

Hypofunction of Right Temporoparietal Cortex During Emotional Arousal in Depression

Stephan Moratti, PhD; Gabriel Rubio, MD; Pablo Campo, PhD; Andreas Keil, PhD; Tomas Ortiz, MD, PhD

Context: Neuropsychological models of depression highlight temporoparietal hypofunction associated with low emotional arousal in major depressive disorder (MDD). These models were derived from indirect measures such as neuropsychological tests and electroencephalography alpha band power.

Objective: To determine if high-arousing stimuli directly modulated activity in attention and arousal-related sensory brain regions in patients with MDD.

Design: Between-group comparison (patients with MDD vs healthy control subjects) of neuromagnetic oscillatory activity driven by flickering emotional and neutral pictures (steady-state visual evoked fields [ssVEFs]).

Setting: Center of magnetoencephalography at a public university and public ambulatory mental health service.

Participants: Fifteen female low-anxious patients with MDD and 15 female controls. The groups were matched with respect to age and handedness.

Intervention: Magnetoencephalographic recordings and self-report ratings.

Main Outcome Measures: Modulation of current source strengths obtained by frequency domain minimum norm source localization of ssVEFs.

Results: Controls and patients with MDD showed enhanced current source strengths at ssVEF frequency in occipital and parietal cortex for high-arousing emotional pictures ($P < .05$ for permutation statistics). While this arousal modulation in controls was pronounced in the right temporoparietal cortex, weak arousal modulation characterized that brain region in patients with MDD ($F_{1,28} = 7.2$, $P < .05$ for interaction group by quadratic contrast).

Conclusions: Although emotional pictures engaged the dorsal visual stream to a greater extent than neutral pictures in both study groups, only controls showed strong arousal modulation in the right temporoparietal cortex. Because the right temporoparietal cortex is associated with the arousal dimension of emotion, subjects with depression may have difficulties in activating arousal-related brain areas, whereas basic stimulus processing related to activation of the dorsal visual stream is intact.

Arch Gen Psychiatry. 2008;65(5):532-541

Author Affiliations: Center of Magnetoencephalography Dr Perez Modrego, University Complutense of Madrid (Drs Moratti, Campo, and Ortiz), and Servicios de Salud Mental Retiro (Dr Rubio), Madrid, Spain; and Department of Psychology, University of Florida, Gainesville (Dr Keil).

PATIENTS WITH DEPRESSION ARE characterized by high levels of anhedonia, blunted affect,¹ and low emotional arousal.² Therefore, depression is regarded as an affective disorder implicating disturbed processing of emotional information (eg, reflected by abnormal startle modulation during emotional stimulation³ and by reduced facial expression⁴).

In emotion research, the concept of motivated attention⁵⁻⁷ emphasizes that affective stimuli activate action dispositions, which can be described in terms of hedonic valence (appetitive vs defensive) and emotional arousal (intensity).⁸ High-arousing emotional stimuli drive motive systems that guide attention processes (eg, reflected by increased orienting responses).^{5,8} These facilitatory pro-

cesses are believed to be mediated by subcortical circuits, including the amygdala⁸⁻¹¹ and the cortical attention networks,^{7,12-14} exerting top-down influences on sensory systems during processing of emotional stimuli.¹³

It has previously been shown that high-arousing affective pictures generate greater steady-state visual evoked potentials (ssVEPs) or steady-state visual evoked fields (ssVEFs) than neutral low-arousing pictures in occipital and right parietal cortical networks, indicating involvement of higher-order attentional mechanisms in the processing of emotional stimuli.^{12,15} Steady-state VEFs are the neuromagnetic counterpart of ssVEPs that can be recorded using electroencephalography (EEG) and are evoked by intensity-modulated stimuli at a certain frequency

Table. Demographic and Clinical Data of the Women in the Study Groups

Group	No.	Handedness	Age, y ^a	Mean (SD)			Treatment		
				Hamilton Depression Rating Scale Score ^b	Hamilton Anxiety Rating Scale Score ^c	Episode Duration, mo	Selective Serotonin Reuptake Inhibitor	Tricyclic Antidepressant	Serotonin and Noradrenaline Reuptake Inhibitor
Patients	15	14 Right, 1 left	40.3 (9.4)	24.7 (4.2)	10.5 (1.4)	16.8 (14.9)	11	1	3
Control subjects	15	14 Right, 1 left	36.4 (10.8)	0.93 (1.5)	2.8 (2.0)

Abbreviation: Ellipses, not applicable.

^a $t_{28} = 1.1$, $P = .30$; 2-sample t test.

^b $t_{28} = 20.8$, $P < .001$; 2-sample t test.

^c $t_{28} = 12.3$, $P < .001$; 2-sample t test.

(eg, a visual flicker) presented during several seconds. Steady-state VEFs are ongoing cortical oscillatory neuromagnetic responses having the same fundamental frequency as the driving stimulus.¹⁶ One of the main advantages of the ssVEF technique is that with few trials a high signal-to-noise ratio with respect to the magnetoencephalography (MEG) signal can be achieved.¹⁷

The neuropsychological model of emotion postulated by Heller and colleagues^{2,18,19} also considers emotion organized around valence and arousal. Approach behavior related to pleasant affect involves the left frontal cortex, and withdrawal behavior related to negative affect engages the right frontal cortex, reflecting the neural substrate of the valence dimension of emotion.²⁰ By contrast, the right temporoparietal cortex has been hypothesized to modulate the arousal dimension of emotional experience.^{18,19}

Regarding dysfunctional emotional processing, this model has emphasized the role of right temporoparietal cortex hypofunction in patients with depression.^{18,19,21-23} This hypothesis is based on perceptual^{21,24} and visuospatial²⁵⁻²⁹ asymmetry measures. After a stroke, patients with brain lesions in the right posterior cortex are more likely to develop depression³⁰ and to demonstrate reduced skin conductance responses in response to emotional stimuli.³¹

Cerebral activity in subjects with depression has also been investigated by assessing EEG alpha band power, a method that assumes an inverse relationship between alpha power and cortical activation.³²⁻³⁴ Electroencephalography alpha band asymmetry indicates less right posterior activation in subjects with depression vs control subjects,³⁵⁻³⁹ supporting the notion of right temporoparietal hemisphere dysfunction in depression.²

However, subjects having depression with vs without a coexistent anxiety disorder differ in their cortical activity asymmetry.⁴⁰ Nonanxious patients with depression show less cortical activity over right than left posterior electrode sites, whereas relative greater cortical activity over right than left frontal and posterior regions is observed in patients with depression and comorbid anxiety, indicating possible hyperreactivity to arousing stimuli.³⁹ Distinguishing between anxious apprehension and anxious arousal, Nitschke and colleagues⁴¹ reported that right hemisphere hyperactivation is associated with anxious arousal only.

However, the proposed models of the pathogenesis of depression are limited because alpha band EEG and perceptual measures do not allow direct localization of cerebral activity. Furthermore, alpha band asymmetries were observed during rest and were not stimulus bound.³⁵⁻³⁹ As already noted, stronger ssVEF responses have been demonstrated in cortical attention networks for high-arousing emotional stimuli. Because this network includes the right temporoparietal cortex⁴² and because patients with depression are hypothesized to be characterized by low emotional arousal related to a dysfunction in this brain area, we hypothesized that patients with low-anxiety unipolar depression would generally show deficient arousal modulations of ssVEFs in cortical attention systems and specifically in the right temporoparietal cortex.

Therefore, we presented flickering pleasant high-arousing, unpleasant high-arousing, and neutral low-arousing stimuli selected from the International Affective Picture System (IAPS)⁴³ to patients with depression and to healthy controls. By using the minimum norm estimation (MNE) technique^{44,45} to estimate the cortical sources of arousal-modulated ssVEF generators, we tested the hypothesis that controls demonstrate greater arousal modulation of occipitoparietal and specifically right temporoparietal cortex activity than patients having unipolar depression with low anxiety.

METHODS

SUBJECTS

Fifteen female patients at the Servicios de Salud Mental Retiro, Madrid, Spain, meeting the DSM-IV diagnosis of unipolar major depressive disorder (MDD) volunteered to participate in the study. Diagnoses were obtained by one of us (G.R.) as part of the treatment protocol using the Structured Clinical Interview for DSM-IV. Patient inclusion criteria were scores above 18 on the Hamilton Depression Rating Scale (HDRS) and below 15 on the Hamilton Anxiety Rating Scale (HARS) and the absence of any anxiety disorder or history of substance abuse. The patients' demographic and clinical data are summarized in the **Table**. Because the patients were receiving treatment, they were all were taking medication.

Fifteen female controls matched with respect to age and handedness participated voluntarily in the study. Selection criteria for controls included no family history of mental illness, no his-

tory of psychotherapy, an HDRS score less than 7 points, and an HARS score less than 15 points. The demographic data of the controls are summarized in the Table.

All participants had normal or corrected-to-normal visual acuity. All subjects gave written consent to participate in the study. Two subjective ratings of the emotional stimuli in each group were lost because of technical problems. The study had approval from the local ethics committee of the University Complutense of Madrid.

STIMULI

Sixty colored pictures from the IAPS⁴³ as in a previous study¹² were presented. Twenty pleasant high-arousing (erotic couples and happy families), 20 unpleasant high-arousing (mutilated bodies and attack scenes), and 20 neutral low-arousing pictures (household scenes and neutral persons) were chosen (the mean normative ratings are given in a study Moratti et al¹²) to provoke arousal modulations in posterior brain regions (details are available in other studies^{7,12,46-48}). Brightness, contrast, and color spectra of the stimuli were matched across picture categories.

The pictures were presented in a pseudorandom order, subtending a visual angle of 10° horizontally and vertically. A fixation cross was depicted throughout the experiment. In each trial, 1 picture was presented in a luminance-modulated mode of 10 Hz (cortical ssVEF responses are greatest using frequencies of 6-15 Hz⁴⁹) for 6 seconds, resulting in 60 on-and-off cycles (same picture shown and not shown) of 50 milliseconds each. The intertrial interval varied randomly from 8 to 12 seconds.

PROCEDURE

Patients were assessed using the HDRS and the HARS within 1 week (mean, 2.5 days [range, 2-7 days]) before the MEG recording. Controls were screened using the HDRS and the HARS immediately before MEG recordings. Handedness was determined by asking subjects and by their performing a writing probe. Thereafter, 4 electrodes for the electro-oculogram were attached for artifact control, 2 near the left and right outer canthus and 2 above and below the right eye. Two electrodes attached at the left and right lower forearm recorded the electrocardiogram, which was monitored during the recording. Head shapes were digitized, and nasion, left and right periauricular, and 2 additional points at the forehead were determined to calculate the relative head position within the MEG helmet for source analysis.

The experiment started with the pseudorandomized presentation of 60 flickering (10-Hz) stimuli. After this first block, subjects were given a brief pause of 1 minute. In a second block, the same 60 pictures were shown in a different order. After MEG recording, subjects rated the 60 affective pictures for emotional valence and arousal using the Self-Assessment Manikin self-report scale.⁵⁰ In subsequent clinical sessions with 1 of us (G.R.), patients did not report adverse psychological distress owing to having seen high-arousing pictures.

MEG RECORDING AND DATA PREPROCESSING

The MEG recordings were continuous (sample rate, 254.3 Hz; bandpass online filter, 0.1-50 Hz) using a 148-channel whole-head system (MAGNES 2500 WH; 4D Neuroimage, San Diego, California). The electro-oculogram and electrocardiogram acquisitions were performed using an amplifier (Synamps; NeuroScan, El Paso, Texas) with silver-silver chloride electrodes (same sample rate and online filters as already given).

The MEG data were digitally band-pass filtered between 1 Hz and 30 Hz (slopes, 6 dB/octave and 48 dB/octave, respec-

tively). Eye artifacts were corrected using commercially available software (BESA; MEGIS Software GmbH, Gräfelfing, Germany).⁵¹ The MEG data were visually inspected for movement artifacts, and trials containing maximum amplitudes above 3 pT were discarded from analysis (mean [SD] number of trials, 117.4 [4.15] for controls and 114.9 [7.4] for patients; $t_{28}=1.1$, $P=.27$).

Thereafter, ssVEFs were derived for each picture category by averaging each channel of MEG data across 6000 milliseconds after picture onset, subtracting a 200-millisecond baseline. Then, a time window of 1000-millisecond length was shifted in 100-millisecond steps (one 10-Hz cycle) across the 6000-millisecond poststimulus interval, and the MEG signal was averaged across each of the time windows to extract 10 cycles of the 10-Hz ssVEF response (as described previously by Keil et al⁵²). This procedure was applied to each condition separately for each subject. Finally, the 1000-millisecond averages were submitted to Fourier analysis, and the real and imaginary parts of the 10-Hz Fourier component were extracted for further analysis.

For each channel, subject, and condition, the amplitude spectrum of the corresponding 1000-millisecond average was determined using the fast Fourier transform technique. Finally, the root mean square of the amplitude spectrum across all 148 channels was calculated for each subject and condition and was averaged across subjects within each group.

Furthermore, grand means (means across subjects) for each group, channel, and part (real and imaginary) of the 10-Hz complex Fourier component were calculated. The real and imaginary parts were averaged so as not to lose polarity information of the magnetic flux. The obtained topographies were spline interpolated and projected on a standard MEG sensor set for each group and condition.

SOURCE ANALYSIS

An MNE procedure^{45,53,54} was applied to estimate the cortical origin of the ssVEF oscillatory brain response. A tessellated cortical mesh template surface derived from the Montreal Neurological Institute (MNI) phantom brain⁵⁵ and implemented in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>) served as a brain model to estimate the current source distribution. This MNI dipole mesh (3004 nodes) was used to calculate the forward solution using a spherical head model.^{56,57} The inverse solution was calculated by applying L2 MNE,⁴⁵ implemented using in-house coding (MATLAB; MathWorks, Natick, Massachusetts).

We estimated the underlying current source density (the source strength at each node of the MNI phantom brain) of the ssVEF at the 10-Hz stimulus driving frequency. Minimum norm estimation was calculated in the frequency domain by submitting the real and imaginary parts of the 10-Hz Fourier component to the MNE analysis (as described by Jensen and Vanni⁵⁸) and by using the root square of the sum of squares of the 2 Fourier parts as an estimate of absolute power.

STATISTICAL ANALYSIS

Current source density maps were submitted to permutation tests, which resulted in statistical maps showing main effects of group and condition (picture category) and interaction effects between the two. Omnibus repeated-measures analysis of variance (ANOVA) with group as the between factor and with condition as the within factor was conducted at each dipole location of the MNE solution. Because of the high number of tests (3004 comparisons), statistically significant *F* values were determined according to the permutation method described previously.^{7,59,60}

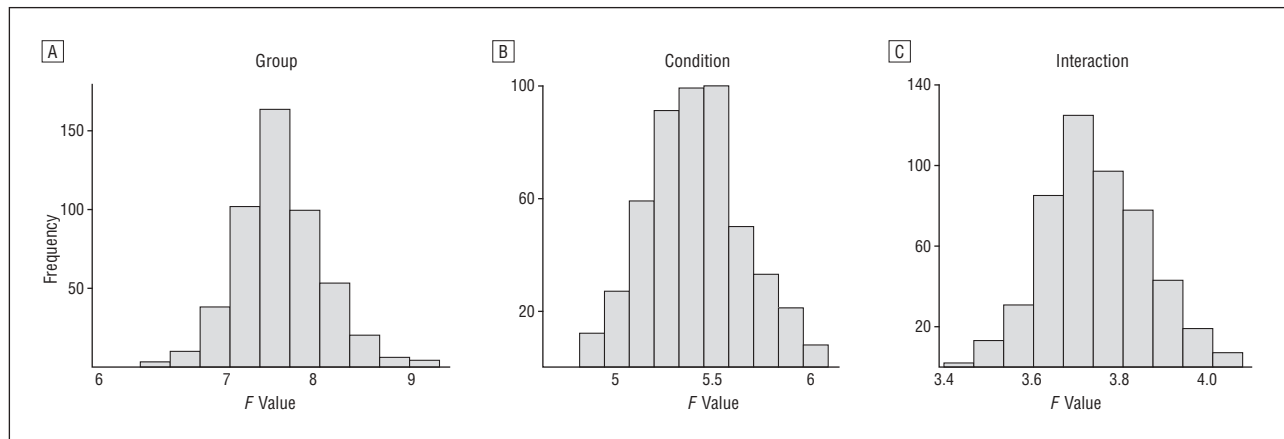


Figure 1. Test distributions of F values from the permutation statistics (500 draws) for the group (patients vs controls), condition (pleasant high-arousing, neutral low-arousing, and unpleasant high-arousing pictures), and interaction (group \times condition) effects.

For each draw (calculating the ANOVA), MNE source strength values of the 3 conditions were shuffled within each subject and at each dipole location, yielding maps of the condition main effect under the null hypothesis of no differences between conditions. To estimate the group and group \times condition interaction effects, patients and controls were randomly exchanged between groups for each draw. Permutation F value distributions were based on 500 draws for each MNE topography, and the maximum F value of all dipole locations obtained from each draw entered the test distribution.

F values with permutation $P < .05$ (critical $F = 8.6$ for group, critical $F = 5.8$ for condition, and critical $F = 3.9$ for interaction) were plotted onto the MNI brain to identify brain regions of interest (ROIs) associated with group, condition, and interaction effects (**Figure 1**). The mean amplitudes across group-effect ROIs were submitted to 2-sample t tests. The mean amplitudes across condition-effect ROIs were further analyzed using linear contrasts, Tukey honestly significant difference (HSD) test for single comparisons (comparing also pleasant vs unpleasant high-arousing conditions to evaluate valence effects), and simple-effect quadratic contrasts according to our hypothesis (pleasant high-arousing pictures were most pleasant, followed by neutral low-arousing pictures, with unpleasant high-arousing pictures as the least pleasant). The quadratic contrast will be referred to as arousal modulation. The mean source strength values across interaction-effect ROIs were reanalyzed by using repeated-measures ANOVA, simple-effect quadratic and linear contrasts, and Tukey HSD test for single comparisons.

To examine laterality effects, homologous dipole sites corresponding to the right temporoparietal cortex (see the "Results" section) in the left hemisphere were included in the ROI analysis to form a within-participants factor of hemisphere (group \times condition \times hemisphere). In all ROI analyses, Greenhouse-Geisser corrections of the degrees of freedom were applied where appropriate.

Valence and arousal ratings were evaluated using repeated-measures ANOVA with group as the between factor and with condition as the within factor. Greenhouse-Geisser corrections of the degrees of freedom were applied where appropriate. Statistically significant interactions were investigated by comparing simple effects and by using Tukey HSD test for single comparisons. Two-sample t tests were applied to evaluate group differences in each condition.

Based on subjective ratings and right temporoparietal activation patterns (see the "Results" section), the relationship between differences in arousal ratings (pleasant minus unpleasant pictures) and the corresponding right temporoparietal MNE

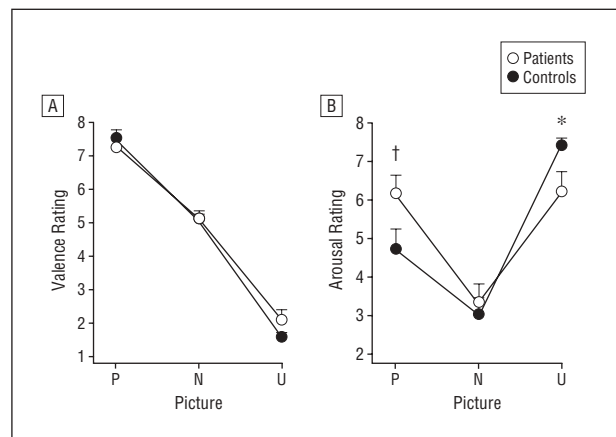


Figure 2. Valence (A) and arousal (B) ratings of control subjects and patients are shown. Error bars depict standard errors. N indicates neutral; P, pleasant; and U, unpleasant. $*P < .05$. Dagger indicates approximately $P = .06$ for 2-sided t tests comparing arousal values between groups.

amplitude differences were analyzed for each group. Finally, the relationship between the HARS scores and the right temporoparietal activity for unpleasant high-arousing pictures was analyzed for each group. Pearson product moment correlation coefficients were used throughout.

RESULTS

SELF-ASSESSMENT MANIKIN RATINGS

Valence ratings differed as a function of valence condition across all subjects ($F_{2,48} = 282.3$, $\epsilon = 0.79$, $P < .001$). There was no interaction between group and condition. Pleasant pictures were rated as most pleasant, followed by neutral pictures, whereas unpleasant pictures were evaluated as least pleasant ($P < .05$ for all comparisons) (**Figure 2A**).

Arousal ratings differed for controls and for patients ($F_{2,48} = 4.5$, $\epsilon = 0.99$, $P = .02$). In both groups, arousal ratings were different across conditions ($F_{2,24} = 36.1$, $\epsilon = 0.89$ for controls and $F_{2,24} = 10.8$, $\epsilon = 0.98$ for patients; $P < .001$ for both). Controls rated pleasant and unpleasant pictures as more arousing than neutral pictures. Arousal ratings of unpleasant pictures were higher than those of

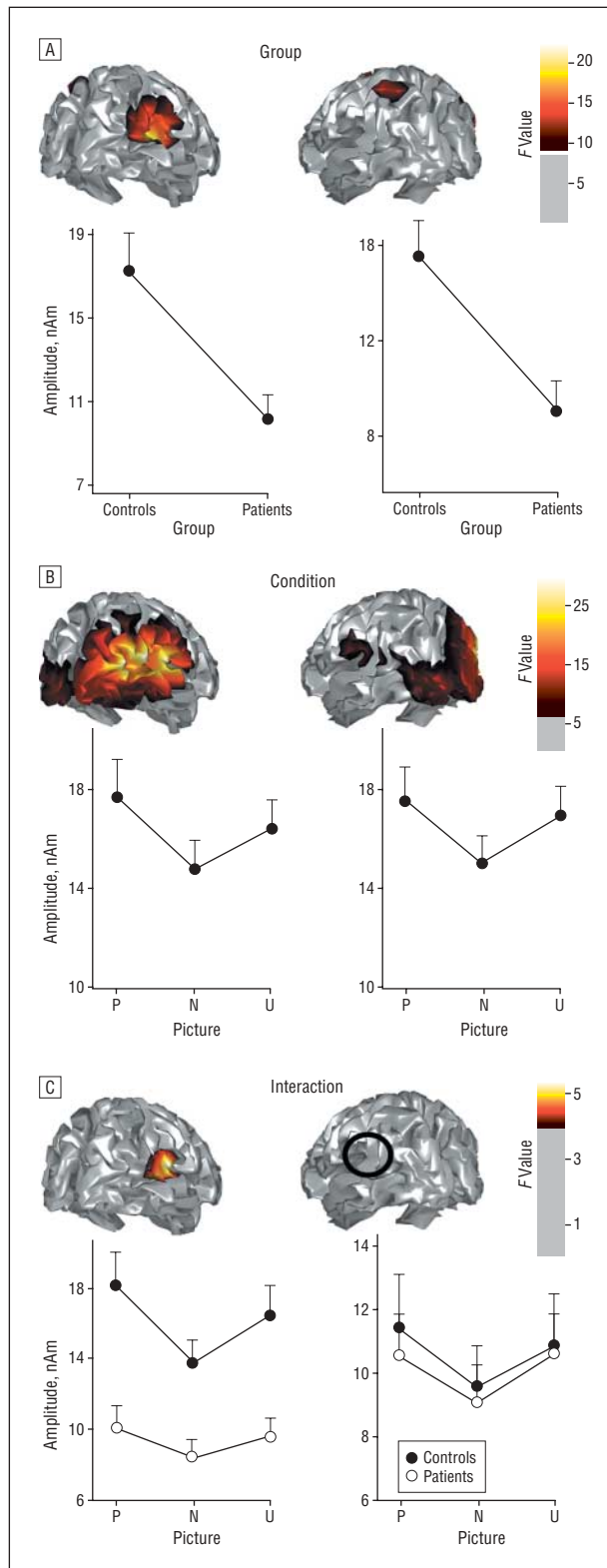


Figure 3. In A through C, the top rows depict cortical sources indicating statistically significant group, condition, and group by condition effects by means of *F* values. Only *F* values exceeding the critical *F* values of 8.6 for the group, 5.8 for the condition, and 3.9 for the group by condition effect derived from the permutation statistics are shown. The color bars indicate the *F* values. The bottom rows of A through C depict the mean source strengths with their corresponding standard errors as error bars across corresponding dipole clusters. The black circle in the top row of C marks the left temporoparietal dipole cluster homologous to its right correspondence that was included in the analysis of laterality. N indicates neutral; nAm, nano Amperemeter; P, pleasant; and U, unpleasant.

pleasant pictures in controls (unpleasant vs neutral, $P < .001$; pleasant vs neutral, $P = .04$; unpleasant vs pleasant, $P < .001$) (Figure 1B). Although patients rated pleasant and unpleasant pictures as more arousing than neutral pictures, pleasant and unpleasant affective images did not differ with respect to arousal (unpleasant vs neutral, $P = .005$; pleasant vs neutral, $P = .003$; unpleasant vs pleasant, $P = .99$) (Figure 2B).

Controls rated unpleasant pictures as more arousing than did patients ($t_{24} = 2.3$, $P = .03$). Patients tended to rate pleasant pictures as more arousing than did controls ($t_{24} = 2.0$, $P = .06$). Neutral pictures were evaluated equally by both groups with respect to arousal.

MNE DATA

Group main effects in right temporoparietal and left parietal brain regions indicated higher ssVEF source amplitudes for controls ($t_{28} = 3.3$ for the right ROI and $t_{28} = 3.3$ for the left ROI, $P < .01$ for both) (Figure 3A). Condition main effects were observed in right occipitotemporoparietal and left occipitotemporoparietal regions best modeled by arousal modulation. In the right ROI, the findings were as follows: $F_{1,29} = 30.3$, $P < .001$ for quadratic contrast; $F_{1,29} = 6.2$, $P = .02$ for linear contrast; $P < .001$ for pleasant vs neutral; $P < .001$ for unpleasant vs neutral; and $P = .02$ for pleasant vs unpleasant. In the left ROI, the findings were as follows: $F_{1,29} = 14.1$, $P < .001$ for quadratic contrast; $F_{1,29} = 1.5$, $P = .23$ for linear contrast; $P < .01$ for pleasant vs neutral; $P < .02$ for unpleasant vs neutral; and $P = .70$ for pleasant vs unpleasant (Figure 3B).

Critical to our hypothesis, the condition effect in the temporoparietal cortex was mainly driven by the controls because controls and patients differed for condition-related activation in that brain region ($F_{2,28} = 5.3$, $\epsilon = 0.89$, $P < .05$ for group \times condition interaction) (Figure 3C). Controls generated greater ssVEF responses in that brain region for emotional high-arousing pictures compared with neutral low-arousing pictures ($F_{1,14} = 34.7$, $P < .001$ for quadratic contrast; $F_{1,14} = 8.6$, $P < .01$ for linear contrast; $P < .001$ for pleasant vs neutral; and $P < .01$ for unpleasant vs neutral). Patients showed weak arousal modulation ($F_{1,14} = 7.3$, $P = .02$ for quadratic contrast; $F_{1,14} = 0.9$, $P = .36$ for linear contrast; $P = .08$ for pleasant vs neutral; $P = .09$ for unpleasant vs neutral; and $P = .99$ for pleasant vs unpleasant). Greater ssVEF responses to pleasant pictures compared with unpleasant pictures were observed only in the right temporoparietal ROI of controls ($P = .03$). Although the ROI analysis resulted in an emotional arousal effect (modeled as a quadratic contrast) in the patient group, this pattern was less pronounced than in controls ($F_{1,28} = 7.2$, $P = .02$ for interaction group by quadratic contrast and $F_{1,28} = 2.6$, $P = .13$ for group by linear contrast).

To test whether the right temporoparietal effect was lateralized, the interaction map of Figure 3C was also examined using a lenient statistical threshold of 2, as depicted in the online figure (eFigure [available at <http://www.archgenpsychiatry.com>]). No interaction could be observed in the left temporoparietal cortex by lowering the *F* threshold. Furthermore, an ROI analysis that included a within factor of hemisphere (Figure 3C) supported the lateralization of the group \times condition inter-

action ($F_{2,28}=2.6$, $\epsilon=0.86$, $P=.08$ for group \times condition \times hemisphere). In the left temporoparietal cortex, patients and controls showed the same modulation by emotional arousal ($F_{2,28}=0.3$, $\epsilon=0.83$, $P=.76$ for ROI group \times condition interaction; $F_{1,28}=9.7$, $\epsilon=0.83$, $P<.001$ for ROI main effect condition; $F_{1,28}=13.0$, $P<.001$ for quadratic contrast; $F_{1,28}=0.5$, $P=.49$ for linear contrast; $P<.01$ for pleasant vs neutral; $P=.01$ for unpleasant vs neutral; and $P=.99$ for pleasant vs unpleasant). Excluding the 2 left-handed subjects from the analysis did not change the interaction with respect to lateralization ($F_{2,26}=2.6$, $\epsilon=0.9$, $P=.08$ for ROI group \times condition \times hemisphere).

To illustrate our findings obtained from frequency domain-transformed data in the source space, **Figure 4** shows the root mean square of the 10-Hz amplitude spectrum across all sensors. Also shown is the grand mean oscillatory neuromagnetic brain response of the MEG channel (channel 85) capturing the maximum signal of the outgoing field (positive values) of the dipolar magnetic grand mean field pattern representing temporoparietal activation in controls and in patients.

CORRELATIONS BETWEEN RIGHT TEMPOROPARIETAL ACTIVATION, RATING PROFILES, AND THE HARS

Patients rated pleasant pictures and unpleasant pictures as equally arousing, whereas controls rated unpleasant pictures as more arousing than pleasant pictures (Figure 2). This pattern was reversed in the right temporoparietal cortex for the controls, who displayed greater ssVEF generator activity for pleasant pictures vs unpleasant pictures. The negative relationship between the arousal ratings and the right temporoparietal activity pattern was systematic across controls as indicated by a statistically significant negative correlation ($r=-0.68$, $P<.01$). Patients did not show such a relationship ($r=-0.14$, $P=.63$) (**Figure 5**). With respect to the HARS scores, the right temporoparietal cortex activation for unpleasant high-arousing pictures was independent of the HARS scores in patients and in controls ($r=0.32$, $P=.23$ for controls and $r=-0.31$, $P=.26$ for patients).

COMMENT

The aim of the present study was to compare ssVEF modulations in cortical sensory and attention networks for high-arousing vs low-arousing affective pictures for patients with depression and for controls. The results speak to the neurophysiologic function of arousal in controls and to its perturbation in depression. Replicating previous work,¹² we observed pronounced ssVEF changes in the right temporoparietal cortex as a function of emotional arousal, with greater ssVEF amplitude related to greater emotional arousal. Critical to our hypothesis, this sensitivity to emotionally arousing picture content was statistically significantly reduced in the right temporoparietal cortex in patients with clinical depression. These findings suggest that the ability to modulate arousal-related cortical structures to emotionally engaging visual content is impaired in clinical depression.

Greater steady-state responses for high-arousing emotional stimuli have been reported across occipitoparietal electrode sides in EEG.⁵² Electroencephalography studies^{47,61,62} using source localization estimations have shown that high-arousing emotional stimuli engage occipitotemporoparietal regions as early as 150 milliseconds after stimulus onset. These brain structures, especially the right parietal cortex, have been implicated in selective attention as well.^{63,64} The involvement of attention-related structures in arousal modulation supports the notion that emotional cues guide selective visual attention.^{5,13,65}

In patients with depression, ssVEFs originating in the dorsal visual pathway varied by emotional content. However, arousal modulation in the right temporoparietal cortex was markedly dampened. The temporoparietal cortex has been associated with emotional arousal in general¹⁹ and specifically with the ability to generate elevated skin conductance responses to emotional stimuli.³¹ Therefore, our data add substantial evidence to the hypothesis of right temporoparietal hypoactivation and related arousal deficits in depression.^{2,35,39,40,66}

Critically, our results were obtained under strict experimental control because we used stimulation with high-arousing vs low-arousing pictures from a standardized international picture set (IAPS⁴³) rather than relying on EEG band-power measures obtained during rest. By applying MNE, the deficient affective arousal modulation in patients could be localized in the right temporoparietal cortex. Therefore, our findings are in accord with reports of reduced P3 amplitude without affective modulation over right parietal electrode sites in depression.⁶⁷

Condition effects were driven by arousal rather than by valence. This result is in line with previous electrophysiologic findings in healthy subjects using similar sets of IAPS pictures. These studies^{11,12,48,52,62,68,69} found amplitude differences in posterior brain regions that varied with emotional arousal when high-arousing stimuli were included. Investigations using low-arousing emotional stimuli have reported anterior amplitude differences related to hedonic valence.¹⁵ Because our intent was to drive posterior cortical systems by arousal in depression, we used high-arousing vs low-arousing emotional stimuli. Future work may examine the interactions of hedonic valence and emotional arousal on ssVEFs systematically using multiple picture categories varying along those dimensions.

Our patient group was characterized by elevated but not severe anxiety scores (HARS score, <15) and did not meet DSM-IV criteria for anxiety disorder. This adds further evidence that low emotional arousal indexed by deficient arousal modulation in the temporoparietal cortex is associated with depression without severe anxiety.^{39,40} Furthermore, there was no correlation between the HARS scores and right temporoparietal activity for unpleasant high-arousing pictures in our patients and controls, which may reflect our inclusion criterion of a HARS score less than 15. Indeed, substantial comorbid anxiety would be expected to mitigate this effect for depression.^{39,40} In the same vein, Mogg and Bradley⁷⁰ suggest that only anxiety without depression should be associated with hypervigilance and hyperarousal.

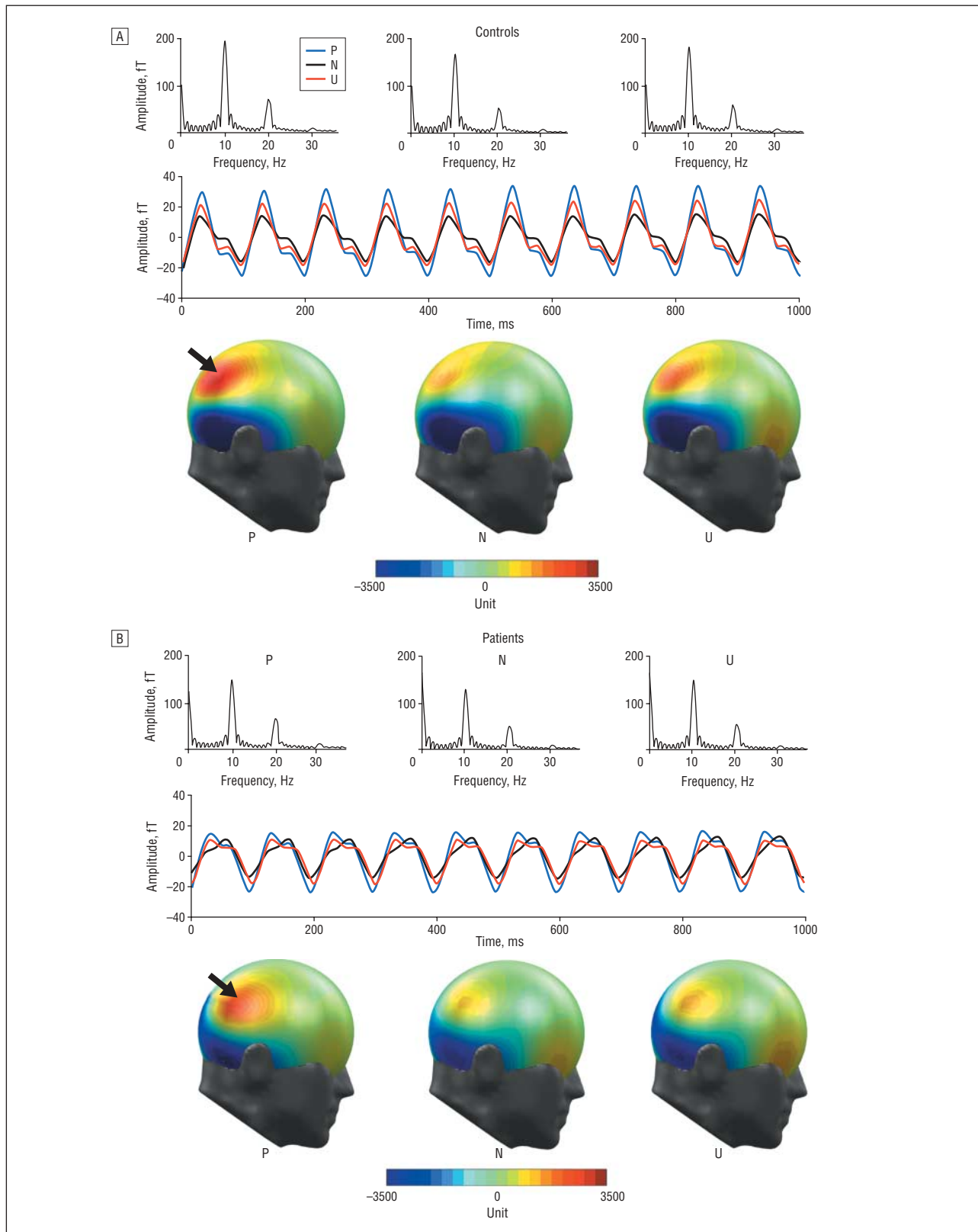


Figure 4. In A (for control subjects) and B (for patients), the top rows show the root mean square values of the Fourier amplitude spectrum for each condition. Note the 10-Hz peak of the stimulation frequency and its harmonics at 20 Hz and 30 Hz indicating high signal-to-noise ratios of the magnetoencephalography signal. The middle rows show 10 cycles of the oscillatory 10-Hz mean steady-state visual evoked field for each condition extracted by the moving window procedure. The bottom rows depict the grand mean for each condition; the black arrows indicate the oscillatory response from channel 85, which best captured the maximum of the outgoing field component associated with right temporoparietal activity. The blue line represents the oscillatory brain response evoked by pleasant pictures, whereas the red and black waveforms represent the unpleasant and neutral conditions, respectively. The color bar indicates the strength of the outgoing (red) and ingoing (blue) fields in units. fT indicates femtotesla (the real and imaginary parts of the 10-Hz Fourier components have arbitrary units); N, neutral; Nc, number of subjects for controls; Np, number of subjects for patients; P, pleasant; and U, unpleasant.

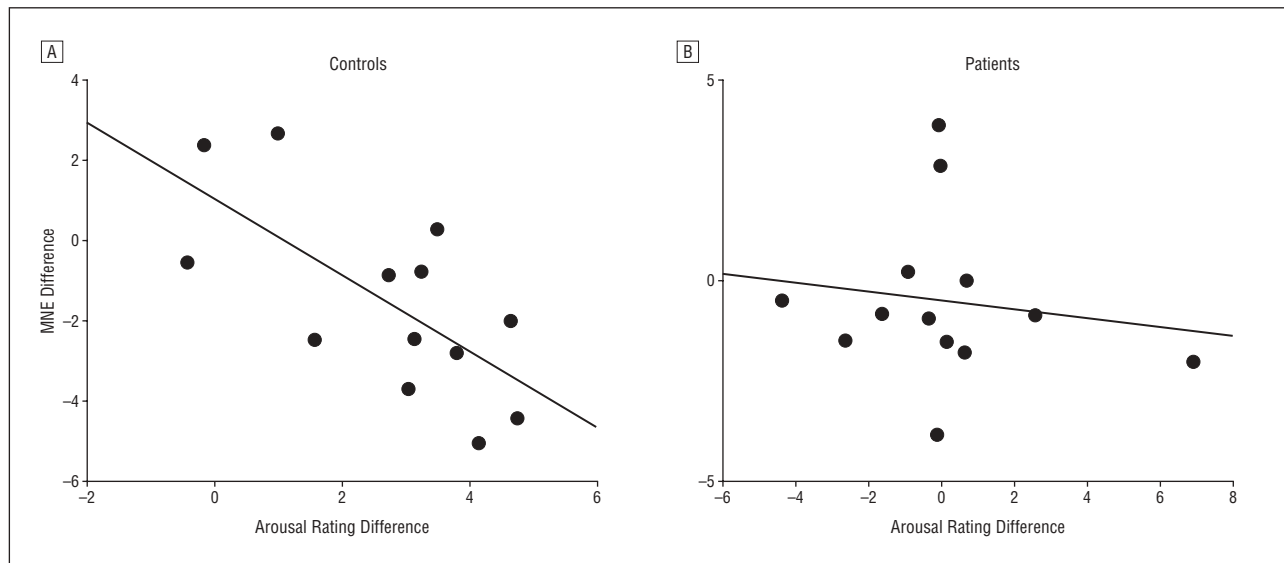


Figure 5. Arousal rating differences (unpleasant minus pleasant picture scores) vs corresponding minimum norm estimation (MNE) amplitude differences (unpleasant minus pleasant measured in nano Amperemeters [nAm]) derived from right temporoparietal source locations (see Figure 3C). A, Controls ($r=-0.68$, $P<.01$); regression line ($R^2=0.47$, $F_{1,11}=9.7$, $P<.01$). B, Patients ($r=-0.14$, $P=.63$); regression line ($R^2=0.02$, $F_{1,11}=0.25$, $P=.63$).

The content-related differences in the right temporoparietal cortex in patients were not reflected in subjective ratings. This is in line with the notion that physiologic reactivity and subjective report dissociate during emotion processing in depression, with normal emotion ratings in patients^{3,4} (vs aberrant emotion ratings in other studies^{71,72}).

Whereas arousal ratings in patients were not related to cortical activation patterns in the right temporoparietal cortex, controls showed a correlation pattern (Figure 5) suggesting that higher temporoparietal activity for pleasant pictures vs unpleasant pictures was associated with reversed arousal ratings. Dissociations between arousal ratings and ssVEP responses to emotional stimuli in control subjects have been reported before.⁷³ Given recent evidence that healthy subjects tend to avoid threat cues,⁷⁴ our finding could reflect a self-regulation process to avoid hyperactivation of arousal-related brain regions. However, this post hoc interpretation is speculative and has to be addressed in future experiments that include behavioral measures of avoidance.

Although all observed effects were mainly driven by arousal, we also obtained a valence effect (pleasant greater than unpleasant) in the right temporoparietal cortex for controls that was not observed in the patients. Kemp et al⁷³ reported activity enhancement for pleasant stimuli and activity reduction for unpleasant stimuli after citalopram hydrobromide administration. Because depression is associated with serotonin depletion,⁷⁵ the cortical activity bias toward pleasant pictures in controls may be linked to differences in serotonin functioning between healthy subjects and patients with depression.

Some limitations regarding our study have to be addressed. First, applying MNE may obscure deep sources because the MNE algorithm tends to emphasize superficial sources.⁷⁶ However, because the aim of the study was to test differences at the cortical level, applying MNE was considered appropriate.

Second, because our patient group was medicated, effects due to antidepressants cannot be ruled out. However, data among nonmedicated subjects support this topography in depression (eg, as described by Heller and colleagues⁶⁶). Keller et al²¹ obtained the same asymmetry results in medicated patients with MDD and in nonmedicated control subjects scoring high on depression questionnaires. Furthermore, the resting EEG study by Bruder et al³⁵ reported less activity over right parietal electrode sides in nonmedicated offspring at risk for depression.

Third, we investigated only female participants. Therefore, we cannot generalize our results to male patients with MDD. In our laboratory, we are sampling male subjects with depression to achieve a sample size necessary for evaluating sex differences.

Fourth, because steady-state responses are sensitive to visual spatial selective attention,⁷⁷⁻⁷⁹ the observed deficient ssVEF arousal modulation in the temporoparietal cortex may be due to cognitive deficits in subjects with depression. Cognitive deficits in the domain of executive functions in depression have been well documented^{23,80} and are still present in patients with remission.⁸¹ However, this interpretation seems unlikely given the behavioral data. Patients' emotion ratings followed the general rating pattern usually observed,⁴³ implying that attention to emotional pictures was similar in patients and in controls.

Furthermore, neuromagnetic oscillatory brain responses in the dorsal visual stream showed a similar arousal modulation pattern across patients and controls (Figure 3B). Hence, it is unlikely that patients simply were less attentive to all pictures during the experiment.

These findings are in line with the consistent notion that patients with depression do not show attentional biases toward emotional stimuli compared with patients with anxiety (reviewed in detailed by Mogg and Bradley⁷⁰), possibly reflecting normal activation in visual spatial attention systems. Attentional biases in depression

have been reported for self-relevant stimuli only.⁷⁰ Therefore, the absence of attentional biases in depression and our observation of normal arousal modulation in the dorsal visual stream—but of dampened arousal effects specifically restricted to the right temporoparietal cortex in patients with depression—point to deficits in arousal-related brain structures along with intact basic visual stimulus processing in depression.

Submitted for Publication: July 11, 2007; final revision received January 11, 2008; accepted January 11, 2008.

Correspondence: Stephan Moratti, PhD, Center of Magnetoencephalography Dr Perez Modrego, University Complutense of Madrid, Pabellón 8, Avenida Complutense, s/n, 28040 Madrid, Spain (moratti@med.ucm.es).

Author Contributions: Dr Moratti had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This work was supported by grant MO 1043/2-1 from the Deutsche Forschungsgemeinschaft Germany (Dr Moratti) and by the Fundación Cerebro y Mente Spain (Dr Rubio).

Role of the Sponsor: The Deutsche Forschungsgemeinschaft Germany and the Fundación Cerebro y Mente Spain participated in the design and conduct of the study and the collection and analysis of the data via the support of Drs Moratti and Rubio.

Additional Information: The eFigure is available at <http://www.archgenpsychiatry.com>.

Additional Contributions: Cristina Saugar, MSc, assisted with the data collection and analysis. Gregory A. Miller, PhD, and Bryan Strange, MD, read the manuscript and provided helpful advice.

REFERENCES

- Loas G, Salinas E, Pierson A, Guelfi JD, Samuel-Lajeunesse B. Anhedonia and blunted affect in major depressive disorder. *Compr Psychiatry*. 1994;35(5):366-372.
- Heller W, Nitschke JB. Regional brain activity in emotion: a framework for understanding cognition in depression. *Cogn Emotion*. 1997;11(special issue 5/6):637-661.
- Forbes EE, Miller A, Cohn JF, Fox NA, Kovacs M. Affect-modulated startle in adults with childhood-onset depression: relations to bipolar course and number of lifetime depressive episodes. *Psychiatry Res*. 2005;134(1):11-25.
- Gehricke J, Shapiro D. Reduced facial expression and social context in major depression: discrepancies between facial muscle activity and self-reported emotion. *Psychiatry Res*. 2000;95(2):157-167.
- Lang PJ, Bradley MM, Cuthbert BN. Motivated attention: affect, activation, and action. In: Lang PJ, Simons RF, Balaban MT, eds. *Attention and Orienting: Sensory and Motivational Processes*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1997:97-135.
- Bradley MM, Codispoti M, Cuthbert BN, Lang PJ. Emotion and motivation. I: defensive and appetitive reactions in picture processing. *Emotion*. 2001;1(3):276-298.
- Keil A, Moratti S, Sabatinelli D, Bradley MM, Lang PJ. Additive effects of emotional content and spatial selective attention on electrocortical facilitation. *Cereb Cortex*. 2005;15(8):1187-1197.
- Lang PJ, Davis M. Emotion, motivation, and the brain: reflex foundations in animal and human research. *Prog Brain Res*. 2006;156:3-29.
- Shi C, Davis M. Visual pathways involved in fear conditioning measured with fear-potentiated startle: behavioral and anatomic studies. *J Neurosci*. 2001;21(24):9844-9855.
- LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000;23:155-184.
- Sabatinelli D, Bradley MM, Fitzsimmons JR, Lang PJ. Parallel amygdala and inferotemporal activation reflect emotional intensity and fear relevance. *Neuroimage*. 2005;24(4):1265-1270.
- Moratti S, Keil A, Stolarova M. Motivated attention in emotional picture processing is reflected by activity modulation in cortical attention networks. *Neuroimage*. 2004;21(3):954-964.
- Vuilleumier P. How brains beware: neural mechanisms of emotional attention. *Trends Cogn Sci*. 2005;9(12):585-594.
- Pourtois G, Schwartz S, Seghier ML, Lazeyras F, Vuilleumier P. Neural systems for orienting attention to the location of threat signals: an event-related fMRI study. *Neuroimage*. 2006;31(2):920-933.
- Kemp AH, Gray MA, Eide P, Silberstein RB, Nathan PJ. Steady-state visually evoked potential topography during processing of emotional valence in healthy subjects. *Neuroimage*. 2002;17(4):1684-1692.
- Regan D. *Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine*. New York, NY: Elsevier Science Inc; 1989.
- Moratti S, Keil A, Miller GA. Fear but not awareness predicts enhanced sensory processing in fear conditioning. *Psychophysiology*. 2006;43(2):216-226.
- Heller W. Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. *Neuropsychology*. 1993;7(4):476-489.
- Heller W, Nitschke JB, Lindsay DL. Neuropsychological correlates of arousal in self-reported emotion. *Cogn Emotion*. 1997;11(4):383-402.
- Davidson RJ. Anterior cerebral asymmetry and the nature of emotion. *Brain Cogn*. 1992;20(1):125-151.
- Keller J, Nitschke JB, Bhargava T, Deldin PJ, Gergen JA, Miller GA, Heller W. Neuropsychological differentiation of depression and anxiety. *J Abnorm Psychol*. 2000;109(1):3-10.
- Heller W, Etienne MA, Miller GA. Patterns of perceptual asymmetry in depression and anxiety: implications for neuropsychological models of emotion and psychopathology. *J Abnorm Psychol*. 1995;104(2):327-333.
- Levin RL, Heller W, Mohanty A, Herrington JD, Miller GA. Cognitive deficits in depression and functional specificity of regional brain activity. In: Atchley R, Iardi S, eds. *Cogn Ther Res*. 2007;31(2):211-233.
- Bruder GE, Quitkin FM, Stewart JW, Martin C, Voglmaier MM, Harrison WM. Cerebral laterality and depression: differences in perceptual asymmetry among diagnostic subtypes. *J Abnorm Psychol*. 1989;98(2):177-186.
- Flor-Henry P. Lateralized temporal-limbic dysfunction and psychopathology. *Ann N Y Acad Sci*. 1976;280:777-795.
- Jaeger J, Borod JC, Peselow E. Depressed patients have atypical hemispace biases in the perception of emotional chimeric faces. *J Abnorm Psychol*. 1987;96(4):321-324.
- Liotti M, Sava D, Rizzolatti G, Caffarra P. Differential hemispheric asymmetries in depression and anxiety: a reaction-time study. *Biol Psychiatry*. 1991;29(9):887-899.
- Bruder GE, Stewart JW, Towey JP, Friedman D, Tenke CE, Voglmaier MM, Leite P, Cohen P, Quitkin FM. Abnormal cerebral laterality in bipolar depression: convergence of behavioral and brain event-related potential findings. *Biol Psychiatry*. 1992;32(1):33-47.
- Miller EN, Fujioka TA, Chapman LJ, Chapman JP. Hemispheric asymmetries of function in patients with major affective disorders. *J Psychiatr Res*. 1995;29(3):173-183.
- Shimoda K, Robinson RG. The relationship between poststroke depression and lesion location in long-term follow-up. *Biol Psychiatry*. 1999;45(2):187-192.
- Meadows ME, Kaplan RF. Dissociation of autonomic and subjective responses to emotional slides in right hemisphere damaged patients. *Neuropsychologia*. 1994;32(7):847-856.
- Shagass C. Electrical activity of the brain. In: Greenbach NS, Sternbach RA, eds. *Handbook of Psychophysiology*. New York, NY: Holt Rinehart & Winston Inc; 1972:263-328.
- Cook IA, O'Hara R, Uijtdebaage SHJ, Mandelkern M, Leuchter AF. Assessing the accuracy of topographic EEG mapping for determining local brain function. *Electroencephalogr Clin Neurophysiol*. 1998;107(6):408-414.
- Oakes TR, Pizzagalli DA, Hendrick AM, Horras KA, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Davidson RJ. Functional coupling of simultaneous electrical and metabolic activity in the human brain. *Hum Brain Mapp*. 2004;21(4):257-270.
- Bruder GE, Tenke CE, Warner V, Nomura Y, Grillon C, Hille J, Leite P, Weissman MM. Electroencephalographic measures of regional hemispheric activity in offspring at risk for depressive disorders. *Biol Psychiatry*. 2005;57(4):328-335.
- Bruder GE, Stewart JW, Mercier MA, Agosti V, Leite P, Donovan S, Quitkin FM. Outcome of cognitive-behavioral therapy for depression: relation to hemispheric dominance for verbal processing. *J Abnorm Psychol*. 1997;106(1):138-144.
- Davidson RJ, Chapman JP, Chapman LJ. Task-dependent EEG asymmetry discriminates between depressed and non-depressed subjects [abstract]. *Psychophysiology*. 1987;24:585.
- Reid SA, Duke LM, Allen JJ. Resting frontal electroencephalographic asymmetry in depression: inconsistencies suggest the need to identify mediating factors. *Psychophysiology*. 1998;35(4):389-404.
- Kentgen LM, Tenke CE, Pine DS, Fong R, Klein RG, Bruder GE. Electroencepha-

- lographic asymmetries in adolescents with major depression: influence of comorbidity with anxiety disorders. *J Abnorm Psychol.* 2000;109(4):797-802.
40. Bruder GE, Fong R, Tenke CE, Leite P, Towey JP, Stewart JE, McGrath PJ, Quitkin FM. Regional brain asymmetries in major depression with or without an anxiety disorder: a quantitative electroencephalographic study. *Biol Psychiatry.* 1997; 41(9):939-948.
 41. Nitschke JB, Heller W, Palmieri PA, Miller GA. Contrasting patterns of brain activity in anxious apprehension and anxious arousal. *Psychophysiology.* 1999; 36(5):628-637.
 42. Mayer AR, Dorfinger JM, Rao SM, Seidenberg M. Neural networks underlying endogenous and exogenous visual-spatial orienting. *Neuroimage.* 2004;23(2):534-541.
 43. Lang PJ, Bradley MM, Cuthbert BN. *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual.* Gainesville: University of Florida; 2005. Technical report A-6.
 44. Hämäläinen MS, Ilmoniemi RJ. *Interpreting Measured Magnetic Fields of the Brain: Estimates of Current Distributions.* Helsinki, Finland: Helsinki University of Technology; 1984 Publication. TKK-F-A559.
 45. Hauk O. Keep it simple: a case for using classical minimum norm estimation in the analysis of EEG and MEG data. *Neuroimage.* 2004;21(4):1612-1621.
 46. Keil A, Muller MM, Gruber T, Wienbruch C, Stolarova M, Elbert T. Effects of emotional arousal in the cerebral hemispheres: a study of oscillatory brain activity and event-related potentials. *Clin Neurophysiol.* 2001;112(11):2057-2068.
 47. Junghöfer M, Sabatinelli D, Bradley MM, Schupp HT, Elbert TR, Lang PJ. Fleeting images: rapid affect discrimination in the visual cortex. *Neuroreport.* 2006; 17(2):225-229.
 48. Schupp HT, Cuthbert BN, Bradley MM, Cacioppo JT, Ito T, Lang PJ. Affective picture processing: the late positive potential is modulated by motivational relevance. *Psychophysiology.* 2000;37(2):257-261.
 49. Müller MM, Teder W, Hillyard SA. Magnetoencephalographic recording of steady-state visual evoked cortical activity. *Brain Topogr.* 1997;9(3):163-168.
 50. Lang PJ. Behavioral treatment and bio-behavioral assessment: computer applications. In: Sidowski JB, Johnson JH, Williams TA, eds. *Technology in Mental Health Care Delivery Systems.* Norwood, NJ: Ablex Publishing; 1980: 119-137.
 51. Berg P, Scherg M. A multiple source approach to the correction of eye artifacts. *Electroencephalogr Clin Neurophysiol.* 1994;90(3):229-241.
 52. Keil A, Gruber T, Muller MM, Moratti S, Stolarova M, Bradley MM, Lang PJ. Early modulation of visual perception by emotional arousal: evidence from steady-state visual evoked brain potentials. *Cogn Affect Behav Neurosci.* 2003;3(3): 195-206.
 53. Hauk O, Keil A, Elbert T, Müller MM. Comparison of data transformation procedures to enhance topographical accuracy in time series analysis of the human EEG. *J Neurosci Methods.* 2002;113(2):111-122.
 54. Hämäläinen MS, Ilmoniemi RJ. Interpreting magnetic fields of the brain: minimum norm estimates. *Med Biol Eng Comput.* 1994;32(1):35-42.
 55. Collins DL, Zijdenbos AP, Kollokian V, Sled JG, Kabani NJ, Holmes CJ, Evans AC. Design and construction of a realistic digital brain phantom. *IEEE Trans Med Imaging.* 1998;17(3):463-468.
 56. Lapalme E, Lina JM, Mattout J. Data-driven parcelling and entropic inference in MEG. *Neuroimage.* 2006;30(1):160-171.
 57. Sarvas J. Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. *Phys Med Biol.* 1987;32(1):11-22.
 58. Jensen O, Vanni S. A new method to identify multiple sources of oscillatory activity from magnetoencephalographic data. *Neuroimage.* 2002;15(3):568-574.
 59. Blair RC, Karniski W. An alternative method for significance testing of waveform difference potentials. *Psychophysiology.* 1993;30(5):518-524.
 60. Karniski W, Blair RC, Snider AD. An exact statistical method for comparing topographic maps, with any number of subjects and electrodes. *Brain Topogr.* 1994; 6(3):203-210.
 61. Junghöfer M, Bradley MM, Elbert TR, Lan PJ. Fleeting images: a new look at early emotion discrimination. *Psychophysiology.* 2001;38(2):175-178.
 62. Schupp HT, Junghofer M, Weike AI, Hamm AO. Emotional facilitation of sensory processing in the visual cortex. *Psychol Sci.* 2003;14(1):7-13.
 63. Posner MI, Dehaene S. Attentional networks. *Trends Neurosci.* 1994;17(2):75-79.
 64. Fernandez-Duque D, Posner MI. Brain imaging of attentional networks in normal and pathological states. *J Clin Exp Neuropsychol.* 2001;23(1):74-93.
 65. Pourtois G, Thut G, Grave de Peralta R, Michel C, Vuilleumier P. Two electrophysiological stages of spatial orienting towards fearful faces: early temporo-parietal activation preceding gain control in extrastriate visual cortex. *Neuroimage.* 2005;26(1):149-163.
 66. Heller W, Koven NS, Miller GA. Regional brain activity in anxiety and depression, cognition/emotion interaction, and emotion regulation. In: Hugdahl K, Davidson RJ, eds. *The Asymmetrical Brain.* Cambridge, MA: MIT Press; 2003:533-564.
 67. Kayser J, Bruder GE, Tenke CE, Stewart JE, Quitkin FM. Event-related potentials (ERPs) to hemifield presentations of emotional stimuli: differences between depressed patients and healthy adults in P3 amplitude and asymmetry. *Int J Psychophysiol.* 2000;36(3):211-236.
 68. Keil A, Bradley MM, Hauk O, Rockstroh B, Elbert T, Lang PJ. Large-scale neural correlates of affective picture processing. *Psychophysiology.* 2002;39(5): 641-649.
 69. Sabatinelli D, Lang PJ, Keil A, Bradley MM. Emotional perception: correlation of functional MRI and event-related potentials. *Cereb Cortex.* 2007;17(5):1085-1091.
 70. Mogg K, Bradley BP. Attentional bias in generalized anxiety disorder versus depressive disorder. *Cognit Ther Res.* 2005;29(1):29-45.
 71. Sloan DM, Strauss ME, Wisner KL. Diminished response to pleasant stimuli by depressed women. *J Abnorm Psychol.* 2001;110(3):488-493.
 72. Sloan DM, Strauss ME, Quirk SW, Sajatovic M. Subjective and expressive emotional responses in depression. *J Affect Disord.* 1997;46(2):135-141.
 73. Kemp AH, Gray MA, Silberstein RB, Armstrong SM, Nathan PJ. Augmentation of serotonin enhances pleasant and suppresses unpleasant cortical electrophysiological responses to visual emotional stimuli in humans. *Neuroimage.* 2004; 22(3):1084-1096.
 74. Wilson E, MacLeod C. Contrasting two accounts of anxiety-linked attentional bias: selective attention to varying levels of stimulus threat intensity. *J Abnorm Psychol.* 2003;112(2):212-218.
 75. Jans LA, Riedel WJ, Markus CR, Blokland A. Serotonergic vulnerability and depression: assumptions, experimental evidence and implications. *Mol Psychiatry.* 2007;12(6):522-543.
 76. Dale AM, Liu AK, Fischl BR, Buckner RL, Belliveau JW, Lewine JD, Halgren E. Dynamic statistical parametric mapping: combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron.* 2000;26(1):55-67.
 77. Morgan ST, Hansen JC, Hillyard SA. Selective attention to stimulus location modulates the steady-state visual evoked potential. *Proc Natl Acad Sci U S A.* 1996; 93(10):4770-4774.
 78. Müller MM, Hillyard S. Concurrent recording of steady-state and transient event-related potentials as indices of visual-spatial selective attention. *Clin Neurophysiol.* 2000;111(9):1544-1552.
 79. Müller MM, Hubner R. Can the spotlight of attention be shaped like a doughnut? evidence from steady-state visual evoked potentials. *Psychol Sci.* 2002;13(2): 119-124.
 80. Veiel HO. A preliminary profile of neuropsychological deficits associated with major depression. *J Clin Exp Neuropsychol.* 1997;19(4):587-603.
 81. Paelecke-Habermann Y, Pohl J, Lepow B. Attention and executive functions in remitted major depression patients. *J Affect Disord.* 2005;89(1-3):125-135.