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Impact of electroconvulsive therapy on magnetoencephalographic correlates of dysfunctional emotional processing in major depression

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Abstract
In major depressive disorder (MDD), electrophysiological and imaging studies provide evidence for a reduced neural activity in parietal and dorsolateral prefrontal regions. In the present study, neural correlates and temporal dynamics of visual affective perception have been investigated in patients with unipolar depression in a pre/post treatment design using magnetoencephalography (MEG). Nineteen in-patients and 19 balanced healthy controls passed MEG measurement while passively viewing pleasant, unpleasant and neutral pictures. After a 4-week treatment with electroconvulsive therapy or 4-week waiting period without intervention respectively, 16 of these patients and their 16 corresponding controls participated in a second MEG measurement. Before treatment neural source estimations of magnetic fields evoked by the emotional scenes revealed a general bilateral parietal hypoactivation in depressed patients compared to controls predominately at early and mid-latency time intervals. Successful ECT treatment, as reflected by a decline in clinical scores (Hamilton Depression Scale; HAMD) led to a normalization of this distinct parietal hypoactivation. Effective

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treatment was also accompanied by relatively increased neural activation at right temporo-parietal regions. The present study indicates dysfunctional parietal information processing and attention processes towards emotional stimuli in MDD patients which can be returned to normal by ECT treatment. Since convergent neural hypoactivations and treatment effects have recently been shown in MDD patients before and after pharmacological therapy, this electrophysiological correlate might serve as a biomarker for objective treatment evaluation and thereby potentially advance treatment options and support the prediction of individual treatment responses.

1. Introduction

There is ample evidence that the pathogenesis of affective disorders is related to dysfunctions of key neuroanatomical network structures responsible for emotion processing and regulation. Based on the idea of a dysbalanced interaction between prefrontal cortical areas and limbic structures in affective disorders, several studies have suggested an insufficient top-down control between the prefrontal cortex and the amygdala in major depression as well as in anxiety disorders. According to these studies, both a decreased prefrontal activity, resulting in reduced top-down regulation of the amygdala, and a hyperreactivity of the amygdala to negative information have been observed (Almeida et al., 2009; Davis and Whalen, 2001; Quirk and Beer, 2006) for a review see (Domschke and Dannlowski, 2010).

Moreover, a distorted neurobiological control has also been related to a biased emotion processing in major depression. Particularly, increased attention to negative and decreased attention to positive stimuli as well as an inability to inhibit inadequate attentional engagement has been attributed to a dysfunctional interplay between the prefrontal cortex, the anterior cingulate cortex and the superior parietal cortex (Disner et al., 2011; Heller et al., 2014). As there is evidence that both in major depression and anxiety disorders patients suffer from this emotional bias, findings on alterations in attention and memory when viewing negative versus neutral emotional stimuli are remarkable (Elliott et al., 2002). Furthermore, investigating neural activation patterns in patients with major depressive disorder (MDD), a decreased neural activity of the parietal lobe has been consistently shown in tasks using aversive emotional faces (Beevers et al., 2011; Surguladze et al., 2015).

However, only few studies have so far investigated the effects of successful antidepressant intervention on these neurobiological alterations in patients suffering from major depression. Most recently, antidepressant pharmacotherapy with mirtazapine - a noradrenergic and specific serotonergic antidepressant (NaSSA) - was suggested to normalize magnetoencephalographic (MEG) correlates of a decreased cortical activation at right parietal and right temporo-parietal regions in patients suffering from major depressive disorder (MDD; Domschke et al., 2015). Prior to treatment, MDD patients revealed a valence independent general hypoactivation at bilateral parietal, bilateral dorsolateral prefrontal and right temporo-parietal regions, as well as abnormal valence-specific reactions at right parietal and bilateral dorsolateral prefrontal (dlPFC) regions. Successful antidepressant pharmacotherapy led to a normalization of the valence independent overall hypoactivations within specifically parietal, temporo-parietal but also dorsolateral PFC regions (Domschke et al., 2015), although the abnormal valence-specific biases within the fronto-parietal network remained unaffected. Therefore, a specific effect of antidepressant medication on cortico-limbic interaction patterns and top-down emotional control was hypothesized and might be attributed to therapeutic effects of antidepressant pharmacotherapy.

However, not all patients respond to antidepressant pharmacotherapy: up to one third of patients do not respond to regular treatment and 50% of patients who recover suffer a relapse within 6 – 12 months (Holtzheimer and Mayberg, 2012; Warden et al., 2007). In these patients, electroconvulsive therapy (ECT) has been suggested as the treatment of choice, as ECT is considered the most powerful antidepressant treatment today showing response rates of up to 80% (Abbott et al., 2014; Sienaert, 2011). Still, the specific mode of action of ECT on a neurobiological level is only sparsely understood. There are assumptions that ECT might reverse dysfunctions of the HPA axis (Bolwig, 2011), and ECT has also been shown to induce changes in cerebral metabolism, blood flow, neurotransmitter activity, and brain functional connectivity (Depping et al., 2014; Zhuo and Yu, 2014). Besides, there is evidence that antidepressant treatment might stimulate hippocampal neurogenesis (Malberg et al., 2000) and recently, ECT intervention has been shown to increase hippocampus volume (Nordanskog et al., 2010, 2014; Redlich et al., in press).

In general, little is known about the reversibility of neural alterations in major depressive disorder (MDD). As described above, we have been able to reveal that a four-week antidepressant treatment led to a normalization of an overall neocortical hypoactivation during emotion processing in MDD patients (Domschke et al., 2015). Thus in the current study, effects of antidepressant treatment with ECT on magnetoencephalographic correlates were investigated in order to further elucidate the possible mechanism of action of ECT and to identify potential common pathways of antidepressant action in both ECT and antidepressant pharmacotherapy.

In this study, the identical emotion processing paradigm from our previous study (Domschke et al., 2015) was applied in MDD patients at baseline and after antidepressant treatment with ECT. We hypothesized, firstly, to replicate findings of an overall hypoactivation emerging from parietal and parietotemporal regions in patients with MDD,