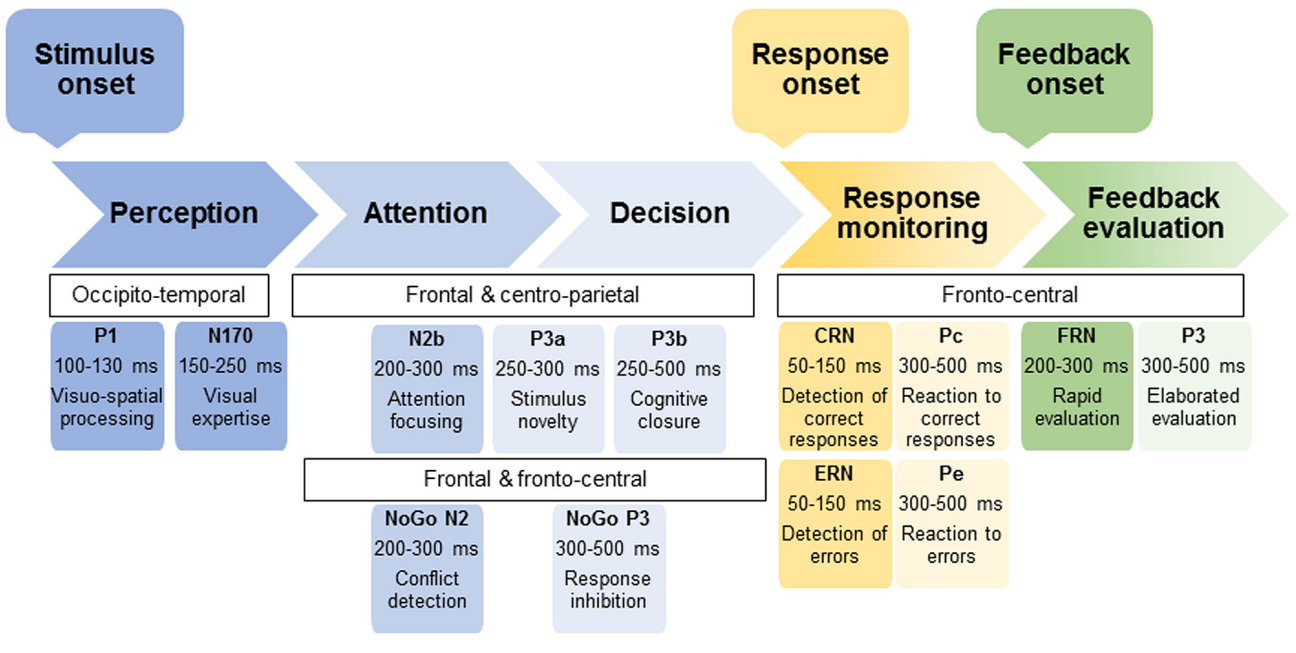

FIGURE 1 | Outline of the sequence of ERP components associated with the successive processing steps of (visual) stimulus, response, and feedback. The name of ERP component usually begins either by P or N to indicate positive or negative voltage deflections, respectively. Particular cases are the Correct-Related Negativity (CRN) and Error-Related Negativity (ERN) as well at the Feedback-related Negativity (FRN). For each ERP, the scalp distribution, time window of the peak as well as main functional significance are provided.

We also report the most robust findings from studies in AD that investigated both systems postulated by dual-process models (see Kamarajan and Porjesz, 2015 for a recent review). Second, we propose new research avenues to renew the investigations of core symptoms associated with KS using ERP and to identify neurophysiological vulnerability markers of the condition. Both parts of the paper are presented through the perspective of the continuity hypothesis and the dual-process models.

WHAT HAVE ERP STUDIES REVEALED ABOUT REFLECTIVE AND AUTOMATIC-AFFECTIVE SYSTEMS?

ERP Investigations in KS

Initial ERP studies in KS were conducted in the 1980s and explored sensory processing. Several of them investigated brainstem auditory evoked responses and showed reversible abnormalities in some KS patients (Chu and Squires, 1980; Chan et al., 1985; Hammond et al., 1986). In the same vein, Chan et al. (1986) recorded visual evoked responses and found that KS patients showed delayed and reduced P1. St Clair et al. (1985) used a two-tone discrimination task and found that KS patients showed reduced amplitudes specifically for early auditory ERP (i.e., N1/P2 complex) as compared with matched non-alcoholic controls. These initial studies thus evidenced that KS is associated with impairments at the early stage of information processing. More recently, Nahum et al. (2015) recorded ERP during a continuous recognition task and showed that KS patients differed from both AD and controls as they showed a lower recognition percentage and an absence of a left medial temporal lobe dependent positivity peaking between 250 and 350 ms following immediate picture repetitions. Although these recent findings shed new light on the brain correlates associated with anterograde amnesia classically observed in KS, it has to be underlined that the current ERP data on KS remain highly scarce, especially regarding high-level processes.

ERP Investigations in AD

Many ERP studies in AD explored the reflective system and showed that the executive dysfunctions classically found by neuropsychological studies (Field et al., 2010; Noël et al., 2007, 2012) were associated with modifications in the amplitude and/or latency of several ERP components during Go–NoGo, Stop Signal, and Flanker Tasks paradigms (see Hansenne, 2006; Kamarajan and Porjesz, 2015 for reviews). The most robust finding is probably related to the P3, with numerous studies showing reduced amplitude and increased latency of P3 in various types of task. In particular, reduced P3 amplitude has been observed in AD during NoGo trials (Cohen et al., 1997; Kamarajan et al., 2005), which can be interpreted as an altered response inhibition (Randall and Smith, 2011). Before that, conflict monitoring also appears to be altered as suggested by reduced N2 peak amplitudes for Go and NoGo conditions in AD compared with controls as well as the lack of significant increase in N2 amplitude in NoGo compared to Go trials in AD (Pandey et al., 2012; see also Donkers and van Boxtel, 2004; Randall and Smith, 2011). However, AD individuals show greater error-related negativity (ERN; Schellekens et al., 2010; Padilla et al., 2011) and correct-related negativity (CRN; Padilla et al., 2011) amplitudes compared with controls. Considering that behavioral performance is preserved, this may suggest a compensatory strategy for inhibition deficits in AD, involving enhanced performance monitoring (Padilla et al., 2011).

Regarding the affective subcomponent, results from ERP studies using an affective oddball paradigm suggest that emotional decoding deficits frequently observed at the behavioral level in AD (e.g., Philippot et al., 1999; Kornreich et al., 2001; Maurage et al., 2009a; D'Hondt et al., 2014a,b, 2015; Donadon and Osório Fde, 2014) are associated with alterations all along the information-processing stream, from early visual (delayed P100) and face-processing (delayed and reduced N170) stages to decision stage (delayed and reduced P3b; Maurage et al., 2007, 2008a). Slower early processing of emotional facial stimuli, as indexed by a delayed frontal P160, has also been observed during gender identification and emotion identification tasks in AD (Fein et al., 2010). Furthermore, using an emotional oddball paradigm with morphed stimuli, Maurage et al. (2008b) reported a specifically disrupted processing of anger (vs disgust) in AD at attentional (delayed N2b/P3a complex) and decisional (delayed and reduced P3b) stages.

Regarding the automatic subcomponent, cognitive bias toward alcohol stimuli appears to be the best predictor of relapse vulnerability (Petit et al., 2015). This bias observed at the behavioral level (e.g., Klein et al., 2013; Woud et al., 2014) may be associated with an enhanced motivational processing of alcohol-related cues as indexed by higher P3 amplitude in response to alcohol-related words (e.g., Genkina and Shostakovich, 1983; Herrmann et al., 2000; but see Hansenne et al., 2003) or pictures (Namkoong et al., 2004) compared with neutral stimuli. Thus, hyperactivity of the automatic subcomponent may explain the increased appetitive value of alcohol-related stimuli in AD, and thus poorly deliberated responses triggered by these cues. Conversely, lower P3 amplitude for incentive stimuli may reflect a reduced processing of other rewards in AD (Porjesz et al., 1987).

To sum up, although ERP studies have provided large evidence of impairments for both reflective and automatic-affective systems in AD, almost nothing is known concerning the electrophysiological correlates of systems' dysfunctions in KS. Importantly, while imbalance between systems is considered as a critical feature of AD (e.g., Field et al., 2010), its electrophysiological correlates remain to be investigated. The main aim of the following perspective section is thus to propose new research avenues to further explore core symptoms of KS and to compare electrophysiological patterns between KS and AD by investigating both systems separately as well as their interactions.

TOWARD NEW ERP INVESTIGATIONS OF REFLECTIVE AND AUTOMATIC-AFFECTIVE SYSTEMS: FROM AD TO KS

Beyond memory impairments, we propose that future ERP studies may determine whether there is a continuity from AD to KS in deficits regarding both systems postulated by dual-process models, and their interactions:

Reflective System Exploration

A gradual decline from AD to KS has been recently hypothesized for inhibition (Brion et al., 2014), given the severe impairments already described in KS (Fujiwara et al., 2008; Pitel et al., 2008). To determine the stage(s) of processing that is (are) potentially concerned by this gradual decline, it would be interesting to use an Eriksen flanker test with NoGo conditions to study response inhibition (e.g., Sokhadze et al., 2008; see **Figure 2**). This kind of modified Flanker paradigm, which allows measuring the classical stimulus-locked and response-locked ERP (see **Figure 1**), would enable determining whether there is a graduated effect of: (1) deficits in inhibition abilities from AD to KS for conflict detection (indexed by reduced NoGo N2) and/or response inhibition (indexed by reduced NoGo P3), both stages being affected in AD; (2) greater allocation of resources to performance monitoring as previously shown by response-locked ERP modifications in AD (i.e., enhanced CRN and ERN amplitudes).

Automatic-Affective System Exploration

Automatic Sub-Component

How the increased "salience" attribution to alcohol-related cues and associated biases in AD (e.g., Field et al., 2009; Vollstadt-Klein et al., 2012) evolve with neurological complication remains an open issue. We propose that ERP

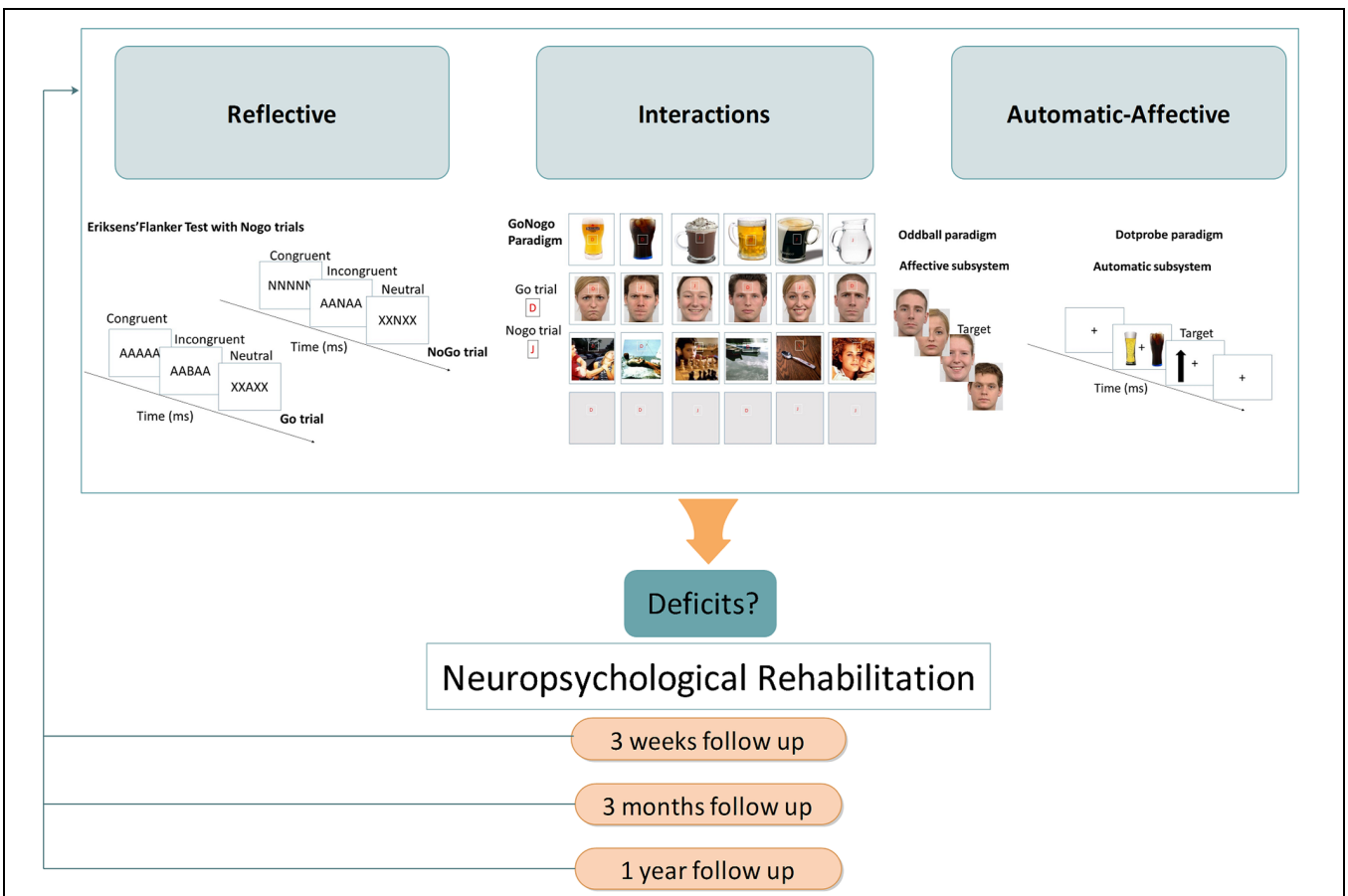

FIGURE 2 | Proposal of an ERP routine from diagnostic until neuropsychological rehabilitation among AD and KS patients within a dual-process framework. Description of the proposed paradigms for the reflective, automatic, and affective systems as well as interactions between systems, respectively: (i) Reflective: a Flanker task with NoGo trials as proposed by Sokhadze et al. (2008) in which participants have to quickly respond to a central target flanked by distracting stimuli. (ii) Automatic: a dot-probe paradigm consisting of two stimuli (i.e., alcohol-related and neutral) that are briefly shown and followed by a probe at the location previously occupied by one of the two stimuli. The participant is required to respond as fast as possible to the probe. (iii) Affective: an emotional oddball paradigm with frequent stimuli (i.e., neutral facial expression) interrupted by deviant ones (i.e., emotional facial expression). (iv) Interactions: a Go/No-Go task using frequent Go signals (letter "D"), and rare No-Go signals (letter "J"). Both letters are superimposed on a background picture, either black, alcohol- (for the study of reflective and automatic interactions) or non-alcohol-related, neutral or emotional (for the study of reflective and affective interactions).

would be particularly helpful to address at least three main questions:

(1) What is the real nature of the biases? Are they perceptual (greater salience associated with "expertise" for these cues), attentional (greater allocation of attentional resources) or decisional (less inhibition at the post-attentional stage)? Visual oddball paradigms (e.g., Petit et al., 2015) should be used to determine whether P3 modifications previously observed in AD are also present and stronger in KS, but also to investigate earlier information processing steps (i.e., perceptual and attentional stages).
(2) Do alcohol-related stimuli capture attentional resources of KS individuals? ERP recording during a dot-probe task (e.g., Bar-Haim et al., 2007) would help to determine whether AD and KS present higher P1 amplitude for targets occurring at locations previously occupied by alcohol-related cues compared to neutral ones. This has been recently observed among social drinkers low in alcohol sensitivity (Shin et al., 2010) and may reflect a potential top-down mechanism by which selective attention for alcohol cues affects early visual processing of subsequent stimuli.
(3) Is the putative hyperactivity for alcohol cues conversely associated with a decreased reactivity for non-alcohol related natural rewards (e.g., money)? Future ERP studies in KS should investigate whether the possible hyperactivity of the automatic subsystem for alcohol-related cues is accompanied by hypoactivity of this subsystem for another type of rewards, as indexed by lower P3 amplitude to incentive stimuli in AD (Porjesz et al., 1987).

Affective Sub-Component

While some behavioral findings suggest emotional impairments in AD and KS (see Brion et al., 2015, for a review), one important question still to be addressed in KS is the onset of dysfunction along the information-processing stream. Given results from ERP studies that showed sensory deficits in KS, future ERP studies should determine whether emotion deficits also arise as soon as visual steps, as observed in AD using an emotional oddball paradigm (Maurage et al., 2007, 2008a; see **Figure 2**), and are more severe in KS. Importantly, further ERP studies should investigate more deeply the putative deficits of visual pathways in KS and the interaction between vision and emotion as recently proposed for AD (D'Hondt et al., 2014b). Indeed, it has been suggested that alterations of magnocellular pathways may impact the coarse and fast visual analysis of emotional information. This hypothesis could be tested by exploring emotional processing of visual stimuli containing only low spatial (i.e., coarse information, mainly related to magnocellular pathways) or high spatial frequencies (i.e., detailed information, mainly related to parvocellular pathways; see D'Hondt et al., 2014b for more details). Moreover, future ERP studies should investigate the possible generalization of emotion decoding deficits to all kind of visual stimuli (e.g., facial expression, natural scene, posture) and sensorial modalities (e.g., prosody) as observed in AD (Maurage et al., 2009a).

Systems Interactions Exploration

Future ERP should directly investigate reflective and automatic-affective systems interactions in AD and KS (Brion et al., 2015) to determine which stage(s) of information processing is (are) concerned by the disequilibrium between systems. To this end, gambling tasks such as the Iowa gambling task (Bechara et al., 1994) and the balloon analog risk task (Lejuez et al., 2002) may be relevant means. Using a gambling task, Kamarajan et al. (2010) found that reward processing was dysfunctional in AD by showing that AD individuals as compared with controls had significantly lower FRN and P3 amplitudes during loss and all outcome conditions, respectively. To go beyond the investigation of ERP components related to feedback processing, it would be interesting to use the version of the Iowa gambling task developed by Cui et al. (2013) to study ERP components related to choice evaluation and response selection. While we believe that this task would be useful, we also think that new strategies should be developed to more directly compare the impact of automatic and affective subcomponents on the reflective system. For instance, a Go/NoGo paradigm should be used in which inhibition occurs in a context where alcohol-related cues (for the automatic sub-system; see Petit et al., 2012 for a recent example) or affective stimuli (for the affective sub-system) are present (see **Figure 2**). ERP components related to inhibition (i.e., NoGo-N2 and -P3) and response monitoring could be therefore studied in the specific context of affective subsystem (emotional stimuli) or automatic subsystem (alcohol-related stimuli).

CONCLUSION: TOWARD A CLINICAL ROUTINE INVOLVING ERP TECHNIQUE

The main aim of this article was to stress the need for developing studies employing ERP, which have been up to now under-used in the domain, to obtain a clearer picture of KS impairments thanks to the high temporal resolution of this technique. We proposed new research avenues within the framework of dual-process models to better understand KS deficits regarding the reflective and automatic-affective systems, whose unbalanced interactions are supposed to be at the heart of AD.

According to the continuity hypothesis from AD to KS, and on the basis of ERP findings showing that activity of both systems is affected in AD, we can suppose: (1) a linear hypo-activation of both reflective system and affective subsystem; and (2) a graduated over-activation of the automatic subsystem. From a cognitive point of view, this assumption would lead to the deterioration from AD to KS of both executive functions and emotional decoding abilities and to a stronger bias toward alcohol-related stimuli. Alternatively, a linear worsening of brain impairments from AD to KS could also lead to a decreased activity in prefrontal and limbic areas and, therefore, a hypo-activation of both reflective and automatic-affective systems. This latter assumption calls into question the continuity hypothesis as it implies that deficits in KS do not result from a mere strengthening of deficits already present in AD. Instead, modifications in the activity of the automatic subsystem would be variable over the course of the disease, with an over-activation

at the early stages (i.e., in AD) and then an under-activation at later stages (i.e., in KS; parallel to the decrease of craving, as after a long abstinence for instance). At this time, maintenance of the AD could be predominantly caused by an accentuation of the reflective system deficits. ERP investigations should help to examine the evolution of the two systems and their interactions during and between AD and KS. Moreover, further ERP studies should also investigate the possible role of a third system involving the insula as recently proposed by Noël et al. (2013) in their "triadic neurocognitive model of addiction." According to this view, the insula, because of its role in the conscious representation of interoceptive signals, would mediate the impact of bodily changes associated with withdrawal, leading to the sensitization of the automatic-affective system and the reduction or the hijacking of the reflective system resources. The putative role of the insula in the imbalance between the automatic-affective and the reflective system needs, therefore, to be considered in both AD and KS.

Owing to its high temporal resolution, ERP technique should: (1) provide a refined diagnosis of KS impairments since, contrary to behavioral measures that give insights about the overall cognitive functioning, electrophysiological measures allow to identify modifications at each step of information processing: (2) help to identify early brain modifications in AD individuals at risk of developing neurological complication, before any detectable cognitive impairment at the behavioral level (see Maurage et al., 2009b for an illustration in binge drinking showing the usefulness of ERP in highlighting brain modifications while no behavioral deficits are observed). The evolution of ERP modifications could thus serve as a neurophysiological marker of KS vulnerability. This proposal is also in line with the recent call for biological markers that could be used in place of subjective clinical parameters currently employed in psychiatric diagnosis since ERP technique is already in full swing in psychiatry at the experimental and clinical levels (Campanella and Colin, 2014; McLoughlin et al., 2014). As recently proposed by Campanella (2013), a clinical routine involving ERP technique should be developed, allowing to refine the diagnosis of KS patients and to initiate individualized therapies, combining medication, psychotherapy and "ERP-oriented cognitive rehabilitation." For instance, training AD response inhibition toward alcohol-related stimuli would promote abstinence (Houben et al., 2011), and, therefore, contribute to thwarting the high risk of patient drop out after detoxification (e.g., Finney et al., 1996; Fadardi and Cox, 2009). The relapse rate in AD may dwindle away with attentional-bias-reduction interventions since bias toward alcohol-related stimuli is correlated with the intensity of craving (Field and Cox, 2008; Field et al., 2009, 2013). Moreover, while behavioral improvements could be subtle, electrophysiological measures before and after rehabilitation would support clinical observation and serve as an indicator of treatment efficacy. Importantly, one possible limitation of the research avenues proposed here (see **Figure 2**) is that the massive cognitive deficits associated with KS would limit the ability of KS individuals to understand tasks instructions, to keep them in memory during the tasks, and to focus their attention during a sufficiently long period to complete the tasks. This explains why we tried to propose experimental procedures as simple as possible However, there are several lines of evidence in favor of the feasibility of our proposal: previous studies have been carried out with KS individuals using complex tasks [e.g., Stroop test, N-back paradigm, Trail making test, fluency, game of dice task, Brixton test (see Brion et al., 2014)]; there are evidence that KS individuals are capable of new learning (Kopelman et al., 2009); there are simple strategies to optimize the feasibility of these studies (such as breaks during the experiment allowing individuals to have a rest and to explain again task instructions)]. As illustrated in **Figure 2**, the perspectives proposed here to better understand electrophysiological correlates of emotion–cognition dysfunctions among KS patients could be ultimately used by clinicians as a tool to identify specific deficits, considering them as therapeutic targets to optimize patient's quality of life, and ensure a follow-up measure of rehabilitation programs.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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Event-related potentials (ERPs) and hemodynamic (functional near-infrared spectroscopy, fNIRS) as measures of schizophrenia deficits in emotional behavior

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Recent research evidences supported the significant role of multimethodological neuroscientific approach for the diagnosis and the rehabilitative intervention in schizophrenia. Indeed both electrophysiological and neuroimaging measures in integration each other appear able to furnish a deep overview of the cognitive and affective behavior in schizophrenia patients (SPs). The aim of the present review is focused on the emotional dysfunctional response taking into account the multimeasures for emotional behavior, i.e., the event-related potentials (ERPs) and the hemodynamic profile functional near-infrared spectroscopy (fNIRS). These measures may be considered as predictive measures of the SPs' deficits in emotional behavior. The integration between ERP and fNIRS may support both the prefrontal cortical localization anomaly and the attentional bias toward some specific emotional conditions (mainly negative).

Keywords: schizophrenia, NIRS, emotion, ERPs, integration

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EMOTIONAL IMPAIRMENT IN SCHIZOPHRENIA

Affective deficits are considered to be a core feature of schizophrenia (Kring and Elis, 2013). Emotional deficits in schizophrenia affect diverse processes, including emotional experience (Myin-Germeys et al., 2000; Blanchard and Cohen, 2006; Horan et al., 2008; Cohen and Minor, 2010; Taylor et al., 2012), emotion expression (Blanchard and Cohen, 2006), and perception and recognition of emotional cues (Couture et al., 2006; Hoekert et al., 2007; Kohler et al., 2010; Horan et al., 2011). In contrast, other emotional skills, such as the ability to appraise the emotional valence of stimuli, appear relatively preserved in schizophrenia (Kring and Moran, 2008). However in some cases inconsistent data were collected (Strauss et al., 2011). Indeed, from one hand, recent evidences on schizophrenia impairment in emotional behavior were based upon the observation that patients displayed "blunted" or "flat" facial and vocal affect, which was supposed to reveal a correspondingly diminished emotional experience. From the other hand, available data suggests that their subjective experience of emotion is not consistently modified (Aghevli et al., 2003; Herbener et al., 2007, 2008). Further, previous studies have indicated that patient self-report of affective experience has high internal consistency (Blanchard et al., 1998; Horan et al., 2006a,b). Moreover, a number of studies have found that patients do not differ from healthy subjects in their ratings of a variety of

affective stimuli with regard to valence and arousal ratings (Kring et al., 2003; Kring and Moran, 2008; Cohen and Minor, 2010). In general, results did not support a primary hedonic deficit in schizophrenia (for example, rating positive stimuli as less pleasant). Rather, data suggested that atypical emotional response is mostly associated with experiencing negative stimuli as being highly unpleasant and arousing. These potential contrasting effects can be also interpreted in terms of two broad social cognitive processes: lower-level versus higher-level (Frith and Frith, 2006; Ochsner et al., 2009; Green and Lee, 2012). Lower-level are social cognitive processes which involve recognizing significance in social and emotional stimuli (such as recognition of facial expression of emotions and vocal emotional features). These processes are considered as partially automatic neural responses to emotional cues and usually rely on specific neural circuits, including amygdala and insula. Higher-level processes involve an ability to make inferences about or contextualize representations that are driven by low-level recognition processes. These two levels may be partially preserved but they may have some difficulties to be connected, generating discordances between emotion experience, expression and recognition (Regan et al., 2015).

In the present review we mainly focused on emotional cue perception and recognition. Indeed emotion perception is one of the most relevant component of social cognition in schizophrenia and it usually involves the identification of emotions displayed in emotional patterns or in facial stimuli.

Electrophysiology (EEG) and functional Magnetic Resonance (fMRI) approaches are able to examine neural correlates for explicit as well as implicit tasks (i.e., the brain response to emotional faces during a gender identification task). It is reasonable to infer that brain imaging is appropriate for identifying various impairments in schizophrenia which are localized brain areas (Champagne et al., 2014). Nevertheless, it is limited by its low temporal resolution that does not support the real-time dynamic of the emotional filed (Logothetis, 2008). In contrast, event related potentials (ERPs), provide rate which allows milliseconds accuracy in exploring cerebral activation and a vast amount of research has already underlined its validity with emotional stimuli (Olofsson et al., 2008). Indeed, although somewhat contrasting, in general the findings from rating scales and EEG show lack of differences between schizophrenia patients (SPs) and healthy subjects: patients appear to recognize emotional stimuli to the same extent as healthy persons, even though in some cases they rate higher on anhedonia scales.

ERPs AS MEASURE OF SCHIZOPHRENIA EMOTIONAL DEFICITS

Event-related potential measure offers the advantage to monitor the dynamical modulations of the emotional processes, taking into account the heterogeneous levels implicated in emotional behavior. Indeed in the next paragraphs we considered ERP variation in response to emotional stimuli and facial expression patterns in SP.

Early/Late ERPs Modulation in Emotional Tasks

Many reviews underlined the utility to apply ERP measurement in emotional study and specifically to schizophrenia (Friedman and Squires-Wheeler, 1994). Indeed it was found to be suitable to measure changes in brain activity at early and late latencies, furnishing a complete overview of the emotional processing across-time. In fact, early and late mechanisms sequentially describe the dynamic variations of subjective response to emotional contexts. This dynamic modulations are not easily accessible by classical neuroimaging measures. Specifically, some ERP deflections were explored in emotional domain, such as P100, N100, P200, P300, and late positive component (LPC; Neuhaus et al., 2010). About the early latency and middle-latency deflections (P100, N100, P200, P300), the ERP data suggest that SP emotional experience are accompanied by normal early stimulus processing and initial resource allocation processes in response to emotional stimuli (Horan et al., 2010). A consistent set of data did not evidence of hypo- or hyper-responsivity to pleasant or unpleasant stimuli in SP among these three ERP components. The topography of P100, P200, and P300 responses was also similar across SP and healthy controls, who show maximal responses in central and parietal regions of the right than left hemisphere. It was previously found that the early latency P100 is sensitive to perceptual stimulus features and indexes early sensory processing, whereas the middle-latency P200 and P300 demonstrated to be highly sensitivite to valence. The P200 response reflects early stimulus discrimination and response selection processes: it was increased in response to emotional pictures reflecting a relatively automatic attentional allocation by emotionally more arousing stimuli. The enhanced P300 amplitude to emotional stimuli is thought to reflect greater allocation of attention to emotionally relevant stimuli.

Therefore these previous results seemed to underline the quite similar profile of SP and control subjects in these early and middle- time response to emotions. However it was also found that emotionally evocative stimuli are differentially processed in SP within the first time interval of 200 ms, and, for this reason, that the early stages of emotional process may be affected (Pinheiro et al., 2013; Champagne et al., 2014). Furthermore, some recent study underlined differences in SP in later components, observing significant difference in the LPC in response to unpleasant pictures (Strauss et al., 2013). This could be due to a possible inability to downregulate emotional response by SP in a later phase of emotion processing. Specifically, about the more later potentials, a higher agreement was obtained across the studies, since the patients differed from controls in terms of valence-related amplitude and topography during the late-latency LPC interval. As in prior studies (Olofsson et al., 2008), controls showed clearly enhanced LPC amplitudes for pleasant and unpleasant as compared to neutral stimuli since LPC enhancement is believed to index sustained attentional processing of motivationally relevant stimuli (Bradley and Lang, 1994). However, the patients showed significantly less LPC differentiation between emotional (mainly pleasant) versus neutral stimuli. Hence, the pattern of results for LPC may suggest a disturbance in sustained attentional processing of pleasant

stimuli in schizophrenia. In some cases LPC modulation also indicated that there was a difference in laterality between SP and control healthy subjects. Controls generally showed greater left than right hemisphere responses for pleasant stimuli whereas patients did not demonstrate any specific laterality (Dolcos and Cabeza, 2002; Cunningham and Zelazo, 2007). The left more than right asymmetry of LPC in controls is consistent with neuropsychological models that propose a significant left hemisphere specialization for pleasant emotion processing in frontal regions (Heller and Nitschke, 1998; Davidson and Irwin, 1999; Balconi et al., 2009; Balconi and Mazza, 2011; Balconi et al., 2012). Therefore these studies pointed out the significance that the lateralization effect may have to explain the emotional behavior disturbance.

It was also suggested the SP' pattern of intact ERPs during initial processing stages but diminished differentiation between emotional versus neutral stimuli during the LPC points toward a disturbance in "affective chronometry." This concept refers to parameters that vary over the time course of emotional behavior (Davidson, 1998). In fact, the earlier components may be represented as more stimulus-driven processes, and the later components as involving more cognitive evaluation and controlled resources. Consistent with this view, recent studies have shown that these later ERP components are regulated by top-down attentional mechanisms (Hajcak and Nieuwenhuis, 2006; Moser et al., 2006; Hajcak and Foti, 2008).

ERP Evidences for Deficit in Emotion "Regulation" and Attention Disengagement in SP

There previous results on ERPs may support the hypothesis that SP would show an impairment in emotion regulation. Emotion regulation refers to the processes by which we modify negative and positive emotions in terms of intensity, duration, and how they are manifested. This conceptualization is based on the idea that emotions unfold as a multicomponential process, which can be regulated by using subjective strategies at different stages of emotion generation. The topic of emotion dysregulation may be explored focusing on the "negative impairment effect" found in many previous studies, which underline the anomalous response to negative patterns by SP. In fact one possible explanation for these increases in state and trait negative emotionality is that SP display impairments in "emotion regulation" (Cohen and Minor, 2010; Cohen et al., 2011; Horan et al., 2011; Strauss et al., 2011, 2013; Strauss and Gold, 2012), since cognitive change is associated with increased prefrontal cortex activity and decreased amygdala activity (Ochsner et al., 2002, 2004, 2012; Ochsner and Gross, 2005; Mocaiber et al., 2011), it is possible that the concomitant ERP findings reflect that SP either have ineffective cortical control over the amygdala and limbic regions or a failure to adequately engage prefrontal and limbic regions when applying cognitive change strategies to perform emotional task.

From another point of view, the ERP measures are usable to verify if SP had greater difficulty disengaging attention from unpleasant stimuli (Strauss et al., 2011). Indeed this impairment may play a critical role in the generation of both negative symptoms and trait negative affect. Problems with disengaging attention from unpleasant stimuli have been proposed to be a major contributor to elevated negative emotional experience in individuals with other psychiatric disorders (e.g., anxiety) (Fox et al., 2001), and SP as well (Kring and Moran, 2008; Cohen and Minor, 2010). An enhanced in negative emotion response may reflect a sustained emotional regulation problem, where patients have difficulty regulating negative mood and negative behavior (Horan et al., 2006a,b; Cohen and Minor, 2010; Cohen et al., 2011).

The present findings are consistent with prior studies demonstrating a sort of disconnection among emotional response subcomponents in SP. For example, it is well documented that SP are less expressive than healthy controls, yet do not differ as much with respect to reported emotional experience or autonomic physiology (Kring and Moran, 2008). Failure to sufficiently process motivationally relevant stimuli could have maladaptive functional consequences for SP (Dolcos and Cabeza, 2002). Diminished attentional processing reflected in the LPC could help explain why SP fail to show the memory enhancements for emotional patterns.

Impairment in Facial Expression Comprehension

A deficit in the recognition of facial emotion is well established in SP (Walker et al., 1984; Archer et al., 1992; Schneider et al., 1995; Salem et al., 1996; Addington and Addington, 1998; Kee et al., 1998; Kohler et al., 2003; Johnston et al., 2005). This deficit appears to be at least partly related to a more general problem in cognitive functions including the categorization, discrimination, and identification of facial stimuli, and also to deficits in working memory and attentional processes (Addington and Addington, 1998; Kee et al., 1998; Kohler et al., 2000). It was revealed that anomalous late-latency activity was related to specific attentional process to facial expression, such as an attenuation of P300 response to different emotional valences (An et al., 2003). Moreover recent evidences were reported for impaired information processing in schizophrenia that occurs at the encoding level of facial stimuli. The findings in the emotion perception analysis probably reveal that SP do not modulate the amygdala to emotional versus non-emotional faces to the same extent as controls. It was also shown that SP exhibited amplitude deficits for both the late components N170, related to processing of structural components of face, and N250, related to the emotional content processing, but a latency deficit only for the N250 (Wynn et al., 2013).

INCOMING DEVELOPMENTS: WHY TO USE FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (fNIRS) IN SCHIZOPHRENIA STUDY ON EMOTIONS

Although the good temporal resolution of ERP enables a precise evaluation of the time-course of neural response in response

to the emotion perception, its low spatial resolution makes less easy to draw accurate conclusions regarding the main neural areas involved. Therefore, the neural substrates responsible for these emotion abnormalities cannot be definitively determined using ERP alone. For this reason, recently fNIRS measure was applied to study emotions in schizophrenia (Koseki et al., 2013). fNIRS has been developed to be non-invasive, easy-to-use, portable, restraint-free, and replicable (Kono et al., 2007). Indeed fNIRS is considered to impose considerably milder physical and psychological burdens than those of classical neuroimaging techniques. It is less invasive than other techniques (for example it does not require injection of radioactive agent), and no side effects are described so far and it is thus suitable for children and patients.

Indeed fNIRS is a functional brain imaging methodology from among other available methodologies such as fMRI and positron emission tomography (PET). While both of them also have excellent spatial resolution, fMRI and PET require uneasy apparatus. In contrast, fNIRS is as portable devices which allows to use it in various and critical conditions, as studies with SP (Matsuo et al., 2003). In addition, the high temporal resolution of fNIRS is useful in characterizing the time course of prefrontal activity of psychiatric pathologies (Suto et al., 2004; Kameyama et al., 2006).

In addition, patients are examined in a normal sitting position in a quiet place without any disturbing noise and examination cost is much lower than other neuroimaging modalities. However, fNIRS also has some limitations: poor spatial resolution, inability to measure deeper cerebral structures, and the possibility of involvement of extra-cerebral structures such as the scalp, fact which makes the validity of fNIRS results to be better evaluated in the future.

Previously fNIRS has been applied to assess brain functions of patients with psychiatric disorders such as schizophrenia, bipolar disorder, depression, dementia, post-traumatic stress disorder, and pervasive developmental disorder (Fallgatter et al., 1997; Hock et al., 1997; Matsuo et al., 2004; Shinba et al., 2004; Suto et al., 2004; Kubota et al., 2005; Kameyama et al., 2006; Kuwabara et al., 2006). fNIRS was clinically applied for the assessment of psychiatric patients, reporting that the frontal lobe activation measured by fNIRS in SP during a verbal fluency task was lower than that in healthy controls (Okada et al., 1994).

Recent developments of studies on schizophrenia which used fNIRS measure has found emotional recognition impairment in SP and the multichannel fNIRS was shown to be a valid measure of this impaired functions (Shoji et al., 2013). In addition, schizophrenia has been shown to have neural network abnormalities in the social brain, which subserves social and interpersonal relationships (Mimura, 2014).

Therefore the integration between ERP and fNIRS measures may describe the main features of the emotional process, that is the dynamical evolution of such phenomenon (by both fNIRS and ERP) and the contribution by specific cortical areas in processing emotions (by fNIRS). No other integrated measures may respond so well to the nature of emotional behavior. However, due the limited number of studies which have used fNIRS actually applied to schizophrenia domain, the potentiality of this technique has to be explored in the next future.

CONCLUSION

As pointed out by previous research, both ERPs and fNIRS measures may well elucidate the cortical correlates and functional features of emotional processing. Allowing a good temporal and spatial resolution, they may furnish a complete overview of SP' deficits in emotional recognition. Moreover, their portability and easiness of application make them the favorite devices to describe the multicomponential domain of emotions.

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Increased Event-Related Potentials and Alpha-, Beta-, and Gamma-Activity Associated with Intentional Actions

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Objective: Internally guided actions are defined as being purposeful, self-generated and offering choices between alternatives. Intentional actions are essential to reach individual goals. In previous empirical studies, internally guided actions were predominantly related to functional responses in frontal and parietal areas. The aim of the present study was to distinguish event-related potentials and oscillatory responses of intentional actions and externally guided actions. In addition, we compared neurobiological findings of the decision which action to perform with those referring to the decision whether or not to perform an action.

Methods: Twenty-eight subjects participated in adapted go/nogo paradigms, including a voluntary selection condition allowing participants to (1) freely decide whether to press the response button or (2) to decide whether they wanted to press the response button with the right index finger or the left index finger.

Results: The reaction times were increased when participants freely decided whether and how they wanted to respond compared to the go condition. Intentional processes were associated with a fronto-centrally located N2 and P3 potential. N2 and P3 amplitudes were increased during intentional actions compared to instructed responses (*go*). In addition, increased activity in the alpha-, beta- and gamma-frequency range was shown during voluntary behavior rather than during externally guided responses.

Conclusion: These results may indicate that an additional cognitive process is needed for intentional actions compared to instructed behavior. However, the neural responses were comparatively independent of the kind of decision that was made (1) decision which action to perform; (2) decision whether or not to perform an action).

Significance: The study demonstrates the importance of fronto-central alpha-, beta-, and gamma oscillations for voluntary behavior.

Keywords: intentional action, event-related potentials, voluntary selection, EEG, oscillatory activity

INTRODUCTION

Executive functions can be seen as a set of cognitive abilities, e.g., planning, adaptive responses to changing environmental requirements, flexible responses, working memory, inhibition of responses, and selection between response alternatives. Executive functions refer to the many skills required to prepare for and execute complex behaviors (Ozonoff et al., 2004). Dysfunctions in the executive system impair the capability to analyze, plan, prioritize, schedule, initiate and complete an activity in a timely manner (Hosenbocus and Chahal, 2012). The psychopathology of many psychiatric diseases seems to be influenced by impairments of the executive system and are considerably associated with functional outcomes, disability and specific problem behaviors (Royall et al., 2002). Executive dysfunction has been linked to divers psychiatric conditions (Robinson et al., 2009), especially to attention deficit/hyperactivity disorder (ADHD) and to autism spectrum disorder (e.g., Happé et al., 2006; Hosenbocus and Chahal, 2012).

Fundamental aspects of executive functions are intentional actions. Intentional processes do not rely on obvious external stimuli but are self-generated, e.g., self-initiated movement and internally generated action plans. It is assumed that decisions are needed to produce intentional behaviors which are not stimulus driven (Brass and Haggard, 2008). By contrast, externally guided actions are influenced by sensory cues. Functional magnetic resonance imaging (fMRI) studies have demonstrated an association of voluntary selection processes and fronto-central areas (Turken and Swick, 1999; Ridderinkhof et al., 2004; Rushworth et al., 2007), including medial frontal areas, the supplementary motor area (SMA), the anterior cingulate cortex (ACC), and the dorsolateral prefrontal cortex (DLPFC) (Frith et al., 1991; Hyder et al., 1997; Jueptner et al., 1997; Lau et al., 2004b; Walton et al., 2004; Forstmann et al., 2006; Karch et al., 2009), the superior parietal lobule and the intraparietal sulcus (Forstmann et al., 2006; Karch et al., 2009).

Electrophysiological studies focusing on voluntary processes have demonstrated a fronto-centrally located negativity after about 200 ms (N2) and a positive deflection about 300 ms after the presentation of the task (P3; Karch et al., 2009, 2010a). In addition, the combination of electrophysiological and functional MRI results in a simultaneous EEG/fMRI study showed that the N2 amplitude was predominantly associated with BOLD responses in medial and lateral frontal brain areas, whereas functional variations of the P3 seemed to be related to both lateral frontal activities and parietal responses (Karch et al., 2009, 2010a). The function of the N2 is not yet clear: various studies focusing on executive functions demonstrated that the N2 is supposed to be a correlate of conflict detection (Van Veen and Carter, 2002), response inhibition (Falkenstein et al., 1999; Bruin et al., 2001; Bekker et al., 2004) or the detection of an endogenous mismatch process (Näätänen and Picton, 1986). The P3 seems to be associated predominantly with attention processes and the processing of information (Donchin and Coles, 1988; Kramer and Strayer, 1988; Polich and Kok, 1995), the selection between action alternatives (Gajewski et al., 2008) as well as response inhibition.

Analyses of intention-related variations in different frequency ranges are rare: one study revealed pronounced activity in high frequency ranges (>30 Hz; gamma band response) during intentional actions (Karch et al., 2012). Overall, numerous studies have demonstrated that cognitive processes, e.g., objects recognition, attention, and memory can modulate gamma band activity (Tiitinen et al., 1993; Yordanova et al., 1997; Debener et al., 2003; Herrmann and Demiralp, 2005). Increased gamma band activity can be found, for example during the concentration on auditory information as well as in subjects focusing attention on motor response preparation (Makeig, 1993; Yordanova et al., 1997) and selective attention (Tiitinen et al., 1993, 1997).

For the participation of higher association areas slower frequency ranges such as theta and alpha seem to play an important role (Klimesch, 1999; Basar et al., 2000). For example, memory processes seem to be related to *alpha activity* (8–12 Hz; Busch and Herrmann, 2003; Herrmann et al., 2004): responses in the alpha frequency range increase with increasing memory load (Schack and Klimesch, 2002; Busch and Herrmann, 2003). *Theta activity* (5–7 Hz) is also believed to be associated with hippocampal neurons and is often found during memory recall (Tesche and Karhu, 2000; Klimesch et al., 2001; Buzsaki, 2002). Altogether, the synchronous occurrence of theta/alpha/beta/gamma activity indicates the existence of distributed oscillatory systems which are interwoven with sensory and cognitive functions (Basar et al., 2000). Oscillations may act as communication networks through large populations of neurons (Basar et al., 2000).

In the current literature, decreased oscillations in cortical recordings are found in most psychiatric pathologies: a decrease of delta activity in almost all diseases, as well as frequency shifts in alpha- and the lower frequencies were recorded (Basar et al., 2015). However, there are paradoxical cases with increased oscillations, e.g., increased beta activity in patients with bipolar disorder, or an increase of gamma activity during cognitive loading in patients with schizophrenia (Basar et al., 2015). Overall, there is great evidence that gamma oscillations associated with cognitive processes are modulated in various psychiatric diseases, including ADHD (e.g.; Yordanova et al., 2001; Karch et al., 2012), schizophrenia (e.g., Leicht et al., 2010, 2015; Basar et al., 2015; Senkowski and Gallinat, 2015) as well as subjects at high risk for psychosis (Leicht et al., 2016), autism spectrum disorders (Stroganova et al., 2015), bipolar disorder (Ozerdem et al., 2010; Basar et al., 2015) and Alzheimer's disease (Basar et al., 2015). It is assumed that impairments reflect disturbed information processing and an interruption of normal neuronal synchronization, e.g., caused by a dysfunctional GABA/glutamate system. It has been suggested that these processes contribute to impairments in the integration of cognitive and affective information (Ozerdem et al., 2010). Brass and Haggard (2008) proposed a model in order to distinguish different aspects of intentional action: the decision about which action to execute (*what* component), the decision about when to execute an action (*when* component), and the decision about whether to execute an action or not (*whether* component; Brass and Haggard, 2008). The *what* component can be addressed when participants can choose between various response alternatives (Botvinick et al.,

2001; Nachev et al., 2007). The rostral cingulate zone and the pre-SMA seem to be especially related to the *what* component (Lau et al., 2004b; Walton et al., 2004; Krieghoff et al., 2009). The *when* component is related to the time-point of decision (Cunnington et al., 2003; Lau et al., 2004a). The superior medial frontal gyrus probably could be more clearly activated in the timing component (*when*; Krieghoff et al., 2009). In daily life subjects often have to decide on their own whether they should act or not. However, the *whether* component has hardly been investigated so far; a specific region in the fronto-median cortex might be related to these processes (Brass and Haggard, 2007).

The aim of the present study was to examine electrophysiological responses associated with intentional actions. Especially the influence of different aspects of voluntary actions (1) the decision about which action to execute (*what* component) (2) the decision to act or not (*whether* component) on electrophysiological responses will be addressed. We hypothesized that voluntary selection processes are related to enhanced N2 and P3 amplitudes in fronto-central brain areas (e.g., Näätänen and Picton, 1986; Gajewski et al., 2008). In addition, alpha-, beta, and gamma-band activity is supposed to be increased in frontal areas during intentional actions compared to externally guided responses.

MATERIALS AND METHODS

Subjects

Twenty-eight healthy male subjects without any neurologic or psychiatric diagnosis (rated by a standardized questionnaire) participated in the EEG experiment. We included only males because several former studies demonstrated a gender effect for electrophysiological responses (Deldin et al., 1994). Several questionnaires were used to determine their actual mental state, e.g., the Beck Depression Inventory (BDI; Beck and Steer, 1987). One participant was excluded from any further analysis because the BDI score was higher than cut-off (cut-off > 14). Hence, 27 participants (aged between 20 and 34 years; mean age: 24.0 $\pm$ 2.71 years; mean BDI score: 2.70 $\pm$ 2.49) were included in the EEG analysis. Participants were recruited from an academic environment (education: mean: 16.4 $\pm$ 1.79 years; verbal intelligence: mean: 118.4 $\pm$ 8.55). The executive abilities of participants were not examined before the participation in the study.

The sample was randomly divided into two sub-samples; these groups were instructed to carry out two different versions of the same task (see *paradigm;* paradigm +/− and paradigm R/L). The two groups did not differ regarding age (paradigm +/−: number of participants: 14; mean age: 24.8 $\pm$ 3.31; paradigm R/L: number of participants: 13; mean age: 23.2 $\pm$ 1.64; $p = 0.139$), education (paradigm +/−: mean: 16.6 $\pm$ 1.96 years; paradigm R/L: mean: 16.3 $\pm$ 1.64 years; $p = 0.631$) and verbal intelligence (paradigm +/−: mean: 117.5 $\pm$ 9.21; paradigm R/L: mean: 119.3 $\pm$ 8.1; $p = 0.593$).

The study was approved by the local ethics committee of the Ludwig-Maximilians-University Munich. The investigation was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant after procedures had been fully explained. Each subject was paid €20 for participation in the study.

Procedure, Paradigm, and Analysis of Behavioral Data

All subjects performed an adapted go/nogo task where auditory stimuli consisted of sinusoidal tones (duration: 50 ms, pressure level: 100 dB) of three differential pitches, delivered binaurally via headphones. Tones were presented pairwise at intervals of 1000 ms. The interval between trials lasted 2000 ms. The *go condition* comprised the combination of a middle frequency tone (1000 Hz; cue stimulus) followed by a high frequency tone (1300 Hz). Subjects were instructed to press a response button with their right index finger and respond as quick as possible after the stimuli were presented, while minimizing any errors. In the *nogo task* the tone with the middle frequency (cue stimulus) was followed by a low frequency tone (800 Hz). During this condition, the prepared behavioral response was to be inhibited. In the *voluntary selection condition,* the cue stimulus was followed by the tone with an identical frequency (1000 Hz; *selection*; information about the paradigm see also Karch et al., 2009, 2012). Instructions regarding the voluntary selection condition differed between the two versions of the paradigm: in the first version, participants were instructed to freely decide whether to press the response button (*selection+*) or not (*selection−*) during the voluntary selection task (*paradigm +/−*). Participants were asked to decide separately in each trial of the *voluntary selection* condition whether they wanted to respond or not. Subjects were told that the ratio *selection+*/*selection−* should be approximately equally often. In addition, subjects were asked not to count how often they pressed the button and not to alternate between button press and not press. In *paradigm R/L,* two response buttons were provided. Subjects were instructed to decide whether they wanted to press a response button with the left (*selection_L)* or the right (*selection_R)* index finger. Participants were instructed to press the response button with the right and left index finger more or less equally often without counting the responses (see **Figure 1**).

In addition, both paradigms included a passive listening task which served as control condition. During the control condition, the tone with the low-frequency was presented first, indicating that no behavioral response was necessary regardless of which tone was presented next (*control condition*: 800–1000 Hz). All conditions were presented in pseudo-randomized order. The *go* condition was presented 160 times, the other conditions were presented 80 times, with an interstimulus interval of 3 s. Prior to the EEG session, all subjects received a practice block in order to ensure that the instructions had been fully understood (see also Karch et al., 2009, 2012).

Auditory stimuli were generated using the Presentation software package (version 14.2) and conducted via a set of headphones placed over the subjects' ears. Participants kept their right index finger mounted on the button of the response box. During paradigm R/L, subjects were also instructed to keep their left index finger on the second response button.

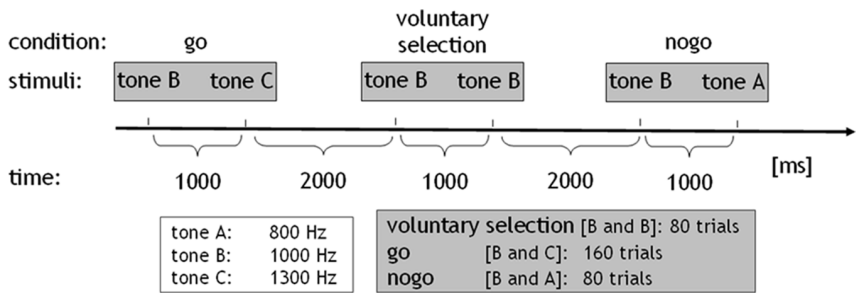

FIGURE 1 | Paradigm: sinusoidal tones of three differential pitches were presented (duration: 50 ms, pressure level: 100 dB). The tones were presented in pairs at intervals of 1000 ms. The interval between trials lasted 2000 ms. The *go condition* comprised the combination of the middle-frequency tone (tone b: 1000 Hz; cue stimulus) followed by the high-frequency tone (tone c: 1300 Hz). In the *nogo task*, the cue stimulus was followed by a low-frequency tone (tone a: 800 Hz). In the *voluntary selection condition,* the cue stimulus was followed by the tone with a same frequency. The *go condition* was presented 160 times, *nogo,* and *voluntary selection* were presented 80 times.

Behavioral Data

Reaction times, errors of omission (during *go task*) and errors of commission (during *nogo condition* and *passive listening task*) were recorded with the Presentation software. Any response delayed by more than 1500 ms after the stimulus was counted as error during the *go* condition. During the *voluntary selection* condition of paradigm +/−, behavioral responses during the interval 0–1500 ms after stimulus presentation were counted as *selection*+; trials without behavioral response within the first 1500 ms after stimulus presentation were counted as *selection*−. In paradigm R/L, responses with the right and the left index finger were recorded during the *voluntary selection* task. The mean reaction times were calculated separately for go and voluntary selection. Behavioral data (response times; error rates) were compared between conditions with ANOVA (within subject factors of paradigm +/−: *go*; *selection*+; within subject factors of paradigm R/L: *selection*; *go*). In addition, *t*-tests were calculated in order to examine differences regarding reaction time, percentage of correct responses and the error rate between paradigm +/− and paradigm R/L.

EEG Acquisition and Data Analysis

The EEG was recorded with 32 electrodes (Neuroscan Synamps) using an electrode cap; Cz served as reference. Electrodes were positioned according to the International 10/20 system including the following electrodes: Fz, Cz, Pz, Fp1, Fp2, F3, F4, F7, F8, C3, C4, Cp5, Cp6, P3, P4, P9, P10, T5, T6, T3, T4, O1, O2, A1, A2, EOG, T1, T2, Fc5, Fc6, Fc1, Fc2. Data were collected with a sampling rate of 1000 Hz and without any filter during acquisition. Impedances were maintained below 5 kΩ. Participants were asked to stay calm and keep their eyes closed during the task. Recording took place in a sound-attenuated and electrically shielded room.

Pre-processing and data analyses were done with the Vision Analyzer Software (Brain Products, Munich). A common average reference was used. EEG data were filtered with a 1 Hz high-pass filter (slope 24 dB/oct), a 100 Hz low-pass filter (slope 24 dB/oct); a notch filter was not used. Eye-blinks were detected automatically and corrected using the correction of Graton & Coles using Fp2 as reference. EEG data were segmented into 2000 ms epochs time-locked to the onset of the second stimulus of each pair of tones, separately for each different condition (*voluntary selection, go, nogo*). The sampling epoch commenced 1000 ms before the presentation of the second tone that indicated which task was to be performed. An amplitude criterion (±70 μV) was used for artifact rejection involving *Fz*, *Cz,* and *Pz*. Baseline correction was done using the 200 ms interval before the second stimulus of each pair of tones. ERP wave-shapes were averaged separately for *go, nogo, voluntary selection condition*. Trials with incorrect responses were rejected prior to averaging. All wave-shapes included at least 30 averages.

In the paradigm +/− 94.2% of *go* trials ($M = 150.7$ trials), 94.8% of the *nogo* trials ($M = 75.8$) and 96.6% of the *voluntary condition* ($M = 77.3$ trials) were included on average for the analyses. Concerning the R/L paradigm 94.9% of *go* trials ($M = 151.8$ trials), 96.9% of the *nogo* trials ($M = 77.5$ trials) and 91.8% of the *voluntary condition* ($M = 73.4$ trials) were included on average for the analyses.

Statistics

SPSS 18.0 program was used for statistical analysis. The significance level was 0.05, *p*-values between 0.05 and 0.1 were marked as a trend.

Event-Related Potentials

ERPs (N2 and P3) were examined at fronto-centro-parietal electrodes (Fz, Cz, Pz). The N2 was defined as the largest relative minimum of the ERP in the search window of 160–230 ms. The P3 was defined as the largest relative maximum of the ERP 230–550 ms after the presentation of the respective task. ANOVAs were run on the maximum ERP-amplitude in each search window (N2, P3) with two within subject factors *task* (*voluntary selection, nogo, go*) and *electrode position* (Fz, Cz, Pz). Because ANOVAs are not robust to violations of sphericity we checked for each within subject factor whether Mauchly's test was significant. If so, the Greenhouse-Geisser corrected values for any effects involving this factor were reported. *Post hoc t*-tests were used in case of significant within subjects factors in order to analyze which task conditions and electrodes differed

significantly from each other. Based on 3 × 3 task conditions, nine different tests were performed. The results of the *t*-tests were Bonferroni corrected.

Wavelet-Analysis

Evoked alpha-/beta- and gamma-activity were calculated using a complex Morlet wavelet transformation [see also (Herrmann et al., 1999; Mulert et al., 2007)]. The wavelet transformation was performed on averaged ERPs to reveal the phase-locked evoked fraction of the alpha-, beta-, and gamma-activity. As a first step, the frequency range from 1 to 60 Hz was divided into 40 frequency steps (distributed on a logarithmic scale) for each subject (Morlet parameter $c = 5$; continuous wavelet transformation; Morlet complex wavelet). In the next step, for each participant separate parameters were calculated for alpha (frequency range 8.06–12.09 Hz; mean: 10.08 Hz), beta (frequency range 20.16–30.25 Hz; mean: 25.21 Hz), and gamma frequencies (frequency range 32.27–48.40 Hz; mean: 40.34 Hz; see also Karch et al., 2012).

Alpha/beta/gamma power was identified at Fz, Cz, and Pz in the time-frame 0–500 ms after the presentation of the second tone of each pair of tones. The length of the interval was adapted to the waveform of the oscillatory responses. Amplitudes were detected automatically using the Brain Vision Analyzer-Software Version 1.05 (see also Karch et al., 2012). ANOVAs were employed to test for differences between electrode position and task condition, as well as between paradigms (paradigm +/− vs. paradigm R/L).

RESULTS

Behavioral Results

The results are shown in **Table 1**. Mean response times were significantly longer in *voluntary selection* trials than in *go* trials in paradigm +/− [$F(1,13) = 101.553$; $p < 0.001$] and paradigm R/L [$F(1,12) = 31.321$; $p < 0.001$]. The percentage of responses was significantly increased in the *go* compared to the *voluntary selection* condition in paradigm +/− [$F(1,13) = 200.96$; $p < 0.001$] and in paradigm R/L [$F(1,12) = 16.78$; $p = 0.001$]. The error rate did not differ significantly between tasks [$F(1,12) = 6.783$; $p = 0.523$].

The comparison of behavioral data of paradigm +/− with those of paradigm R/L revealed comparable reaction times ($p = 0.273$) and comparable percentages of correct responses ($p = 0.543$) during *go*. In addition, the reaction time did not differ significantly during the *voluntary selection* task ($p = 0.635$). The percentage of responses was significantly higher in paradigm R/L compared to paradigm +/− ($p < 0.001$). Participants used the left button in 53.7% of voluntary selection trials (reaction time: $M = 861.6$ ms) and the right button in 45.4% of trials (reaction time: $M = 840.3$ ms). Error rates were comparable in both groups ($p = 0.122$).

Comparison of ERPs During *go, Nogo, and Voluntary Selection* Condition

Results are shown in **Figures 2** and **3**.

TABLE 1 | Behavioral data: the response times were significantly longer in *voluntary selection* trials than in *go* trials in paradigm +/− and paradigm R/L.

	Paradigm +/−		Paradigm R/L	
	M	***SD***	***M***	***SD***
Reaction time (ms)				
Go	516.0	116.93	568.7	127.49
Voluntary selection	811.0	178.95	850.2	242.42
Percentage of responses (%)				
Go	97.95	1.81	97.31	3.34
Voluntary selection	56.34	10.63	94.38	3.18
Error rate (%)				
Responses during nogo or control	3.74	2.41	2.23	2.50

In addition, the percentage of responses was significantly increased in the go compared to the voluntary selection condition in both versions. The error rate did not differ significantly between tasks. M, Mean value; SD, standard deviation; ms, milliseconds; %, percentage.

Paradigm +/−

N2

Regarding the N2-amplitude, in paradigm +/− the main effect of *condition* (*go*, *nogo*, *voluntary selection*) [$F(2,26) = 6.376$; $p = 0.006$] and the main effect of *electrode position* (Fz, Cz, Pz) [$F(2,26) = 4.922$; $p = 0.034$] turned out to be significant. The interaction between *electrode position* and experimental *condition* was not significant [$F(4,52) = 1.918$; $p = 0.162$]. Further analyses revealed that the N2 was significantly less pronounced in the *go* task compared to the *voluntary selection* condition ($p = 0.015$) as well as the *nogo* ($p = 0.032$). The N2 did not differ between *voluntary selection* and *nogo* ($p = 1.0$). When focusing on the localisation of the N2 (*electrode position*), the N2 was enhanced in Fz compared to Cz ($p = 0.010$). The comparison of Fz and Pz ($p = 0.280$) as well as Cz and Pz ($p = 1.0$) did not reveal significant differences.

P3

The results of the P3-amplitudes showed significant main effects of *condition* [$F(2,26) = 23.267$; $p < 0.001$] and *electrode position* [$F(2,26) = 3.437$; $p = 0.047$] as well as a significant interaction effect (*condition* × *electrode position*) [$F(4,52) = 9.392$; $p < 0.001$]. The P3 amplitude was increased in *nogo* trials compared to *go* trials ($p < 0.001$) and the *voluntary selection* condition ($p = 0.008$). Apart from this, *voluntary selection* associated P3 amplitudes were increased compared to those of the *go* task ($p = 0.005$). Regarding the position of the electrodes, there was a significantly increased P3 in Cz compared to Fz ($p = 0.020$). The P3 in Fz and Pz ($p = 1.0$) as well as Cz and Pz ($p = 0.171$) did not differ significantly.

Post hoc tests of the interaction effect revealed significant differences in Fz and Cz between *go* and *nogo* (Fz: $p = 0.001$; Cz: $p < 0.001$), *go* and *voluntary selection* (Fz: $p = 0.021$; Cz: $p = 0.015$) as well as *nogo* and *voluntary selection* (Fz: $p = 0.035$; Cz: $p = 0.004$). The differences in Pz were not significant (*go* vs. *nogo*: $p = 0.385$; *go* vs. *voluntary selection:* $p = 0.205$; *nogo* vs. *voluntary selection:* $p = 1.000$).

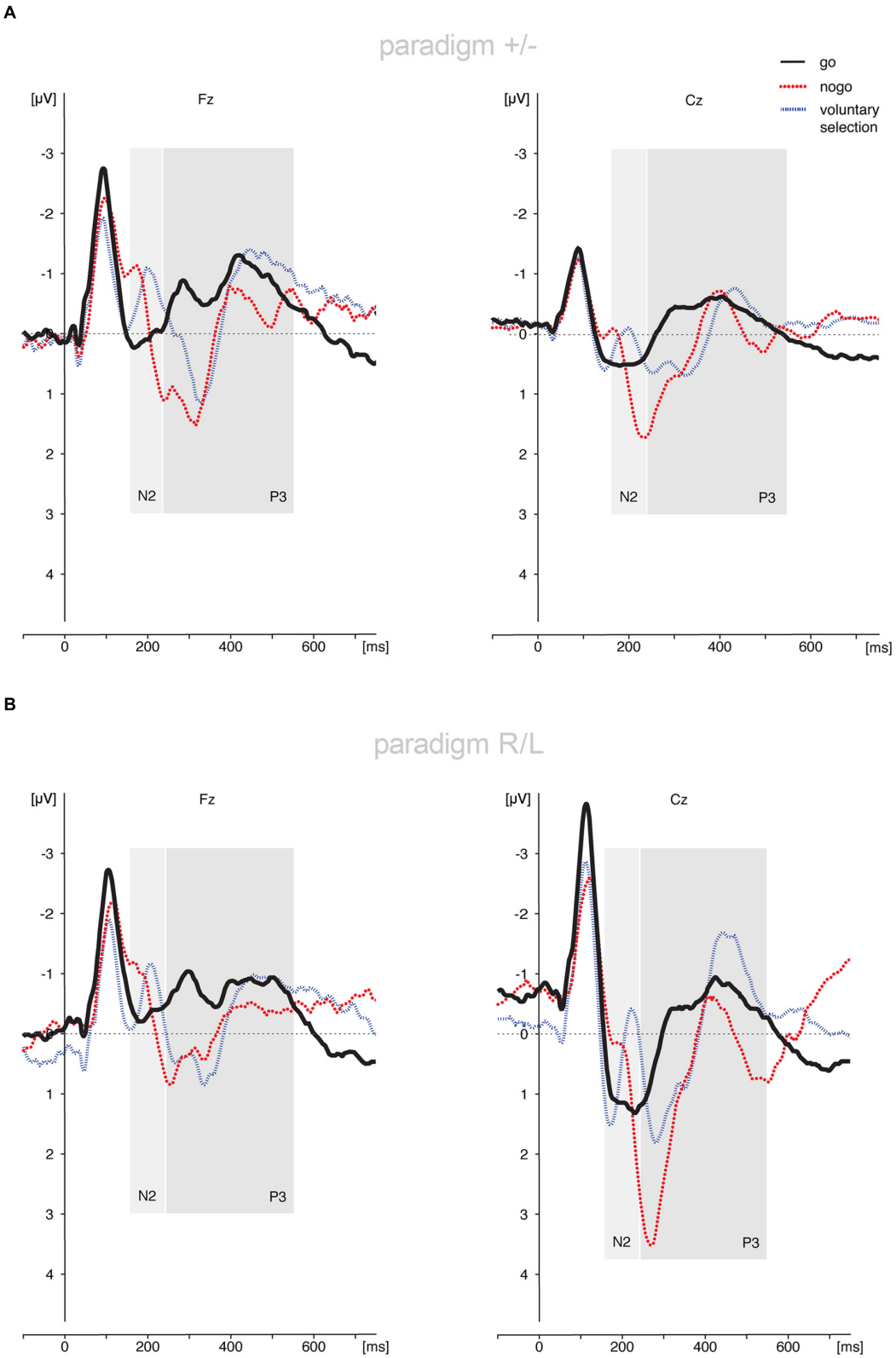

FIGURE 2 | Auditory evoked potentials of healthy controls. (A) ERPs concerning the paradigm +/−; **(B)** ERP results regarding the paradigm R/L. Subjects showed increased fronto-centrally located N2 amplitudes during the *voluntary selection task* and *nogo condition* compared to *go*. The P3 amplitude was located in fronto-central brain areas during the *nogo* condition and the *voluntary selection* condition. Abbreviations μV, microvolt; ms, milliseconds.

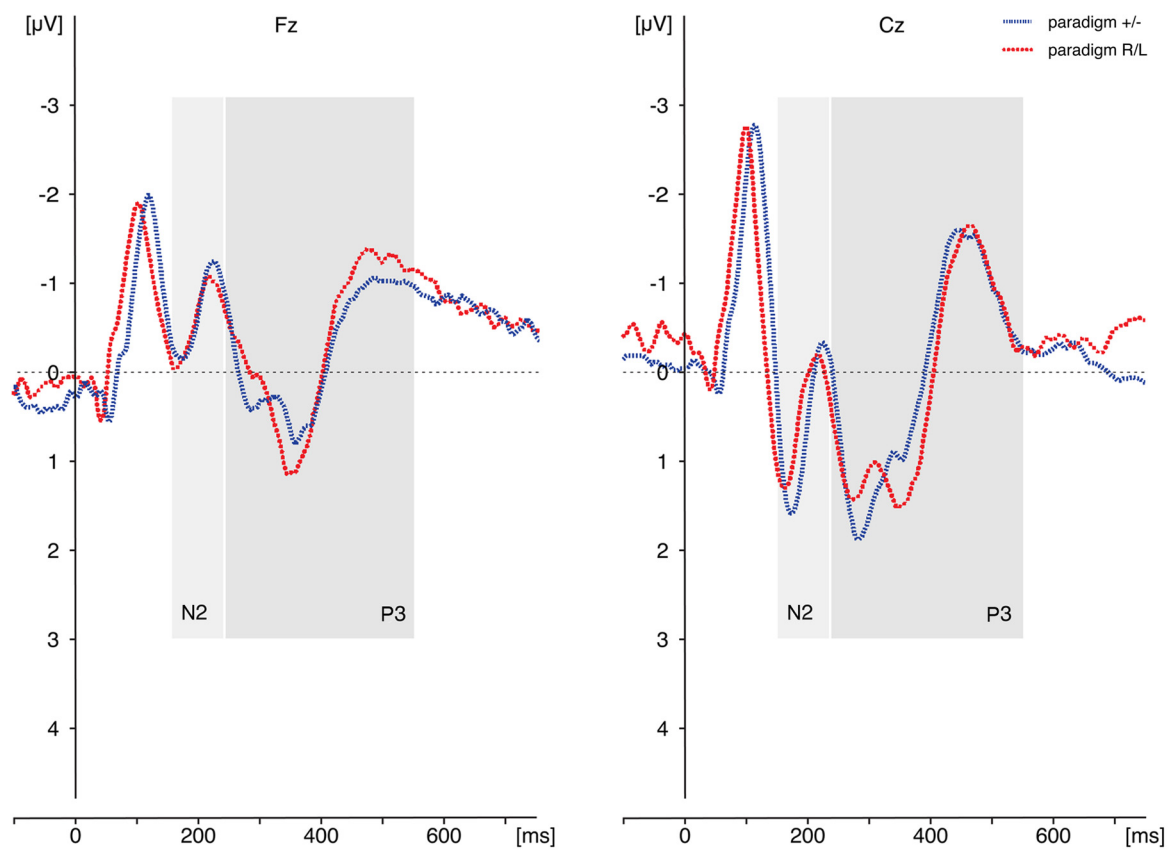

FIGURE 3 | Comparison of the *voluntary selection*-related responses during paradigm +/− and paradigm R/L. The ERP results differed only marginally between paradigms. Abbreviations μV, microvolt; ms, milliseconds.

Paradigm R/L

N2

The assessment of the N2 amplitude demonstrated that the main effects of *condition* [$F(2,24) = 7.163$; $p = 0.004$] and *electrode position* [$F(2, 24) = 12.230$; $p < 0.001$] were statistically significant; the N2 amplitudes were more negatively in Fz compared to Cz ($p < 0.001$) and Pz ($p = 0.008$). The N2 did not differ between Cz and Pz ($p = 1.0$). In addition, the N2 was less pronounced in *go* trials compared to *nogo* trials ($p = 0.041$) and *voluntary selection* trials ($p = 0.041$). The results of *nogo* and *voluntary selection* were comparable ($p = 1.0$). The interaction effect (*condition* × *electrode position*) was not significant [$F(4,48) = 0.866$; $p = 0.491$].

P3

The P3-amplitudes differed significantly between *conditions* [$F(2,24) = 11.218$; $p < 0.001$] and *electrode positions* [$F(2,24) = 8.574$; $p = 0.007$]. Apart from that, the interaction effect (*condition* × *electrode position*) was significant [$F(4,48) = 6.001$; $p = 0.004$]. *Post hoc* tests showed smaller P3 amplitudes in *go* compared to *nogo* ($p = 0.008$) and *voluntary selection* ($p = 0.008$); the P3 in nogo and voluntary selection was comparable ($p = 0.152$). Regarding the localisation, the P3 was decreased in Fz compared to Cz ($p = 0.005$) and Pz ($p = 0.003$); the difference between Cz and Pz was not significant ($p = 0.602$).

Post hoc tests of the interaction effect revealed significant differences in Fz and Cz between *go* and *nogo* (Fz: $p < 0.001$; Cz: $p = 0.023$), *go* and *voluntary selection* (Fz: $p = 0.006$; Cz: $p = 0.023$). The difference between *nogo* and *voluntary selection* was not significant for Fz ($p = 0.368$) but Cz ($p = 0.045$). The differences in Pz were not significant (*go* vs. *nogo*: $p = 1.000$; *go* vs. *voluntary selection:* $p = 0.608$; *nogo* vs. *voluntary selection:* $p = 1.000$).

Comparison of the Results of Paradigm +/− and Paradigm R/L

N2

The N2-amplitudes differed significantly between *conditions* [$F(2,50) = 12.947$; $p < 0.001$] and *electrode positions* [$F(2,50) = 12.997$; $p < 0.001$]. The interaction effects *condition* × *electrode position* reached trend level [$F(4,100) = 2.533$; $p = 0.076$]. The interactions *condition* × *group*

[$F(2,50) = 0.181$; $p = 0.835$], *electrode position* × *group* [$F(2,50) = 0.106$; $p = 0.828$] and *condition* × *electrode position* × *group* [$F(4,100) = 0.190$; $p = 0.868$] were not statistically significant. The *group* effect (paradigm +/−; paradigm R/L) was not statistically significant ($p = 0.921$). *Post hoc* analysis revealed enhanced N2 amplitudes during *nogo* trials compared to *go* trials ($p = 0.001$) and in *voluntary selection* trials compared to *go* trials ($p = 0.001$), but no differences between *nogo* and *voluntary selection* ($p = 1.0$). With respect to the localisation of the N2 amplitudes, the results showed an increased N2 amplitude in Fz compared to Cz ($p < 0.001$) and Pz ($p = 0.007$) whereas the N2 in Cz and Pz did not differ significantly ($p = 1.0$).

P3

Regarding the P3-amplitude there were significant main effects of *condition* [$F(2,50) = 32.524$; $p < 0.001$] and *electrode position* [$F(2,50) = 10.831$; $p < 0.001$]. In addition, the interaction *condition* × *electrode position* [$F(4,100) = 14.495$; $p < 0.001$] was significant. By contrast, the interactions between *condition* × *group* [$F(2,50) = 0.382$; $p = 0.632$], *electrode position* × *group* [$F(2,50) = 2.239$; $p = 0.117$] and *condition* × *electrode position* × *group* [$F(4,100) = 0.292$; $p = 0.883$] were not significant. In addition, the *groups* did not differ significantly [$F(1,25) = 0.010$; $p = 0.921$].

Post hoc *t*-tests indicated a significantly increased P3 amplitude during *nogo* trials compared to *go* trials ($p < 0.001$) and *voluntary selection* trials ($p = 0.001$). In addition, *selection*-related P3 amplitudes were increased compared to *go*-associated responses ($p < 0.001$). The P3 was increased in central areas compared to frontal regions (Cz > Fz; $p < 0.001$); the difference between Fz and Pz ($p = 0.150$) as well as Cz and Pz ($p = 0.082$) was not significant.

Post hoc tests of the interaction effect revealed significant differences in Fz and Cz between *go* and *nogo* (Fz: $p < 0.001$; Cz: $p < 0.001$), *go* and *voluntary selection* (Fz: $p < 0.001$; Cz: $p = 0.002$) as well as *nogo* and *voluntary selection* (Fz: $p = 0.009$; Cz: $p < 0.001$). The differences in Pz were not significant (*go* vs. *nogo*: $p = 0.237$; *go* vs. *voluntary selection:* $p = 0.077$; *nogo* vs. *voluntary selection:* $p = 1.000$).

Results of the Wavelet-Analysis

The results of the wavelet-analysis are shown in **Figure 4** and **Table 2**.

Alpha Frequency Range

Regarding alpha activity, responses related to paradigm R/L did not differ significantly from those related to paradigm +/− [$F(1,25) = 0.120$; $p = 0.732$]. The main effect of *condition* [$F(2,50) = 6.538$; $p = 0.003$] was significant and demonstrated increased responses during *voluntary selection* compared to *go* ($p = 0.005$) but not between voluntary selection and nogo ($p = 1.0$) or nogo and go ($p = 0.078$).

The alpha response was significantly increased in the central area compared to frontal and parietal areas (Cz compared to Fz ($p < 0.001$), and Cz compared to Pz ($p < 0.001$) [$F(2,50) = 25.477$; $p < 0.001$]; Fz compared to Pz did not differ significantly ($p = 1.0$). The interactions were not significant {condition × group: [$F(2,50) = 1.546$; $p = 0.223$]; electrode position × group [$F(2,50) = 0.365$; $p = 0.696$]; elect rode position × condition: [$F(4,100) = 1.938$; $p < 0.110$]; condition × electrode position × group: [$F(4,100) = 0.703$; $p = 0.592$]}.

Post hoc tests indicated increased alpha power during voluntary selection compared to go ($p = 0.005$); the results of voluntary selection and nogo ($p = 1.0$) and nogo and go ($p = 0.078$) did not differ.

Beta-Frequency Range

We did not find any difference in beta power between paradigm +/− and paradigm R/L [$F(1,25) = 1.401$; $p = 0.248$]. The beta activity differed significantly between *conditions* [$F(2,50) = 8.952$; $p < 0.001$] with increased responses during the *voluntary selection* condition compared to the *go* condition ($p < 0.001$) and compared to the *nogo* task ($p = 0.031$), but no differences between *go* and *nogo* ($p = 0.857$). In addition, there was a significant main effect of *electrode position* [$F(2,50) = 6.666$; $p = 0.003$] with an increased activity in Cz compared to Pz ($p = 0.002$) whereas the results of Fz and Pz ($p = 0.231$) and Fz and Cz were comparable ($p = 0.282$).

All interactions were not significant [*condition* × *group*: $F(2,50) = 0.688$; $p = 0.507$; *electrode position* × *group*: $F(2,50) = 0.229$; $p = 0.796$; *condition* × *electrode posi tion:* $F(4,100) = 0.403$; $p = 0.806$; *condition* × *electrode position* × *group:* $F(4,100) = 0.917$; $p = 0.457$].

Gamma Frequency Range

Gamma power related to the paradigm +/− and the paradigm R/L did not differ significantly [$F(1,25) = 0.741$; $p = 0.398$]. However, the main effects of *condition* [$F(2,50) = 10.492$; $p < 0.001$] and *electrode position* [$F(2,50) = 11.378$; $p < 0.001$] as well as the interaction between *condition* and *electrode position* [$F(4,100) = 5.232$; $p = 0.001$] were significant.

Gamma activity was more pronounced in *voluntary selection* trials compared to *go* trials ($p = 0.001$) and *nogo* trials ($p = 0.002$); gamma activity of *go* and *nogo* did not differ ($p = 0.654$). Gamma activity was especially located in frontal and fronto-central areas: differences between Fz and Pz ($p < 0.001$) as well as Cz and Pz ($p = 0.013$) associated gamma activity were significant. Differences between Fz and Pz were not significant ($p = 1.0$). The interaction effects *condition* × *group* [$F(2,50) = 0.331$; $p = 0.675$], *electrode position* × *group* [$F(2,50) = 0.591$; $p = 0.557$] and *condition* × *electrode position* × *group* [$F(6,306) = 0.158$; $p = 0.959$] were not significant.

DISCUSSION

Intentional actions are supposed to be purposive and goal-directed as well as endogenously controlled (Brass and Haggard, 2008). In addition, attention is required in intentional actions and they offer a choice between alternatives (Jahanshahi, 1998). The aim of the present study was to distinguish electrophysiological correlates (ERPs; alpha, beta, gamma power) of intentional

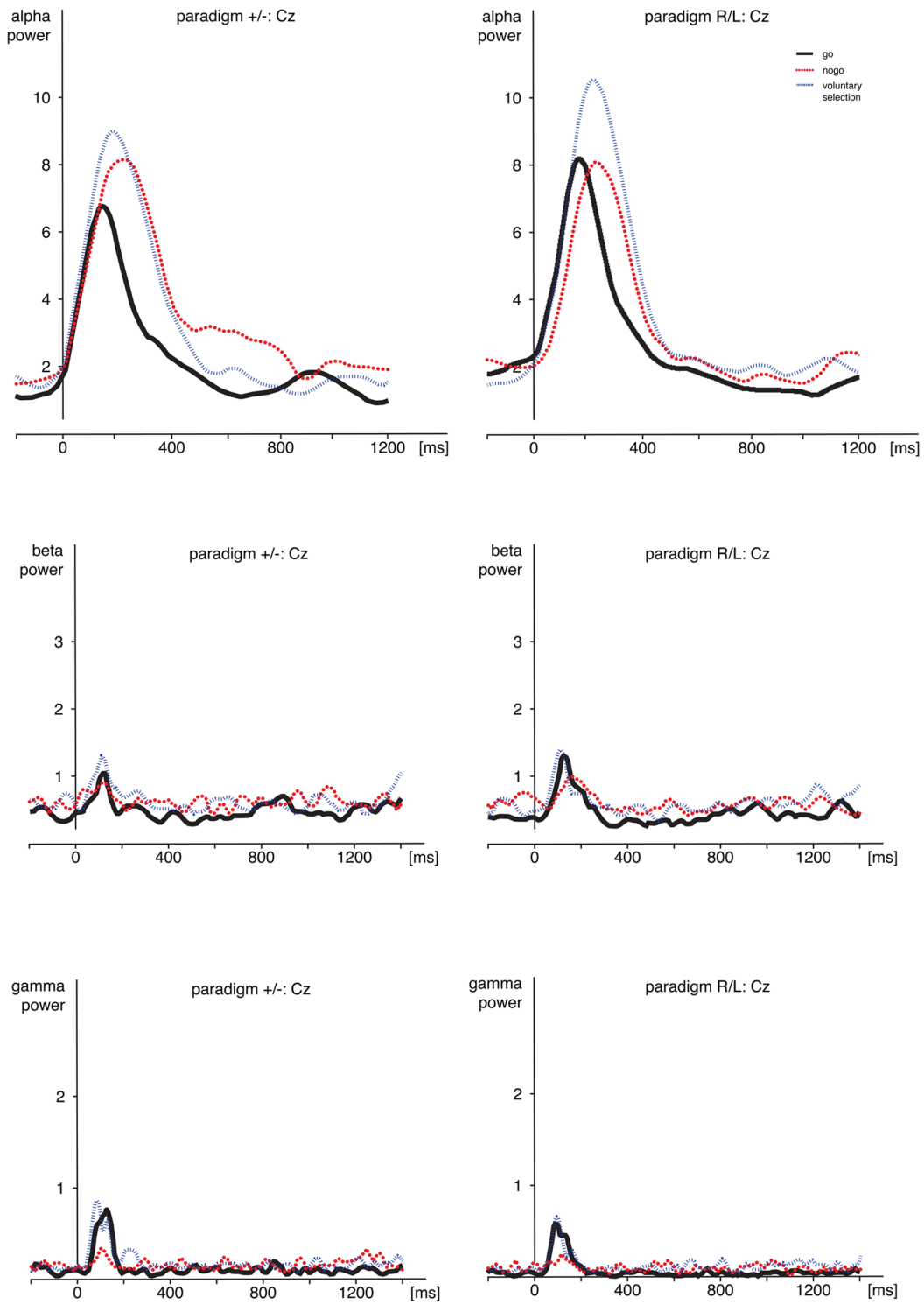

FIGURE 4 | Time frequency analyses. Comparison of alpha-, beta-, and gamma-power during *go*, *nogo,* and *voluntary selection* in Cz. Activity was increased during *voluntary selection* compared to *go* and *nogo* condition. ms, milliseconds.

actions and externally guided actions. In addition, we compared neurobiological findings of different aspects of intentional actions: (1) "*what*" component comprising the decision, which action to perform; (2) "*whether*" component, which refers to the decision, whether or not to perform an action (Brass and Haggard, 2007, 2008). For that purpose, subjects were

TABLE 2 | Wavelet analysis: mean value of alpha, beta, and gamma power during *go*, *nogo,* and *voluntary selection* in paradigm +/− and paradigm R/L.

	Paradigm +/−			Paradigm R/L		
	Fz	Cz	Pz	Fz	Cz	Pz
Alpha power						
Go	5.48	7.05	4.06	5.36	8.35	5.30
Nogo	7.51	9.48	6.27	6.15	9.08	5.61
Voluntary selection	5.80	9.64	6.53	6.68	10.75	6.54
Beta power						
Go	1.26	1.28	0.96	1.28	1.61	1.17
Nogo	1.26	1.37	1.23	1.42	1.50	1.15
Voluntary selection	1.39	1.57	1.29	1.49	1.65	1.41
Gamma power						
Go	1.06	1.23	0.31	0.74	0.91	0.35
Nogo	0.88	0.62	0.49	0.72	0.53	0.50
Voluntary selection	1.63	1.39	0.63	1.33	1.04	0.55

instructed to decide voluntarily whether they wanted to respond by button press or not (paradigm +/−; "*whether*" component). Another experimental task included the decision to respond with their right or their left index finger (paradigm R/L; "*what*" component).

With regard to the behavioral data, we found increased reaction times associated with intentional actions (*voluntary selection*) compared to externally guided responses (*go*). These findings are in line with the results of earlier studies using the same paradigm (Karch et al., 2009, 2010b). In addition, the responses of the participants during *voluntary selection* were carefully monitored by the instructor in order to prevent that the responses were systematically (e.g., alternating response and no response). Taking this information together may indicate that an additional cognitive process is essential for the processing of intentional responses compared to stimulus-driven actions. Reaction times did not differ, irrespective of the kind of intentional process (decision what to do or whether to respond or not).

In the present study, intentional processes were associated with a fronto-centrally located N2 and P3 potential. The N2 and P3 amplitude were increased during voluntary selection processes compared to instructed responses (*go*). The findings of some former studies regarding voluntary selection are similar to those of the present study (Karch et al., 2009, 2010a,b). By contrast, the results of Waszak et al. (2005) regarding electrophysiological correlates of intentional and stimulus-based actions differ considerably from the findings of the present study. Their results demonstrated that electrophysiological responses occurred much earlier in the intention-based condition compared to the stimulus-based condition. The response-locked lateralised readiness potential remained relatively invariant between conditions. The authors assumed that the results provide evidence for two different modes of action selection: one mode seems to be stimulus-driven, the other seems to be mainly intention-driven (Waszak et al., 2005). The differences between the results of the present study and the study of Waszak et al. (2005) could be influenced by differences regarding the experimental paradigm.

Information about the functional meaning of the N2 and P3 is inconsistent: there is some evidence that the N2 is associated with the selection of a response and influences subsequent stages of processing reflected in the P3. Unexpected revisions of the response program seemed to delay and enhance the N2 (Gajewski et al., 2008). Forstmann et al. (2007) suggested that the choice-related N2-P2 complex might reflect early sensory-perceptual processing, whereas the P3 is associated with the evaluation of the stimulus (Forstmann et al., 2007). The authors assumed that a choice between several task sets invokes medial frontal activity. Apart from that, a number of other brain regions seemed to be relevant for choices including parieto-occipital areas (Forstmann et al., 2007).

The ability to localize generators of ERP components is limited because of the low spatial resolution of EEG recordings. The results of a simultaneous EEG and functional MRI study using the voluntary selection paradigm showed that N2-related neuronal responses were mainly associated with medial and lateral parts of the frontal cortex. By contrast, the P3 was predominantly related to enhanced neuronal responses in lateral frontal brain areas and the temporo-parietal junction (Karch et al., 2010a). This may indicate that the frontal cortex is involved at an earlier stage than temporal and -parietal regions (Karch et al., 2010a).

Medial frontal areas, including the rostral cingulate zone, have already shown to be involved in the control of voluntary behavior as well as conflict monitoring, error detection and decision making (Jenkins et al., 2000; Botvinick et al., 2001; Garavan et al., 2002; Lau et al., 2004b, 2006; Nachev et al., 2005; Forstmann et al., 2006; Karch et al., 2009). These concepts might be partly overlapping: Krieghoff et al. (2011), for example, suggested that response conflict and volition represent two sides of the same coin and that there is no will without "conflicting" ideas (Krieghoff et al., 2011).

N2 and P3 amplitudes were not only detected during intentional actions but also during response inhibition. The N2 amplitude during *nogo* and *voluntary selection* did not differ significantly. By contrast, fronto-central P3 amplitudes were increased during response inhibition compared to both voluntary behavior and stimulus-dependent responses. Our findings of pronounced nogo N3 and P3 potentials are in line with former studies: response inhibition processes were frequently associated with a fronto-centrally located N2 potential and P3 potential (Pfefferbaum et al., 1985; Kopp et al., 1996; Bruin et al., 2001; Donkers and van Boxtel, 2004; Smith et al., 2004; Bekker et al., 2005). The nogo N2 appeared to be located in medial frontal regions (Bekker et al., 2005). It is assumed that the N2 is relevant for the suppression of incorrect response tendencies (Falkenstein et al., 1999) and could be associated with the rare presentation of stimuli (Donkers and van Boxtel, 2004; Bartholow et al., 2005), or is linked to stimulus classification (Ritter et al., 1983) as well as conflict (Randall and Smith, 2011). The frontally located P3 seemed to be more clearly associated with response inhibition and could be an indicator of both cognitive and motor inhibition (Smith et al., 2008), alternatively it reflects the cancelation of a planned response (Randall and Smith, 2011).

Concerning oscillatory responses, we detected increased alpha, beta, and gamma activity during intentional actions compared to instructed responses (*go*). Apart from that, beta- and gamma-power were more pronounced during voluntary responses compared to the inhibition of behavioral responses. Increased oscillatory activity was predominantly located in frontal and fronto-central areas. These results may indicate that oscillatory responses might be more helpful to further distinguish functional correlates of voluntary responses and response inhibition.

In general, there is a broad consensus that different kinds of oscillation denote different brain activity states and that oscillatory fluctuations across time are representative of the dynamic interplay between different cell types in various cortical and subcortical circuits (Buzsaki, 2006). The application of sensory or cognitive stimuli influences these responses. Oscillatory phenomena are strongly interwoven with sensory and cognitive functions: oscillatory processes could play a major role in relation to memory and integrative functions (Basar et al., 2000).

Especially gamma-band synchronization has attracted considerable interest over recent years because mechanistic roles have been proposed in phase coding, perceptual integration, and flexible routing of information in the visual system (Fries, 2009; Vinck et al., 2013), and furthermore because of its appearance in multiple cortical and subcortical structures (Fries, 2009). Former studies have demonstrated that oscillations in higher frequency ranges, especially gamma activity, are influenced by a various cognitive processes including object recognition, attention and working memory as well as the preparation of motor responses (Tiitinen et al., 1993; Yordanova et al., 1997; Engel et al., 2001; Debener et al., 2003; Basar-Eroglu et al., 2007). In addition, gamma activity increases with increasing task difficulty (Senkowski and Herrmann, 2002; Posada et al., 2003; Mulert et al., 2007). Midline areas, especially the dorsal part of the ACC and the medial frontal cortex, are assumed to be related to gamma-band responses (Mulert et al., 2007). These processes are assumed to be influenced by inhibitory interneurons and pyramidal cells (Bartos et al., 2007; Cardin et al., 2009; Sohal et al., 2009). Bosman et al. (2014) assumed that gamma band activity originates from the interplay between inhibition and excitation. Overall, gamma band oscillations support multiple cognitive processes rather than a single one. At a higher functional level, gamma-band oscillations seem to be influenced by visual attention, decision-making, response timing, motivation and short- and long-term memory (Bosman et al., 2014). They coordinate neuronal activity in hippocampal and neocortical networks (Kann et al., 2014). Cortico-cortical communication and the large scale integration of disturbed sets of neurons are needed for a well functioning cognitive ability and require synchronous neural gamma oscillations (Rodriguez et al., 1999).

EEG oscillations in the alpha and theta band reflect cognitive and memory performance (Klimesch, 1999). In addition, alpha band responses have been associated with working memory (Schack and Klimesch, 2002; Busch and Herrmann, 2003; Klimesch et al., 2005). Alpha activity was shown to grow with increasing memory load (Klimesch et al., 2005). Thalamo-cortical circuits as well as hippocampal areas are supposed to be relevant for the generation of alpha responses (Basar, 1998, 1999).

In addition, a recent review provides evidence that theta band activities over the mid-frontal cortex seem to reflect a common computation used for realizing the need for cognitive control (Cavanagh and Frank, 2014). Theta band processes may be used to communicate this need and subsequently implement such control across disparate brain regions. Thus, frontal theta is a compelling candidate mechanism by which emergent processes, such as 'cognitive control,' may be biophysically realized (Cavanagh and Frank, 2014).

The results of the present study are in line with the assumptions concerning the function of alpha, beta, and gamma oscillations: intentional responses might require pronounced cognitive process including cognitive control mechanisms as well as higher cognitive processes including decision-making in order to be effective. Overall, the results provide evidence that intentional actions might be more complex and seem to be related to cognitive control compared to instructed responses as well as response inhibition.

Intention-related variations in the alpha, beta, and/or gamma band activity seem to be measurable with the paradigm. This may provide the possibility to determine functional variations that are related with intentional actions in various neuropsychiatric disorders, e.g., in patients with ADHD or schizophrenia. It has been suggested that impairments regarding brain oscillations reflect disturbed information processing and a disruption in normal neuronal synchronization, e.g., caused by dysfunctional GABA/glutamate system, may contribute to deficits in cognitive and affective integration (Ozerdem et al., 2010). Basar et al. (2015) assume that oscillatory activity obtained by various input modalities are capable of displaying the relationship between any given neuropsychiatric disturbance and different neurotransmitter systems. In addition, brain oscillations may also show plasticity or compensation (Basar et al., 2015): a decrease in one frequency range may occur in parallel with the increase in a different frequency range.

In future, differences regarding intention-related neuronal responses between different neuropsychiatric disorders as well as the effect of psychotherapeutic interventions and pharmacological treatment on intention-related neuronal processes may be determined.

Another important aspect of the present study was a dissociation of neural correlates of different aspects of intentional actions. We did not find reliable differences regarding both ERPs and oscillatory responses: alpha-, beta-, and gamma-activity did not differ significantly between "whether" and "what" decisions. In addition, the N2 and P3 amplitudes were comparable. These results are somewhat surprising. However, up to now only a few studies exist that focus on this topic. Krieghoff et al. (2009) showed that the rostral cingulate zone is involved in the decision of which action to perform. By contrast, a part of the superior frontal gyrus in the paramedian frontal cortex seemed to be involved in the decision of "when" to perform action (Krieghoff et al., 2009). Brass and Haggard (2007) examined neural aspects of the "whether" component: in their study subjects were instructed

to cancel an intended response at the last possible moment. Functional MRI results demonstrated the involvement of the dorsal fronto-median cortex (Brass and Haggard, 2007). To our knowledge, "what" and "whether" decisions have not been compared directly so far. In addition, these studies focused on functional differences concerning the localisation of the functional correlates of decisions. Differences regarding the localisation were not examined in the present study because of the low spatial resolution of electrophysiological responses. By contrast, differences regarding the functional meaning of the processes involved were addressed.

Altogether, the results of the present study indicate that intentional actions are related to fronto-centrally located N2 and P3 potentials. These responses seemed to be more pronounced than those related to instructed responses and the instructed inhibition of responses. In addition, alpha-, beta-, and gamma-band responses were increased during the voluntary selection between response alternatives, compared to instructed responses. These results suggest that an additional cognitive process is needed for intentional actions compared to instructed behavior. The neural responses were comparatively independent of the kind of decision that was made.

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Methodological Considerations about the Use of Bimodal Oddball P300 in Psychiatry: Topography and Reference Effect

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Event-related potentials (ERPs) bimodal oddball task has disclosed increased sensitivity to show P300 modulations to subclinical symptoms. Even if the utility of such a procedure has still to be confirmed at a clinical level, gathering normative values of this new oddball variant may be of the greatest interest. We specifically addressed the challenge of defining the best location for the recording of P3a and P3b components and selecting the best reference to use by investigating the effect of an offline re-reference procedure on recorded bimodal P3a and P3b. Forty young and healthy subjects were submitted to a bimodal (synchronized and always congruent visual and auditory stimuli) three-stimulus oddball task in which 140 frequent bimodal stimuli, 30 deviant "target" stimuli and 30 distractors were presented. Task consisted in clicking as soon as possible on the targets, and not paying attention to frequent stimuli and distractors. This procedure allowed us to record, for each individual, the P3a component, referring to the novelty process related to distractors processing, and the P3b component, linked to the processing of the target stimuli. Results showed that both P3a and P3b showed maximal amplitude in Pz. However, P3a displayed a more central distribution. Nose reference was also shown to give maximal amplitudes compared with average and linked mastoids references. These data were discussed in light of the necessity to develop multi-site recording guidelines to furnish sets of ERPs data comparable across laboratories.

Keywords: event-related potentials, bimodal P300, P3a, P3b, topography, reference

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INTRODUCTION

Event-related potentials (ERPs) are of strong interest in psychiatry. They consist of a change in the electroencephalogram (EEG) indexing the neural processing of a stimulus. Thanks to their high temporal resolution, they can give a wide outlook at information processing in normal and/or pathological subjects (Hansenne, 2006). Indeed, analyses of different ERPs may allow the assessment of many stages of cognitive treatment, thanks to earlier components [such as sensory gating P50 or mismatch negativity (MMN)] but also to later components (P300 or N400; Rugg and Coles, 1995). Therefore, it is possible through ERPs to study cognitive functions and processes

of psychopathological conditions by comparing clinical populations to matched healthy controls (Polich and Herbst, 2000). However, up to this day, only some ERPs of interest in psychiatry benefit from detailed guidelines regarding the recommended recording and analysis parameters (Duncan et al., 2009). Therefore, there is still a crucial need for the development of multi-sites guidelines as the *a priori* choice of parameters such as the reference or the electrodes of interest defined by topography may be a source of bias introduced by the experimenter (Murray et al., 2008). Those choices can thus impact the statistical outcomes and the interpretation of the data. With this in mind, this paper addresses a first overview of some recording and analysis parameters for the bimodal P3a and P3b on healthy participants in a task implementable in psychiatry.

Since their discovery (Walter et al., 1964; Desmedt et al., 1965; Sutton et al., 1965), ERPs raised a hope to contribute to the elaboration of differential diagnosis for mental diseases (Boutros et al., 2011) as they were considered as potentials biological markers of psychopathology. Among others, one component was mainly expected to play the role of psychophysiological marker of psychiatric disorders: the P300 (Hansenne, 2006). The P300 is a parieto-central positive wave occurring roughly 300 ms after the presentation of a stimulus. It appears when a subject consciously detects an informative task-relevant stimulus (Huang et al., 2015). More specifically, the P300 appears to be the neural reflection of a revision process of mental representations in working memory, induced by the apparition of a stimulus: when a stimulus appears, it is compared to representations available in working memory. If a change is detected, the representations in working memory are updated thanks to attentional processes which are concomitant to the P300 (Polich, 2007). The P300 is usually recorded during an oddball paradigm in which two types of stimuli are presented: one frequent occurring around 80% of trials and one deviant, occurring around 20% of trials. Subjects have to detect the deviant target stimuli, typically by pressing a button or by mental counting.

Many studies were interested in P300 as potential state, trait and vulnerability markers in disorders such as schizophrenia, depression, and alcoholism. Schizophrenia is, by far, the most studied pathology in regards with ERP analysis. The P300 has been shown to be impaired in schizophrenia as schizophrenic patients display a less ample P300 than controls. The difference seems to persist whether the patient is in an acute phase or in remission, which suggests the P300 is a trait marker of schizophrenia (see Mathalon et al., 2000 for review). Regarding depression, results are more equivocal, some studies on depressive patients in acute phase suggest a reduced P300 amplitude is associated with a longer latency while other studies failed to replicate those results (Hansenne, 2006). Heterogeneity of the findings is probably due to the heterogeneity of the psychiatric population itself, since different subgroups of depressive patients display different kind of P300 alterations (the P300 seems to be influenced by suicidal risk, anxiety or the presence of psychotic symptoms; Hansenne, 2006). Despite those variations, the reduction of P300 amplitude is considered as a state marker of depression as its amplitude tends to increase during the treatment (e.g., Anderer et al., 2002). On the other hand, alcoholic patients exhibit a reduced P300 amplitude (e.g., Maurage et al., 2007) but this finding seems to be also true for children of alcoholic parents (e.g., Polich et al., 1994), which suggests this decrease in amplitude might play a role of vulnerability factor in alcoholism.

The P300 was first regarded as a potentially useful tool in diagnosis but happened to be mostly useful as an index of cognitive performances, as it provides physiological measures associated with attentional engagement and memory operations in task (Polich, 2004, 2007). Because the latency of an ERP component is thought to reflect the speed of processing and the amplitude is viewed as the amount of resources allocated to the task (Hansenne, 2006), the analysis of the P300 might be of great help in order to assess cognitive abilities of a patient. However, the clinical use of the P300 is very low, mostly due to its tremendous variability and to its lack of sensitivity (Hansenne, 2006; Mathalon et al., 2010). With this consideration, attempts were made to strengthen the oddball paradigm in order to generate a more sensitive P300. Campanella et al. (2010) suggested oddball paradigm might be lacking of sensitivity since it is administrated in a single sensory modality (visual or auditory). Indeed, in everyday life, sensory events are multimodal and integrated into a unitary perception thanks to higher level integrative processes. Hence, they created a bimodal oddball paradigm in which stimuli were presented simultaneously in an auditory and visual modality. This "bimodal" task proved to be more sensitive to subclinical groups, as subjects with anxiety and depressive tendencies exhibited lower P300 amplitudes compared to controls in the bimodal oddball task only. Those findings have been confirmed in emotional paradigms (Campanella et al., 2010) and neutral conditions (Campanella et al., 2012; Delle-Vigne et al., 2014). Moreover, the discriminative power of the P300 has also been observed on other (sub)clinical populations, as in subjects with alexithymia (Delle-Vigne et al., 2014). This suggests that P300 might still be an indicator of a difference in the neural process of subjects presenting subclinical tendencies but only when confronted with an adapted, more sensitive and more ecological task.

Overall, even if these data still have to be extended to clinical populations, the bimodal P300 oddball design disclosed up to now preliminary encouraging results, pointing to an increased sensitivity of the P3b to subclinical differences as compared to unimodal classical conditions. Therefore, two additional points seem to be important to be faced with: (i) the promotion of multi-site guidelines to record electrophysiological measures that may be compared and used across studies is primordial, as this could help to avoid functional misinterpretations of the data as well as to prevent the emergence of controversial results from different laboratories (Campanella and Colin, 2014); and (2) the P3a or novelty P3 is of high interest in psychiatry, as it has been shown to be more sensitive than the classical P3b to depression (e.g., Bruder et al., 2009), alcoholism (e.g., Hada et al., 2000) and psychosis (e.g., Atkinson et al., 2012). The best way to measure the P3a is with a three-stimulus type oddball task including frequent stimuli, deviant targets, and distractors (Polich and Criado, 2006). Distractors are referred to novel and

unexpected stimuli that the subjects have to ignore, occurring at the same frequency as deviant target stimulus. Those novel stimuli trigger a positive brain potential maximal at fronto-central areas occurring between 250 and 550 ms, the P3a, which is thought to be the marker of orientation of attention (Knight, 1996). In this way, including the P3a in the evaluation of psychiatric populations through the P300 appears as a priority in ERPs research in psychiatry. The main aim of the present paper is then triple: first, we tested the implementation of a third type of stimulus (distractors) in a very simple bimodal task usable in psychiatry in order to measure the P3a in addition of the P3b classically referred as P300; second, we investigated which electrodes appear to be the most well-suited to register the bimodal P3a and P3b components the most accurately; and finally, we also investigated which reference electrode appears as the most adapted to the recording of a bimodal P3a and P3b.

Indeed, to our knowledge, no paradigm ever attempted to measure a bimodal P3a, whose sensitivity could also benefit from a bimodal procedure in the image of bimodal P3b. Therefore, we created a visual × auditory bimodal oddball task with three types of stimulus: frequent, deviant target, and distractors. Young and healthy subjects underwent the procedure, allowing us to explore the implementation of the P3a in a bimodal paradigm. In the same way, addressing the challenge of selecting the best reference for the recording of the bimodal P3a and P3b is essential, as the activity on reference sites affects measurements at all active electrode sites (Yao et al., 2007). To the best of our knowledge, this question has never been addressed before in a bimodal task as no recording recommendations exist for this very new paradigm. In this view, we investigated the reference effect through an offline re-reference procedure. Amplitudes and latencies of the P3a and P3b were measured and compared through average, nose, and linked mastoids references.

MATERIALS AND METHODS

Participants

Forty young and healthy participants were recruited through a dedicated platform on a social network for this study. Most of them were students at our university. Subjects had to be 20–30 years old. Exclusion criteria, assessed during a short anamnesis, were as follow: previous or current neurological problem such as head trauma and epilepsy; previous or current psychiatric disorder including suspicion of an addictive disorder other than smoking; current medical treatment that could affect cognitive performances; and uncorrected visual or auditory deficiency. Group characteristics are reported in **Table 1**.

TABLE 1 | Demographic and clinical characteristics.

	Mean	Standard deviation
Age (years)	24.29	3.03
Education (years)	15.71	2.36
Alcohol consumption (drinks per week)	6.94	6.23
Tobacco consumption (cigarettes per day)	3.47	6.93
Depression (Beck score)	8.03	6.82
Anxiety (State) (STAI-A score)	45.29	8.30
Anxiety (Trait) (STAI-B score)	48.38	8.83
Impulsivity (UPPS score)	93.65	19.96

Oddball Task

The task consisted of a bimodal (visual and auditory) oddball paradigm. Participants were confronted with three types of stimuli: frequent standard stimulus, rare target (deviant stimulus), and rare non-target stimulus (distractor). Frequent stimulus consisted of a woman face combined with a woman voice pronouncing the French word "papier," deviant target consisted of a man face along with a man voice pronouncing the French word "papier" and non-target distractors consisted of a picture of an animal along with his call (six different animals) for one half of the sample. For the other half, frequent stimuli consisted of the man face and deviant target stimuli of the women face. Subjects were asked to click as quickly as possible on a button with their right hand for each deviant target stimulus and to ignore any other stimuli. They were not informed that distractors would be presented.

The task was presented in one block of approximately 10 min, consisting of 140 frequent stimuli (70%), 30 deviant target stimuli (15%), and 30 distractors (15%). Each picture was presented for 700 ms. A black screen was displayed between pictures for a random duration of 600–1200 ms (**Figure 1**).

Response times and percentages of correct answers were recorded.

Procedure

The local ethics committee at the Brugmann Hospital ("Comité d'Éthique Hospitalier OM 026") approved our study. Informed written consent was first obtained from each participant. They received an explanation of the nature and duration of the study and were informed of what was expected from them. They were told that they were free to participate or not, as well as to leave the study at any time without having to justify their decision.

The experiment started with the oddball task: participants sat in a darkened room on a chair approximately 1 m from a computer screen. Following the task, participants were asked to complete the following questionnaires: the State-Trait Anxiety Inventory (STAI-A and STAI-B; Spielberger and Gorsuch, 1983); the Beck Depression Inventory (BDI-II; Beck et al., 1987); and the Urgency Premeditation Perseverance and Sensation seeking impulsive behavior scale (UPPS; Whiteside and Lynam, 2003), as anxiety, depression and impulsivity are personality factors known to induce P300 modulations, even at a subclinical level (e.g., Rossignol et al., 2005, 2008; Fritzsche et al., 2011). Finally, a short anamnesis assessing alcohol and drugs consumption, neurological and psychiatric history, and education was administrated. They were paid 25 Euros for their full participation.

EEG Recording and Analysis

During the testing phase, EEG activity was recorded with 33 electrodes mounted on a Quik-Cap and placed in standard

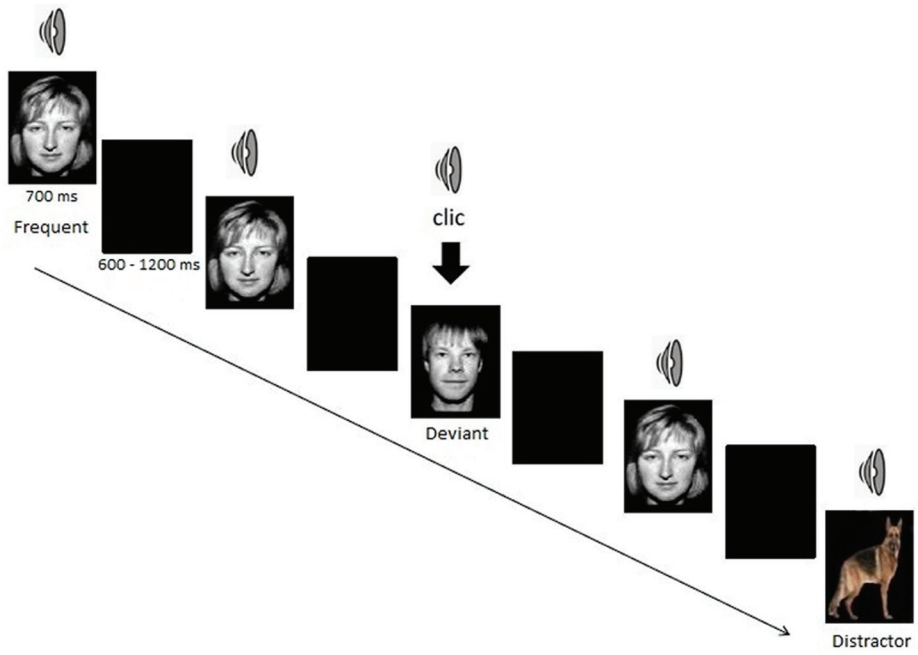

FIGURE 1 | The bimodal oddball task.

(based on the 10–20 system) and intermediate positions. Recordings were made with a common average, re-references were computed offline (nose and linked mastoids). The EEG was amplified with battery-operated ANT® amplifiers with a gain of 30,000 and a bandpass of 0.01–100 Hz. The impedance of all electrodes was maintained below 10 kΩ. EEG was recorded continuously at a sampling rate of 1024 Hz with ANT Eeprobe software. 99.9% of the participants' responses were correct (i.e., a finger tap given for deviant target stimuli). Only correct answers were considered for analysis of reaction times and EEG activity. The trials contaminated by eye movements or muscular artifacts were manually eliminated offline and discarded from further analyses. The number of included trials in subsequent statistical ERP analyses was of 24.32 (/30) ± 4.67 for the novelty P3 and of 25.85 (/30) ± 3.55 for the P3b. Epochs starting 200 ms before the onset of the stimulus and lasting for 800 ms were created (Bruder et al., 2009; Duncan et al., 2009). The data were filtered with a 30 Hz low-pass filter. To compute averages of P3a/P3b to distractors/target stimuli for each subject, two parameters were coded for each stimulus: (i) the type of stimulus (frequent; deviant target; distractor); and (ii) the type of response [correct responses: keypress for deviant target stimuli and no keypress for frequent stimuli and distractors; errors: no keypress for deviant targets (omissions) or keypress for frequent stimuli and distractors (commissions)]. A general time window was first determined globally for the identification of the components of interest (P3a and P3b) based on the literature. The measurement window was then tailored for each participant: for each subject, both P3a and P3b were investigated by gathering individual values of maximum peak amplitudes and peak latencies for each stimulus type in a 300–600 ms time range (Comerchero and Polich, 1998, 1999; Duncan et al., 2009). These data were obtained on the following electrodes: Fz, F3, F4, FC1, FC2, Cz, Pz, P3, P4, and Oz. Measurements were gathered for P3a and P3b with three references: common average (A), nose (Nz), and linked mastoids (Lke).

ERP Statistical Analysis

We analyzed ERP and behavioral data using analysis of covariance (ANCOVA) and analysis of variance (ANOVA). Our aims were to investigate the topography of P3a and P3b on a bimodal oddball task as well as the effect of the reference used on those two ERPs. Four levels (Fz, Cz, Pz, and Oz) within subjects ANCOVAs were first performed on amplitudes of P3a and P3b separately for each reference to evaluate the midline topography of those components with personality variables (STAI-A, STAI-B, UPPS, and BDI-II) as covariables. As those variables had no effect on the results (all $p > 0.05$), we removed them from the analysis and conducted our analysis as ANOVAs. Secondly, three levels (A, Nz, Lke) within subjects ANOVAs were computed for P3a and P3b to evaluate which reference displays the best results on peak amplitudes. Finally, 2 × 4 within subjects ANOVAs were performed in order to compare the topography of the P3a vs P3b on each reference. Latencies of P3a and P3b at the site of interest were compared in each reference condition. Greenhouse–Geisser correction was applied to all ANOVAs when necessary. Bonferroni *post hoc* *t*-tests were used to explore interactions effects. All analyses were conducted with SPSS 20.00, with the level of significance at 0.05.

RESULTS

Among the 40 participants, six had to be excluded of the analysis: two presented clinical signs of a psychiatric disorder (assessed during the short anamnesis) and four displayed a bad signal-to-noise ratio (three had a number of averaged trials inferior to 10 for one component at least and one subject presented a signal contaminated by alpha waves). At the individual level, novelty P3 and P3b were visible for each remaining participant.

Behavioral Results

The average performance on target detection was of 29.97 (/30) $\pm$ 0.17 with an average reaction time of 450 $\pm$ 45 ms. Subjects made on average 0.029 $\pm$ 0.17 omissions and 0.118 $\pm$ 0.33 commissions errors (pressing on a stimulus other than deviant target).

Topography of P3a and P3b

Four levels within subjects ANOVAs (Fz, Cz, Pz, and Oz) on amplitude showed a significant electrode effect for P3a and P3b with the average, nose, and linked mastoid references (all $p < 0.001$). Bonferroni *post hoc* *t*-tests specifically showed that P3b had its maximal amplitude at Pz for all three references used. Similarly, P3a also displayed its maximal amplitude at Pz for all three references. We compared the topography of P3a and P3b with a 2 $\times$ 4 levels within subjects ANOVA (P3a and P3b $\times$ Fz, Cz, Pz, and Oz). Results showed a significant principal effect of electrodes for nose and linked mastoids references ($p < 0.001$ for Nz and Lke references, $p = 0.077$ for A reference) and a significant interaction effect ($p < 0.001$). Bonferroni *post hoc* showed that P3a had a more parieto-central distribution while P3b had a more strict parietal distribution (see **Figure 2**). Results are displayed in **Table 2**.

Regarding the latencies of P3a and P3b, we calculated an average score for latencies of P3a and P3b on parietal electrodes (P3, Pz, and P4). Paired Student's *t*-tests were computed on those average scores, showing that latencies of P3a and P3b were significantly different for nose [$t(33) = -4.953$; $p < 0.001$] and linked mastoids [$t(33) = -5.741$; $p < 0.001$] but not for the common average reference [$t(33) = -0.927$; $p = 0.361$].

Reference Effect

A three levels within subjects ANOVA (Lke, Nz, A) on the mean amplitude score calculated on parietal electrodes (P3, Pz, and P4) showed a significant reference effect both on P3a and P3b (all $p < 0.001$). More precisely, Bonferroni *post hoc* *t*-tests showed that, for P3a and P3b, the nose reference displayed the highest amplitude (all $p \leq 0.001$), followed by the linked mastoids reference, itself displaying higher amplitudes than the average reference (all $p < 0.001$; see **Figure 2**).

DISCUSSION

The main goal of this study was triple: (i) to implement a third type of stimulus, the distractors, in the bimodal oddball task in order to generate the P3a component; (ii) to test which electrodes generate maximal P3a and P3b amplitudes; and (iii) to specifically test the effect of different references on bimodal P3a and P3b recording. This study has first enabled us to determine the topography of bimodal P3a and P3b. Results showed that both P3a and P3b are best measured at parietal sites. P3a and P3b displayed a different topography as P3b appeared as a parietal wave occurring around 400 ms while P3a was defined as a more precocious parieto-central wave, occurring around 370 ms. Regarding the reference effect, amplitudes were significantly higher with a nose reference than a linked mastoids or a common average reference. Moreover, the differential distribution of P3a vs P3b was better shown with nose and linked mastoids references.

Taken together, these data furnished important methodological considerations. First, we were able to create a rather short task (10 min) allowing us to easily measure in healthy subjects both bimodal P3a and P3b by adding distractors in a classical two-stimulus type oddball task. The parietal nature of the P3b component in this task is consistent with findings in unimodal paradigms, as P3b seems to occur as a consequence of attentional resource activations promoting memory operations in temporal–parietal areas (Huang et al., 2015). On the other hand, P3a is often described as a component with a more fronto-central topography than the parietal-maximum P3b (Polich, 2007) given that P3a is thought to be the reflection of frontal attention mechanisms (Bruder et al., 2009), as it appears to be related to neural changes in the anterior cingulate cortex (Huang et al., 2015). While our results showed a more central distribution compared with P3b, they still suggest a parietal-maximum topography for P3a as well. This finding raises different questions: is the recorded component really a P3a that has the particularity to have a more parietal topography in bimodal oddball paradigm or is the recorded brain activity for distractors more a reflection of context updating in working memory, and therefore should be considered as a P3b? First, we observed that the latencies of our P3a were significantly shorter than the latencies for P3b. Since the P3a is believed to precede P3b (Kayser and Tenke, 2006), this observation goes in the favor of a generated P3a. Second, fronto-central P3a is often recorded in unimodal paradigms for which it is observed that an auditory task generates higher amplitudes in Fz and Cz while a visual task generates higher amplitudes in Pz and Cz locations (Comerchero and Polich, 1998). In this way, we cannot exclude the idea that a P3a generated in a bimodal visual $\times$ auditory oddball task could induce higher amplitudes in parieto-central electrodes. Third, the topography observed in our results matches the one obtained by Polich and Comerchero (2003) in an "easy task." The authors manipulated the degree of perceptual distinction between the deviant target and the frequent stimulus, creating an "easy condition" and a "hard condition" (with the target physically similar to the frequent stimulus). In regard with the P3a, in the easy condition, the distractors elicited a parietal maximal P300, with a shorter latency and smaller amplitude than the P3b generated by the deviant targets while the P3a generated in the hard condition was larger, more central, and had a shorter latency. This suggests that the processing of distractors is affected by the discrimination task difficulty. As our task was built to be of

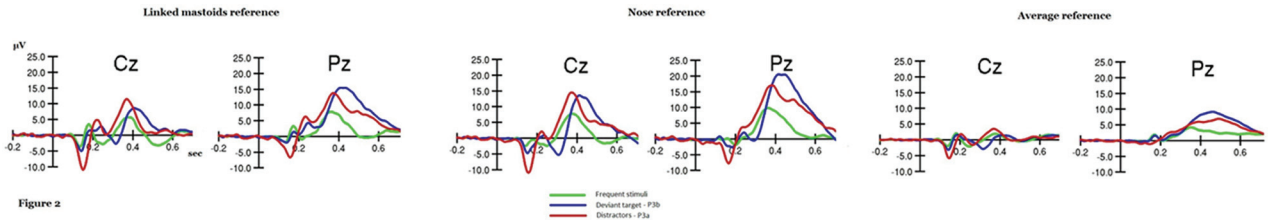

FIGURE 2 | Original P3a, P3b, and frequent stimuli waves at Cz and Pz sites, for linked mastoids, nose, and average references.

TABLE 2 | Average amplitude (in microvolts) on Fz, Cz, Pz, and Oz electrodes for P3a and P3b, regarding nose (Nz), linked mastoids (Lke), and average references.

		Fz		Cz		Pz		Oz	
		Mean	**Standard deviation**	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**
Nz	P3a	11.55	6.63	15.69*	7.10	18.22***	6.86	12.28	7.64
	P3b	9.83	6.12	16.52	8.22	23.10 ***	8.39	15.99	7.59
Lke	P3a	8.32	7.66	12.48**	7.25	14.96***	6.05	8.63	5.49
	P3b	5.95	8.29	11.99	9.01	18.18***	7.92	10.73	4.63
Average	P3a	0.36	4.02	3.86	3.45	5.87**	3.02	2.15	5.64
	P3b	−1.91	4.78	3.02	4.64	8.83***	3.80	4.33	5.11

****Different from all other electrodes at the level of $p < 0.001$. **Different from all other electrodes at the level of $p < 0.01$. *Different from all other electrodes at the level of $p < 0.05$.*

simple use with psychiatric patients, the discrimination difficulty might be too low for control subjects to generate a fronto-central maximal P3a.

Second, analyses of the reference effect on P3a/P3b amplitudes favor the use of a nose reference in bimodal oddball paradigm. However, the literature emphasizes on the use of an average reference in unimodal paradigm (Duncan et al., 2009). The use of the average reference is of great interest in the search of a "closer-to-neutral" reference. Indeed, given the very nature of EEG recording, based on a potential difference, this technique is in need of a point of reference whose activity will affect measurements at all active reference electrode sites (Yao et al., 2007, 2005). In this way, an ideal reference electrode should deliver an activity constant over time and independent of the activity recorded at active electrodes (Bertrand et al., 1985). The average reference has therefore been considered as a suitable candidate, based on theoretical arguments suggesting that the integral of the potential distribution over a sphere including current dipoles is null (Bertrand et al., 1985). However, the use of the average reference in our paradigm had the main effect to lower amplitudes and to lessen the topographic differences between P3a and P3b. As a broadly distributed ERP component, the P300 dominates the activity that is "subtracted out" by the referencing procedure. In this way, a common average could decrease its amplitude. Although the use of a nose reference seems less theoretically justified and more arbitrary, we should keep in mind that an inactive or silent recording site does not exist anywhere on the body and, therefore, any choice of reference is inevitably arbitrary (Kayser and Tenke, 2015a,b). With this consideration, we believe that the reference choice can be driven by the will to use a conventional standard which allows easy comparisons and emphasize some features of brain activity (Dien, 1998). This led, for instance, to the choice of a nose reference in the recording of the MMN, as it specifically allows the discrimination between the MMN and the N2b (Näätänen et al., 2007). Since the use of a common average reference seems to obscure some patterns of brain activity in the case of a visual × auditory cross-modal oddball paradigm, we believe the use of a nose reference would be the most appropriate.

Overall, main data of the present study are (1) P3a is maximally recorded at centro-parietal sites, with a latency around 375 ms, and a mean amplitude value of 17 μV with nose reference; while (2) P3b displays a maximal amplitude at parietal sites with a latency around 409 ms and a mean amplitude value of 22 μV with the nose reference. These methodological considerations are highly relevant to furnish a simple task that can be easily adapted in every labs to favor multi-site recordings (comparable data tagging exactly similar cognitive functions). Obviously, our study has also some limitations: we have a rather small number of participants, methodological considerations should therefore be very carefully taken on this sample as we were not able to control the influence of gender, age, education level and mostly personality parameters since our sample lacked of variability on those aspects (we tested only young and healthy subjects, most of them being students in our university). Our data are therefore preliminary and should be confirmed on bigger sample, controlling for the influence of the cited parameters. Another limitation is that we did not counterbalance the physical characteristics of our stimuli across all categories. Indeed, if male and female faces were counterbalanced between frequent stimuli and deviant targets, animal images and shouts were only used as distractors. This was done following previous research about the

novelty P3 (Friedman et al., 2001; Polich and Comerchero, 2003; Bruder et al., 2009) in order to generate a novelty P3 of high amplitude with a very simple task, which can be critical when working with psychiatric patients. As the amplitude of the novelty P3 is directly correlated to the degree of novelty of a stimulus and to the physical characteristics of the stimuli (Gaeta et al., 2003; Polich and Comerchero, 2003), we used six different distractors stemming from environmental sounds to restrain the impact of repetition on the amplitude of the novelty P3 and to increase the probability of having a novelty P3 of high amplitude (Cycowicz and Friedman, 2004). However, future research regarding the general use of a bimodal three-stimulus oddball paradigm should control for the impact of the physical characteristics of the stimuli on the generated P3a and P3b. Finally, another limitation is that our subjects gave a motor response only for deviant target stimuli. While this is what is usually done in multiple studies with control subjects and psychiatric patients (Polich and Comerchero, 2003; Bruder et al., 2009; Campanella et al., 2010), this might be an issue as motor response has been shown to have an interference effect on recorded ERP parameters (Starr et al., 1997; Kotchoubey, 2014). A solution might be to ask to subjects to mentally count the targets instead of giving a motor response (Verleger, 1991). However, as the goal is for this task to be implementable in psychiatry, this solution could be too challenging for patients.

CONCLUSION

Finding sensitive tools is one of the main current challenges in experimental psychopathology. In this way, advances were specifically made in the field of ERPs. For instance, the addition of the P3a to the classical P3b analysis in depression allowed a better discrimination between depressive and healthy controls (Bruder et al., 2009). Similarly, it was previously thought that early-phase psychotic patients did not display a constant diminution of MMN amplitude (Salisbury, 2012) but recent studies showed a higher sensitivity of the MMN when recorded during an adapted, more sensitive paradigm (Rudolph et al., 2015). Those studies all meet the same purpose of finding biological markers of psychiatric diseases as such markers might help to (1) index the recovery of a patient during the follow-up and (2) highlight cognitive dysfunctions in order to orient neurocognitive and/or neuromodulative remediations. This paper constitutes a first step toward the use of adapted paradigms in psychiatry, by offering a first glance of multi-site guidelines on bimodal P3a and P3b.

AUTHOR CONTRIBUTIONS

ES contributed to study design, data recording, analysis and interpretations, statistical analysis, and paper writing. HK contributed to the design and critically reviewed the paper. CK and PV critically reviewed the paper. SC was the principal designer of the study and contributed to its implementation, supervised data recording, interpretation, and paper writing.

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