OXFORD

RESEARCH ARTICLE

Magnetoencephalographic Correlates of Emotional Processing in Major Depression Before and After Pharmacological Treatment

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Abstract

Background: In major depressive disorder (MDD), electrophysiological and imaging studies suggest reduced neural activity
in the parietal and dorsolateral prefrontal cortex regions. In the present study, neural correlates of emotional processing in
MDD were analyzed for the first time in a pre-/post-treatment design by means of magnetoencephalography (MEG), allowing
for detecting temporal dynamics of brain activation.
Methods: Twenty-five medication-free Caucasian in-patients with MDD and 25 matched controls underwent a baseline MEG
session with passive viewing of pleasant, unpleasant, and neutral pictures. Fifteen patients were followed-up with a second
MEG session after 4 weeks of antidepressant monopharmacotherapy with mirtazapine. The corresponding controls received
no intervention between the measurements. The clinical course of depression was assessed using the Hamilton Depression
scale.
Results: Prior to treatment, an overall neocortical hypoactivation during emotional processing, particularly at the parietal
regions and areas at the right temporoparietal junction, as well as abnormal valence-specific reactions at the right parietal
and bilateral dorsolateral prefrontal cortex (dlPFC) regions were observed in patients compared to controls. These effects
occurred <150 ms, suggesting dysfunctional processing of emotional stimuli at a preconscious level. Successful antidepressant
treatment resulted in a normalization of the hypoactivation at the right parietal and right temporoparietal regions. Accordingly,
both dlPFC regions revealed an increase of activity after therapy.

Conclusions: The present study provides neurophysiological evidence for dysfunctional emotional processing in a fronto-parieto-temporal network, possibly contributing to the pathogenesis of MDD. These activation patterns might have the potential to serve as biomarkers of treatment success.

Keywords: Dorsolateral prefrontal cortex, IAPS, MDD, EEG, MEG, parietal hypoactivation, temporoparietal junction

Introduction

In major depressive disorder (MDD), attention and memory biases in favor of negative as compared to positive or neutral information have been observed, which is reversible by antidepressant treatment (Everaert et al., 2012; Harmer and Cowen, 2013). Although such "negative bias effects" dominate the depression literature, researchers also found "positive attenuation effects" in depression, with either reduced sensitivity to positive relative to other stimuli or an absence of a "positivity bias" (Everaert et al., 2012).

As a possible mechanism of a negative bias in depression, the frontal/prefrontal cortex has been suggested to provide insufficient top-down inhibitory control on limbic systems. Indeed, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies reveal a generally decreased activation in the dorsolateral and dorsomedial prefrontal cortex (PFC) in combination with increased activation of the ventrolateral and orbitofrontal cortical areas in depression (Davidson et al., 2000).

Event-related-potential (ERP) studies consistently showed P300, N400, and slow-wave amplitudes to be elevated in response to negative and reduced in response to positive stimuli in depressive patients and subjects at risk of depression during various behavioral decision tasks (e.g. Shestyuk et al., 2005; Krompinger and Simons, 2009; Bistricky et al., 2014). These findings support both enhanced attention towards negative as well as reduced attention towards positive emotional stimuli in depression.

ERP studies on the processing of emotional scenes without additional task sets and without patients making judgments about emotional stimuli are sparse. In one study (Kayser et al., 2000), depressive patients revealed a reduced emotional reaction towards negative pictures at right parietal sensors, peaking around 460 ms. Right parietal sensors also showed a reduced reaction of MDD patients, specifically towards faces with positive expression, though at an earlier N200 component (Deldin et al., 2000). A reduced reaction towards emotionally arousing pictures at right temporo-parietal regions has also been shown by a magnetoencephalography (MEG) study (Moratti et al., 2008). The time course of this effect, however, remained unknown due to the specific steady-state stimulation protocol used in this study.

Electrophysiological resting-state activity in depression consistently showed abnormal regional hemispheric asymmetries of alpha activity, with a relative increase of alpha-band activity in the left versus right frontal electrodes and a relative increase of alpha power in the right verus left electrodes at posterior sites (Henriques and Davidson, 1991; Bruder et al., 1997; Thibodeau et al., 2006; Stewart et al., 2011). Since the posterior alpha is typically inversely correlated with cortical activity (Feige et al., 2005), an enhanced right parietal alpha is interpreted as indicative of a neural hypoactivation, especially at right parietal regions. An enhanced alpha asymmetry (right > left) has also been found in high-risk children and grandchildren of MDD patients (Bruder et al., 2007), supporting the hypothesis of right parietal hypoactivity as an endophenotypic marker of major depression.

Posterior, and especially right hemispheric, alpha has also been suggested as a predictor of antidepressant responses, since depressive patients with low posterior alpha seem to respond less to serotonin reuptake inhibitor treatment (Tenke et al., 2011).

Reduced parietal, and especially right parietal, activity in depression, as revealed by electrophysiological event-related and resting state alpha studies, is corroborated by fMRI findings showing decreased parietal metabolism in depression and sadness (Mayberg, 1997; Liotti et al., 2000).

In the present study, we aimed to investigate baseline as well as post-treatment neural correlates of passive emotional picture processing without additional tasks in patients with MDD by means of whole-head MEG. The measure of event-related magnetic fields, in combination with inverse source modeling, allows for detecting even rapid, transient, and preconscious cortical activations, which may not necessarily result in measurable hemodynamic changes and may become object to hemodynamic masking due to compensatory attempts of attenuating the expression or experience of aversive emotions (Drevets, 2007). Our predictions were that medication-free patients with depression as compared to healthy controls would show an overall decreased sensitivity towards arousing pictures, in correlation with a particularly right-sided temporo-parietal hypoactivation and a dysfunctional affective modulation at prefrontal cortex regions. These magnetoencephalographic correlates of disturbed affective processing were expected to normalize along with a clinical response to a standardized antidepressant pharmacological therapy.

Patients and Methods

Subjects

For the present case-control study, 25 right-handed Caucasian in-patients (16 females) with MDD as ascertained by a standardized clinical interview (SCID-I) were recruited at the local Department of Psychiatry (Table 1). Patients with bipolar or psychotic disorders, comorbid substance abuse or anxiety disorders, mental retardation, neurological or neurodegenerative disorders, or other clinically unstable medical illnesses impairing psychiatric evaluation, as well as pregnant patients, were not included in this study. All patients were medication-free at the time of inclusion, either being drug naive at the time of admission or having being tapered off antidepressant medication according to the respective half-life, which was ascertained by drug plasma levels. Patients having received neuroleptic or any other psychotropic medication during a 6-month period before the study were excluded. Benzodiazepines were not used apart from lorazepam (max. 3 mg/d) only until 24 h before the MEG session.

For the follow-up study, a subgroup of 15 patients (Table 1) subsequently underwent a 4-week standardized antidepressant monopharmacotherapy with mirtazapine (45 mg/d) in a naturalistic clinical in-patient setting. As co-medication, only

Table 1. Demographic and Clinical Data of Patients with MDD and Healthy Controls

Pre-treatment sample	Patients	Controls	p-value
Males/females [a]	9/16	9/16	1.000
Age (mean ± SD) [b]	44.3 ± 14.7	44.0 ± 14.7	0.939
Age of onset (mean ± SD)	33.7 ± 14.9	-	-
CGI score (mean ± SD) [c]	4.8 ± 0.6	-	-
GAF score (mean ± SD) [c]	48.1 ± 6.8	-	-
HAMD score (mean ± SD) [b, c]	22.2 ± 5.3	1.1 ± 1.6	<0.001
HAMA score (mean ± SD) [b, c]	26.5 ± 9.1	3.0 ± 3.0	<0.001
PANAS positive (mean ± SD) [b, c]	19.3 ± 5.1	31.6 ± 5.4	<0.001
PANAS negative (mean ± SD) [b, c]	26.8 ± 7.4	11.2 ± 1.8	<0.001

Pre-post-treatment sample	Patients		
Males/females	5/10		
Age (mean ± SD)	45.3 ± 15.8		
CGI score (mean ± SD) [c]	4.8 ± 0.4		
GAF score (mean ± SD) [c]	48.1 ± 5.7		
HAMD score pre (mean ± SD) [c]	22.3 ± 6.0		
HAMD score post (mean ± SD) [d, e]	7.9 ± 8.4		<0.001

[a] Chi-square test; [b] two-sample t-test; [c] scores taken at admission within 2 days before time of inclusion; [d] scores taken after 4 weeks of treatment with mirtazapine; [e] one-sample t-test (pre vs. post therapy).
CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; HAMA, Hamilton anxiety scale; HAMD, Hamilton depression scale; MDD, major depressive disorder; PANAS, Positive and Negative Affect Schedule; SD, standard deviation.

lorazepam was allowed (max. 3 mg/d) up until 24 h before the second MEG session. The clinical course of depression was assessed on a weekly basis by experienced psychiatrists using the Hamilton Depression scale (HAMD) and showed significant treatment response (Table 1). Ten patients were not included in the follow-up study, because they either required a change in medication according to clinical judgment (n = 4) or refused participation in a second MEG session (n = 6). These patients (age, 42.8 ± 13.6; Clinical Global Impression, 4.7 ± 0.8; Global Assessment of Functioning, 48.1 ± 8.5; HAMD, 22.1 ± 4.2) did not differ from the ones included in the follow-up study regarding age or clinical characteristics at admission (Table 1; all $p > 0.69$).

As a control group, 25 healthy participants matched for gender, age, years of education, and handedness were recruited. Inclusion criteria were no history of mental illness as ascertained by SCID-I interview.

All participants had normal or corrected-to-normal visual acuity. The study was approved by the local ethical committee and informed consent was obtained from each participant.

Design, Procedure, and Stimulus Material

All 25 patients and corresponding controls underwent a pretreatment baseline MEG session. A subgroup of 15 patients treated with a standardized antidepressant pharmacotherapy and corresponding 15 matched controls were followed up with 4 weeks later. MEG volume conductor modeling was based on anatomical T1-MRI images. For later spatial coregistration of anatomy and function, gadolinium landmarks (MRI) and landmark coils (MEG) were attached to the auditory canals and the nasion during the respective scanning.

Based on the normative ratings of emotional valence and arousal, 500 pictures from the International Affective Picture System (Lang et al., 2005) were divided evenly into five picture categories: high arousing positive (erotica, sports, etc.), low

arousing positive (family, landscapes, etc.), neutral (people, road-traffic, etc.), low arousing negative (illness, pollution, etc.), and high arousing negative (attack, mutilation, etc.). Statistical tests revealed that critical physical picture parameters did not differ across picture categories. In the MEG session, all pictures were randomly presented for 660 ms each as Rapid Serial Visual Presentation (RSVP) without perceivable interstimulus intervals (Junghöfer et al., 2001). Participants were asked to passively view the stream of stimuli while keeping their eyes focused on an overlaid fixation cross.

After RSVP, participants rated hedonic valence and emotional arousal of 36 representative pictures using a computerized version of the Self-Assessment-Manikin (SAM). Hamilton Anxiety Scale (HAMA), State-Trait Anxiety Inventory (STAI), and Positive Affect Negative Affect Schedule (PANAS) scores were taken immediately before and after the respective MEG sessions.

Apparatus and Data Analysis

Visual evoked magnetic fields were acquired using a 275 MEG whole-head sensor system (VSM Medtech Ltd.), sampled down offline to 300 Hz and filtered between 0.01 and 148 Hz. Data were aligned to the stimulus onset, with an averaging epoch ranging from 200 ms before to 600 ms after the stimulus onset and baseline-adjusted using a 150 ms pre-stimulus interval. Single trials were edited and artifacts were corrected following the method for statistical control of artifacts in high-density EEG/MEG data as proposed by Junghöfer and coworkers (2000). In this method, channels contaminated by artifacts are interpolated by weighted spherical splines and trials are removed when too many channels are contaminated. After artifact rejection and averaging, cortical sources of the event-related magnetic fields were estimated using the L2-Minimum-Norm-Estimates method (L2-MNE; Hämäläinen and Ilmoniemi, 1994). The L2-MNE is an inverse modeling technique applied to reconstruct the topography of the primary current underlying the magnetic field distribution. It allows the estimation of distributed neural network activity without *a priori* assumptions regarding the location and number of current sources. A spherical shell with a radius roughly corresponding to the individual grey matter depth was used as a source model. Topographies of source-direction-independent neural activities were calculated for each participant, condition, and time point. For visualization purposes, source reconstruction results were projected onto a quasi-realistic brain model.

Statistical Data Analysis

Regarding the hypothesis of parietal hypoactivation in depression, t-tests comparing picture-category-independent sustained activity of patients and controls were calculated for the time interval from 0 to 500 ms. Guarding against false positive correlations, nonparametric cluster level statistics were applied as suggested by Maris and Oostenveld (2007), with $p < 0.05$ on both sensor and cluster levels. As this analysis revealed widely distributed effects covering parietal but also right temporal areas, symmetric left and right hemispheric regions of interest were identified based on the dominant difference activations between patients and controls. A repeated-measures ANOVA with the factors of group and hemisphere were performed based on this time interval and—to allow an identification of the temporal onset of sustained hypoactivation—also on moving averaged time intervals of 20 ms length. Repeated-measures ANOVAs with the factors of group, affective category, hemisphere, and

gender were then calculated for the revealed time interval of sustained hypoactivation (120–500 ms).

Testing group–specific differential processing of positive or negative pictures independent of picture arousal, estimated neural activities evoked by low and high arousing positive pictures, as well as low and high arousing negative pictures were averaged for each subject. Subsequently, ANOVAs with the limited factors of valence (positive, negative), group, hemisphere, and gender were applied.

Linear correlations with the Hamilton Depression Scale scores were estimated for the overall cortical activity within the group of 25 patients, as well as for the positive minus negative valence difference activity. Again, cluster-level statistics with significance levels of $p < 0.05$ on both the sensor and cluster levels were applied. MEG data analysis was conducted with the Matlab-based EMEGS software (Peyk et al., 2011).

Results

Psychological Assessment

Patients and controls differed significantly with respect to their pre- and post-experiment STAI state as well as PANAS scores (all $p < 0.001$). However, there was no significant difference in STAI state or PANAS scores pre-/post-MEG session within the patient or control group (data not shown).

Behavior

SAM ratings of valence and arousal at baseline were analyzed using repeated-measures ANOVAs, including the factors of group and affective category. Affirming the stimulus selection, participants distinguished between stimulus categories, as indicated by differential valence ($F_{4,192} = 67.5$, $p < 0.001$) and arousal ratings ($F_{4,192} = 66.4$, $p < 0.001$). However, patients and controls did not differ in their valence or arousal ratings (Fs < 1).

MEG Data Baseline Activation Patterns

Parietal Hypoactivation
The t-test comparing the sustained (0–500 ms) event-related neural activity (Figure 1A, left) and the overall cortical difference activation (Figure 1A, right) between groups revealed a profound diminished neural activity over bilateral parietal areas in patients compared to controls. This was confirmed by a significant main effect of group ($F_{1,48} = 7.9$; $p < 0.01$) and a missing interaction with hemisphere in a group x hemisphere ANOVA. The moving average ANOVA (Figure 1B) revealed a first significant main effect of group within the time interval of 50–70 ms ($F_{1,48} = 4.3$; $p < 0.05$), but the following sustained hypoactivation did not get significant before 110–130 ms ($F_{1,48} = 4.5$; $p < 0.05$). The group x hemisphere x affective category x gender ANOVA covering the sustained hypoactivation (120–500 ms) revealed a significant main effect of hemisphere ($F_{1,46} = 4.6$; $p < 0.05$) with overall stronger right hemispheric activity and a significant main effect of group ($F_{1,46} = 5.7$; $p < 0.05$), but no interaction of both factors and no interactions with affective category or gender.

Differential Positive and Negative Picture Processing at Right Parietal Regions
In the 250–300 ms time interval of strongest group effects, a significant valence x group x hemisphere interaction occurred ($F_{1,46} = 11.5$; $p < 0.001$). Hemisphere-specific analyses revealed that preferences of patients and controls differed in the right parietal region only ($F_{1,46} = 7.2$; $p < 0.01$), with controls reacting
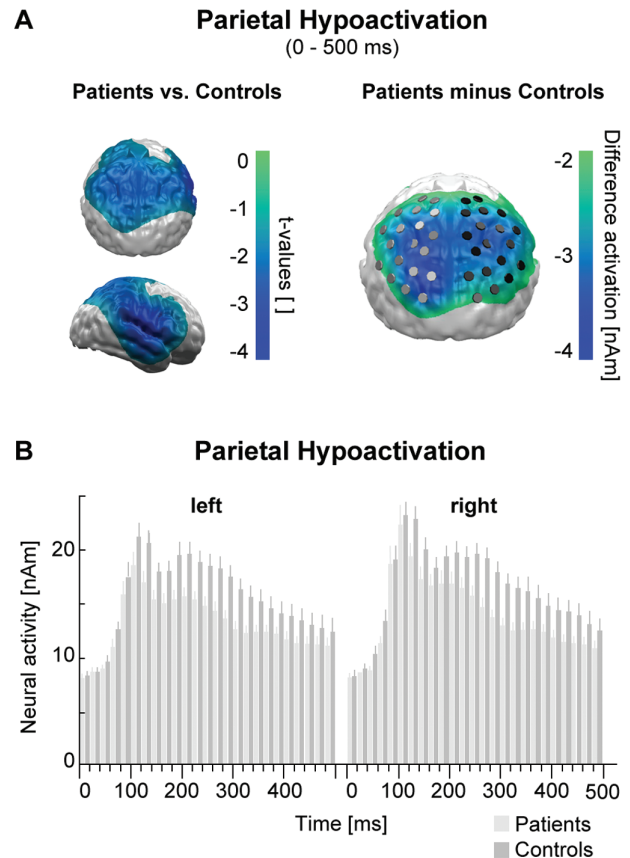

A **Parietal Hypoactivation**
(0 - 500 ms)

Patients vs. Controls   **Patients minus Controls**

B **Parietal Hypoactivation**

Figure 1. (A) Left: topography of t-tests comparing overall picture category independent activity of patients and controls. Areas with significant sustained (0–500 ms) hypoactivations in the patient group are color coded (masked at random permutation cluster level $p < 0.05$). Right: topography of overall difference activations between patients and controls. Markers indicate inverse test sources at right and left parietal regions of interest. (B) Time course of left and right parietal neural activation for patients and controls. A first significant hypoactivation appeared between 50 and 70 ms and was sustained after 120 ms.

stronger to positive images ($p < 0.07$), but patients stronger to negative pictures ($p < 0.05$). Although this right parietal group x valence interaction was strongest in the 250–300 ms interval, qualitatively identical and significant effects also appeared at 150–200 ms and 350–400 ms intervals, and thus in a 10 Hz (alpha) rhythm. None of the investigated parietal effects correlated with patients' depression or anxiety scores (data not shown).

Temporoparietal Junction Hypoactivation Correlating with Depression Severity
Linear correlations of mean cortical activity with the patients' HAMD score for the 0–500 ms time interval identified an area of significant negative correlations around the right temporoparietal junction (TPJ; Figure 2A, top), with the strongest effects between 200 and 350 ms (Figure 2A, bottom). The group x affective category x hemisphere x gender ANOVA for this interval and bihemispheric regions of interest again revealed an overall right hemispheric dominance (hemisphere, $F_{1,46} = 15.4$; $p < 0.001$) and confirmed an overall TPJ hypoactivation for patients compared to controls (group, $F_{1,46} = 11.0$; $p < 0.005$), predominately at the right hemisphere (group x hemisphere, $F_{1,46} = 4.1$; $p < 0.05$). The strongest negative correlations appeared for high arousing positive ($r = -0.55$; $p < 0.005$) and low arousing negative pictures ($r = -0.54$; $p < 0.005$). However, responses towards all picture categories showed at least trends for negative correlations,

A Hypoactivation at right TPJ

left   right

0 - 500 ms

200 - 350 ms

Correlation [r-values]
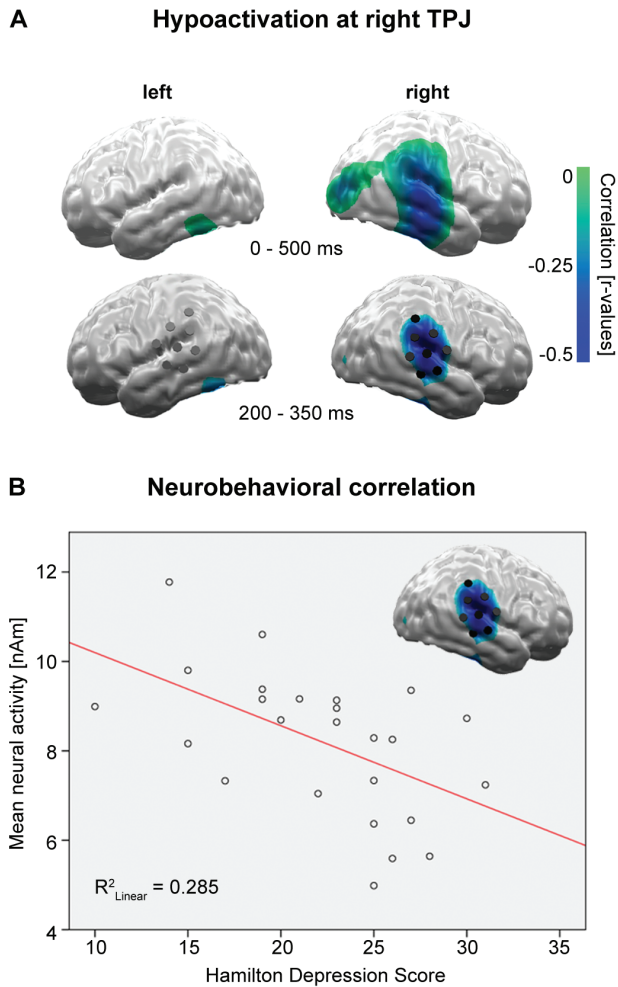
0
-0.25
-0.5

B Neurobehavioral correlation

Figure 2. (A) Top: linear correlations of neural activity with depression severity (Hamilton depression scale) identified an area of significant negative correlation at the right occipito-temporo-parietal regions. Bottom: the strongest linear correlations were found in a 200–350 ms time interval at the right temporo-parietal junction (TPJ; $p < 0.05$ at cluster level). (B) Linear correlation of Hamilton depression scale score and right TPJ activity.

explaining the overall strong correlation of HAMD and right TPJ activity ($r = -0.53$; $p < 0.006$; Figure 2B). Right TPJ activity did not correlate with anxiety (HAMA; $r = 0.04$).

Differential Appetitive and Aversive Picture Processing at dlPFC Correlating with Depression Severity

Linear correlations of differential valence reactions (positive minus negative) with the patients' HAMD score for the 0–500 ms time interval identified an area of significant positive correlations at the right dorsolateral prefrontal cortex (dlPFC; Figure 3A, left), which showed the strongest effects between 200 and 400 ms. Within this limited interval, a corresponding left hemispheric dlPFC region also revealed significant correlations (Figure 3A, right).

Inspection of the correlation coefficients identified one outlying patient, and extraction of this outlier increased the correlation from $r = 0.35$ ($p < 0.05$) to $r = 0.57$ ($p < 0.005$; Figure 3B).

A parametric linear regression analysis of HAMD scores and right dlPFC activity revealed both negative ($T_{23} = -3.2$; $p < 0.005$) and positive ($T_{23} = +2.7$; $p < 0.05$) interrelations, indicating decreased neural activity to negative pictures and increased neural activity to positive pictures with rising depression severity, respectively (overall regression, $F_{2,23} = 5.7$, $p = 0.01$, R-Square = 0.35).
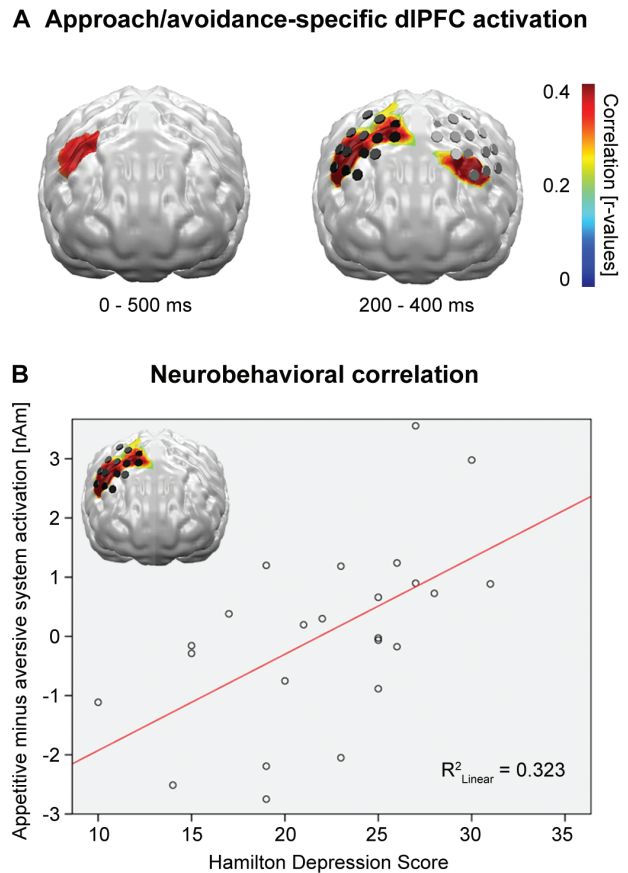
A Approach/avoidance-specific dlPFC activation

0 - 500 ms   200 - 400 ms

Correlation [r-values]

0.4
0.2
0

B Neurobehavioral correlation

Figure 3. (A) Left: linear correlations of neural activity evoked by positive minus activity evoked by negative pictures with depression severity (Hamilton depression scale) identified a dorsolateral PFC (dlPFC) area with decreasing activity for aversive and increasing activity for appetitive picture processing with rising severity. Right: strongest linear correlations were found in a time interval between 200 and 400 ms, now at the bilateral dlPFC regions ($p < 0.05$ at cluster level). (B) Linear correlation of Hamilton depression scale score and right dlPFC difference activity.

The corresponding left hemispheric dlPFC area revealed a converging significant regression, with qualitatively identical direction of effects ($F_{2,23} = 3.9$, $p < 0.05$, R-Square = 0.26; negative interrelation, $T_{23} = -2.6$; $p < 0.05$; positive interrelation, $T_{23} = +1.9$; $p < 0.07$).

Again, corresponding regression analyses with anxiety scores (HAMA) did not show any effects (all Fs < 1).

MEG Data Antidepressant Treatment Effects

Parietal Hypoactivation

The time course in Figure 4 illustrates a decreasing parietal activation in the control group from the first to second session, but a relative increase in patients after therapy, confirmed by a session x hemisphere x group interaction ($F_{1,26} = 4.6$; $p < 0.05$, 0–500 ms). Post hoc analyses revealed a significant interaction of session x group in the right ($F_{1,28} = 5.8$; $p < 0.05$), but not left hemispheric region (F < 1). T-tests affirmed the significant hypoactivation for patients compared to controls before therapy, even in this smaller group of patients and controls ($t_{28} = -2.6$; $p < 0.02$), while after therapy the activity of patients and controls did not differ any more (t < 0.05). Analysis for the limited time interval of strongest pre-therapy hypoactivation (200–300 ms) resulted in an even stronger session x group x hemisphere interaction [$F(1,26) = 5.9$; $p < 0.02$] and stronger but qualitatively identical post hoc effects. However, Figure 4 indicates residual differences
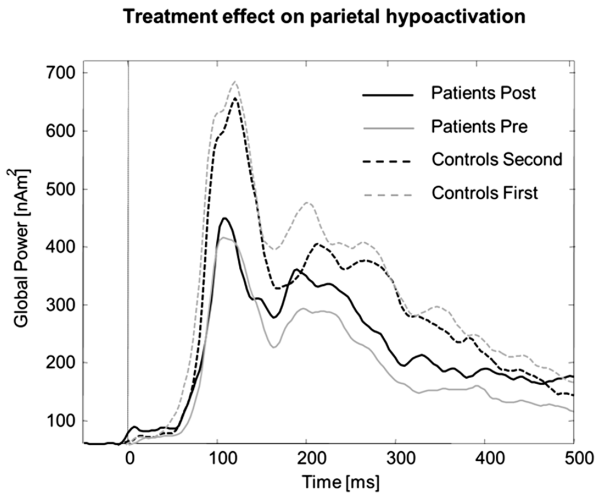
Treatment effect on parietal hypoactivation

Figure 4. Time course of parietal cortex activity for 15 major depressive disorder patients who participated in both the pre- and post-therapy magnetoencephalography (MEG) sessions, and their matched healthy controls in their first and second MEG sessions. While parietal activation, most probably due to habituation and reduced vigilance, decreased in the control group, patients showed increased parietal activity after therapy in direction normalization.

in the MEG waveforms between patients after treatment and controls in the second session, particularly in an early time interval before 150 ms after stimulus onset.

Differential Appetitive and Aversive Picture Processing at Right Parietal Regions

The system x group x hemisphere interaction in the 250–300 ms time interval did not change after therapy (F < 1).

Temporoparietal Junction Hypoactivation

Convergent to the parietal areas, a significant session x group x hemisphere interaction was discerned ($F_{1,26}$ = 5.9; $p < 0.02$) for the above defined bilateral TPJ areas (200–350 ms). Again, the right ($F_{1,28}$ = 6.0; $p < 0.02$) but not the left (F < 1) TPJ area revealed a significant session x group interaction. Post hoc t-tests showed a significantly reduced activation for patients before therapy in the right hemisphere (t_{28} = -3.3; $p < 0.005$), which disappeared after therapy (t < 1).

Differential Appetitive and Aversive Pictures Processing at dlPFC

The above defined bihemispheric dlPFC areas (200–400 ms) revealed a significant session x group ($F_{1,26}$ = 4.9; $p < 0.05$) and a significant session x group x hemisphere interaction ($F_{1,26}$ = 5.3; $p < 0.05$). Separate analyses revealed a trend effect for session in the left ($F_{1,28}$ = 4.0; $p < 0.06$) and a significant interaction of session x group in the right hemisphere ($F_{1,28}$ = 6.7; $p < 0.02$). While left dlPFC activity increased across sessions for both groups, right dlPFC activity increased for patients, but decreased for controls.

Discussion

To the best of our knowledge, this is the first study investigating electrophysiological correlates of emotional processing in depression in a pre-/post-treatment design, and the first study revealing alterations of the spatio-temporal dynamics of passive emotional picture processing in this patient group. The present pre-treatment data provide evidence for an overall neocortical hypoactivation during emotional visual processing in medication-free patients with depression, particularly at parietal

regions and areas at the right TPJ, as well as abnormal valence-specific reactions at the bilateral dlPFC and right parietal regions. Four weeks of antidepressant monopharmacotherapy with mirtazapine resulted in a normalization of the patients' hypoactivation at the right parietal and right temporoparietal regions. Accordingly, both dlPFC regions revealed an increase of activity in the patient group after therapy.

The parietal cortex, and particularly the inferior parietal lobe, is strongly connected to the limbic and frontal system (Morecraft et al., 1993) and has repeatedly been implied in the regulation of emotional arousal, emotional awareness, and attention to emotional contents (for review see Adolphs, 2002). Consistently, weaker activation of the inferior parietal lobes has been observed in patients with depression in response to fearful face presentation (Surguladze et al., 2010) and also during a task on cognitive control over emotional cues (Beevers et al., 2010), while in healthy probands suppression of fearful faces was associated with increased activity in inferior parietal cortices (Amting et al., 2010). Reciprocally, activity of the parietal cortex has been suggested as a potential substrate for successful pharmacological or non-pharmacological treatment of depression (e.g. Mayberg et al., 2000; Sperling et al., 2000; Schutter and van Honk, 2005). Both bilaterally and in the right hemisphere, dominant parietal hypoactivation of the presently event-related neural activity is also in good accordance with relative increased resting state alpha power in right versus left electrodes at posterior sites (e.g. Bruder et al., 1997; Stewart et al., 2011), which is interpreted as hypoactivation in depression, especially at the right parietal regions. However, while increased resting state alpha over right parietal sites does not change with therapy and appears as an endophenotypic marker of major depression (Tenke et al., 2011), the event-related parietal activation measured here increased in direction to normalization with successful treatment.

In emotion-theoretic research, the TPJ has been suggested as a key component of stimulus-driven attentional orienting (Corbetta et al., 2000; Corbetta and Shulman, 2002; Behrmann et al., 2004; Geng and Mangun, 2011). Stimulus-driven shifts of spatial attention in both visual fields (Shulman et al., 2010) and evaluation of the behavioral relevance of salient events outside the current focus of attention (Gruber et al., 2010) have been shown to evoke right-hemisphere dominant temporoparietal activity. The TPJ has thus been suggested to issue a control signal acting as a "circuit breaker" of ongoing cognitive activity when a behaviorally relevant stimulus is perceived (Corbetta and Shulman, 2002). The observed negative correlation of a significantly diminished right TPJ activation with increasing depression severity might thus reflect a dysfunctional capture of the attention mechanism by emotional stimuli in depression.

In addition to the valence independent parietal hypoactivation, activity at the right parietal regions was modulated by picture valence. While controls revealed a typical U-shape emotional arousal–driven reaction with preferential processing of both appetitive and aversive pictures in this region, patients showed a negativity bias, with stronger activations for negative compared to positive pictures. The observation of a left parietal and right temporoparietal general hypoactivation, as well as a valence-specific hypoactivation in the right parietal and temporoparietal regions, is in accordance with an MEG study by Moratti and coworkers (2008). However, while Moratti and colleagues revealed a flattened response towards emotionally arousing pictures in patients compared to controls at the right temporoparietal regions, patients in the study at hand even showed a negativity bias with a disproportionate reduction of appetitive

picture processing. The parietal hypoactivation already revealed the first phasic significance around 60 ms and showed sustained effects after 120 ms, and even the right parietal negativity bias started already around 150 ms. Although these early onsets clearly precede the assumed limit of conscious perception of around 300 ms (Dehaene and Changeux, 2011) and argue for disturbances of automatic, preconscious processing, issues of automaticity or consciousness have not been specifically tested in this study.

In addition to the right TPJ, activity at the dorsolateral PFC regions strongly correlated with depression severity. The dlPFC has been implied as the main source of top-down control signals to the visual cortex (Desimone and Duncan, 1995; Miller and Cohen, 2001) and serves the purpose of cognitive-emotional control (Ochsner and Gross, 2008). In the present study, bilateral dlPFC regions showed valence-specific effects, with positive correlations for positive but negative correlations for negative picture processing. The first is in line with findings of a positive correlation of bilateral dlPFC activation with global depression severity during appetitive picture processing (Keedwell et al., 2005), with right frontal (though ventral) regions overregulating positive affect in depression, decreasing along with the therapeutic effect of antidepressants (Light et al., 2011), as well as increasing left dlPFC activation with increasing positivity judgment of pleasant pictures in MDD (Grimm et al., 2008). Decreased dlPFC activity, as presently observed during negative picture processing, has been associated with attentional deficits and cognitive distortion in depression, diminished emotion regulation in depression, and is in line with decreased activity of the dlPFC in functional imaging studies of depression (see Drevets, 1998, and Mayberg, 2003, for comprehensive reviews). The presently observed increase of activity at bilateral dlPFC sites in the patient group after antidepressant treatment might thus reflect a recuperation of cognitive control (inhibition) over particularly negative emotion processing and therefore a normalization of the top-down control of the cortical on the limbic system as previously suggested by fMRI, PET, and MEG studies (e.g. Buchsbaum et al., 1997; Sperling et al., 2000; Kennedy et al., 2001; Mayberg, 2003). However, this interpretation is quite hypothetical and should in the future be tested by relating an increase of dlPFC activity with the efficacy of negative affect self-regulation.

The present finding of both right TPJ and frontal abnormality in depressed subjects is also in line with early evidence for altered activation in these brain regions in depressed patients and normalization with antidepressant pharmacological treatment, respectively. For instance, a classical study by Kronfol et al. (1978) observed poor performance on a variety of right hemispheric neuropsychological tests in depressed patients. Of note with respect to the present results, right hemispheric performance normalized after successful electroconvulsive treatment (Kronfol et al., 1978). In a study of hypnotic induction of depressed mood in healthy probands, Tucker et al. (1981) observed that the depressed mood involved activation (alpha suppression) over the right hemisphere specifically.

Limitations

Since all patients included in the pre-/post-therapy arm responded well to antidepressant pharmacotherapy, the design of the present study does not allow for differentiating brain activation patterns between responders and non-responders. Although the spherical shell conductivity model used here is a quite good approximation of the human head, especially at the

fronto-parietal regions of interest, and circumvents the problem of necessary regularization of quasi-radial sources in realistic MEG head modeling (Steinsträter et al., 2010), identification of disorder-related activities at regions with less good spherical fits might benefit from realistic head modeling. Due to the limited depth resolution of MEG and the specific emphasis of the L2-MNE on cortical sources, we here disregarded the potential involvement of subcortical structures.

Summary and Outlook

The present study provides magnetoencephalographic evidence for dysfunctional parietal, temporoparietal, and dorsolateral prefrontal cortex activity to underlie distorted early emotional processing, potentially contributing to the pathogenesis and retention of major depression. In addition to a general flattening of responses, especially in the right hemispheric parietal and temporoparietal regions, simultaneous negative bias and positive attenuation effects were observed in the right parietal and especially the bilateral dlPFC areas. Antidepressant pharmacotherapy normalized the general hypoactivations, but did not affect the valence-specific biases of emotional processing.

Acknowledgments

Conflict of Interest

The authors report no biomedical financial interests or potential conflicts of interest related to the present manuscript.

Dr Arolt declares that over the last 3 years he has received compensations for his contributions as member of the advisory boards and for presentations from the following companies: Astra-Zeneca, Eli Lily, Janssen-Organon, Lundbeck, Otsuka, Servier, and Trommsdorff. These cooperations have no relevance to the work that is covered in the manuscript.

Dr Kugel declares that over the last 3 years he has received consultation fees from MR:comp GmbH, Testing Services for MR Safety. This cooperation has no relevance to the work that is covered in the manuscript.

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