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Changes in Electric Brain Response to Affective Stimuli in the First Week of Antidepressant Treatment: An Exploratory Study

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Keywords
EEG · Alpha asymmetry · Theta · Treatment response · Depression

Abstract
Introduction: Asymmetrical alpha and frontal theta activity have been discussed as neurobiological markers for antidepressant treatment response. While most studies focus on resting-state EEG, there is evidence that task-related activity assessed at multiple time points might be superior in detecting subtle early differences. ***Methods:*** This was a naturalistic study design assessing participants in a psychiatric in- and outpatient hospital setting. We investigated stimulus-related EEG asymmetry (frontal and occipital alpha-1 and alpha-2) and power (frontal midline theta) assessed at baseline and 1 week after initiation of pharmacological depression treatment while presenting affective stimuli. We then compared week 4 responders and nonresponders to antidepressant treatment. ***Results:*** Follow-up analyses of a significant group × emotion × time interaction ($p < 0.04$) for alpha-1 asymmetry showed that responders differed significantly at baseline in their asymmetry scores in response to sad compared to happy faces with a change in this pattern 1 week later. Nonresponders did not show this pattern. No significant results were found for alpha-2, occipital alpha-1, and occipital alpha-2 asymmetry or frontal midline theta power. ***Discussion:*** Our study addresses the gap in comparisons of task-related EEG activity changes measured at two time points and supports the potential value of this approach in detecting early differences in responders versus nonresponders to pharmacological treatment. Important limitations include the small sample size and the noncontrolled study design.

Introduction

Major depressive disorder is a highly prevalent psychiatric illness that is associated with substantial individual and societal burden [1]. This burden is increased by lengthy periods required to determine the adequate pharmacological treatment for the individual patient [2]. Most of the current guidelines agree that the initial pharmacological treatment needs to be tried for at least

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4 weeks at an adequate dose to determine its benefit [3].

To abridge these trial-and-error periods, a significant amount of research has been dedicated to identify neurobiological predictors of treatment response using scalp-recorded electric brain activity [4–6]. Two promising candidates in this area are resting-state asymmetrical alpha and frontal theta activity, which are shown to be associated with depression and depressive symptoms per se [5, 7–11].

Regarding frontal theta in studies investigating treatment response predictors, Iosifescu et al. [12] and Arns et al. [13] reported lower pretreatment frontal theta power in treatment responders than nonresponders. Theta power was negatively correlated with reductions in depressive symptoms after 8 weeks of treatment. An association between pretreatment frontal theta power and changes in depressive symptoms was also found by Knott et al. [14] and Spronk et al. [15]. However, in these studies [14, 15], a positive correlation between theta power and a reduction in depressive symptoms was found. Studies examining pretreatment alpha asymmetry indicate differences in responders and nonresponders for global [16], frontal [17, 18], and occipital alpha asymmetry [19]. However, negative findings were also reported [20–22].

Of particular interest, Bares et al. [20] did not find alpha asymmetry differences between responders and nonresponders at the pretreatment level; however, they observed group differences in changes of alpha asymmetry from pretreatment baseline to the assessment 1 week after the initiation of treatment. Studies on frontal theta activity also point to the benefit of investigating early changes within the parameters of interest during the initiation of antidepressive treatment (e.g., after 1 week) [12, 23–25]. Such an approach may have the advantage that changes within a parameter might be more suitable to reflect the interaction between the individual brain state and the individual medication selected to treat the depressive episode and, therefore, potentially indicate the clinical trajectory more individually [26, 27] while also reducing the impact of interindividual variation.

Most studies investigating alpha asymmetry and frontal theta power as treatment response predictorsfocus on the brain's resting-state activity. However, evidence suggests that EEG activity assessed during emotional stimulation might be a more powerful indicator [28, 29]. Such an approach can potentially reduce uncontrolled variance and challenge the individual brain's ability to regulate emotional responses [28–30], which may be relevant in longitudinal studies on depressive disorders. This is also supported by studies showing that antidepressants modulate emotional processing early in the treatment process in depressed patients [31–34].

This study aimed to compare responders and nonresponders to antidepressant treatment with regard to early changes in task-related EEG activity to contribute to the search for treatment response predictors. We therefore investigated patients with unipolar depression regarding their rhythmic brain activity in response to affective stimuli before and 1 week after the start of pharmacological treatment. Emotional challenge was established by using a simple task design employing happy and sad face stimuli. We investigated the asymmetry of alpha-1 and alpha-2 sub-bands [20] at frontal and occipital sites and frontal midline theta based on the reported findings to this date. However, it should be noted that previous studies examining alpha asymmetry and theta power as response predictors differed widely in methodology and showed partly conflicting or mixed results. In the current study, we investigated frontal midline theta as opposed to the theta obtained over several frontal electrodes found more widespread in cortical areas, as the latter may be more likely to indicate drowsiness [5, 13].

We hypothesized more pronounced early changes in electric brain activity, that is, alpha asymmetry and frontal midline theta power, in responders than in nonresponders. Given the inconsistency of previous findings and the scarce research on task-related alpha asymmetry and theta power in response prediction, we did not have a directional hypothesis regarding the direction of these changes or the affected alpha sub-bands.

Materials and Methods

The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from each participant before enrollment in the study. Participants did not receive financial compensation. The study was conducted in accordance with the Declaration of Helsinki as revised in 1989.

Participants

Participants were recruited at the in- and outpatient clinics of the Charité – Universitätmedizin Berlin and had received a diagnosis of a major depression according to the DSM-IV criteria by the consensus of 2 independent, experienced psychiatrists (one of whom was the patient's treating psychiatrist).

For inclusion in the study, participants had to be right handed, be between 18 and 60 years of age, and have had received a rating greater than 19 in the Montgomery-Asberg Depression Rating Scale (MADRS) [35], that is, at least a moderate depressive episode [36]. Participants' treatment plan was to be changed due to lack of im-

Table 1. Demographic and clinical data

	Nonresponders (n = 33)		Responders (n = 12)		Statistic	
	mean	SD	mean	SD	$t(43)$	p value
Age, years	42.45	10	33.17	10.69	2.71	0.010
MADRS score at T0	30.61	4.94	28.58	4.38	1.25	0.219
MADRS score at T4	23.94	4.21	11.42	3.75	9.06	<0.001
Age at first depressive episode, years	36.67	11.34	29.67	11.63	1.82	0.076
Duration of current episode, weeks	39.45	28.73	32.92	18.08	0.73	0.467
Number of depressive episodes, lifetime	2.61	2.62	2.42	2.17	0.50	0.618
Treatment trials of current episode[1] (min-max)	0.45 (0–2)	0.67	0.42 (0–2)	0.67	0.169	0.87
MWT[2]	27.91	4.6	27.6	5.27	0.135	0.894
	N	%	n	%	$\chi^2(1)$	p value
Females	21	63.6	8	66.7	0.04	0.851
Relationship status (single)	17	51.5	5	45.5	0.121	0.728
German higher school certificate	12	36.4	7	58.3	0.306	0.164
Employment status currently working/student	16	50.0	10	83.3	4.24	0.12
Children[3]	18	54.5	6	50	0.073	0.525
Double depression	16	48.5	4	33.3	1.18	0.366
First depressive episode	13	39.4	5	41.7	0.019	0.891
Melancholic features[4]	29	87.88	9	75	1.11	0.292
Psychiatric comorbiditiy[5]	18	54.5	3	25	3.09	0.079

Depicted are mean ± standard deviation or number (%) and statistics. MADRS, Montgomery-Asberg Depression Rating Scale. [1] Number of different pharmacological treatment strategies for the current episode. [2] Estimate of premorbid intelligence as assessed by the MWT-B. [3] One or more children. [4] Number of patients who fulfilled the criteria for melancholic features. [5] Presence of at least one nonaffective psychiatric comorbidity.

provement as assessed by the patient's treating psychiatrist. This included participants whose current treatment plan comprised starting an antidepressant medication to treat the index (current) episode (these patients were either receiving no antidepressant medication or were receiving maintenance medication at that time), escalation of the current antidepressant treatment regime (high-dosage treatment or a second antidepressant), switching to a different class of antidepressants, or augmenting the current treatment with an additional medication (lithium, neuroleptic). Further inclusion criteria for analyses were as follows: (i) first EEG recording (T0, baseline) within 2 days before and second EEG recording (T1) within 6–10 days after the change in treatment; (ii) MADRS ratings at T0, T1, and after 4 weeks of treatment (T4); and (iii) no additional changes in antidepressant pharmacologic treatment regime until week 4 rating.

Exclusion criteria were reports of the presence of any relevant medical or neurological condition (e.g., stroke, prior brain surgery, history of chronic inflammatory brain diseases, past loss of consciousness for more than 10 min, malignant diseases, rheumatic disorders, untreated endocrinological diseases, hepatitis C, or HIV); an abnormal thyroid function laboratory test; clinically relevant abnormal liver enzymes and clinically relevant abnormal blood counts; the presence of any DSM-IV axis I comorbidities other than anxiety disorders; posttraumatic stress disorder; obsessive-compulsive disorder; dysthymia; alcohol, benzodiazepine, or illicit drug use disorder with use within the last 6 months; and reported pregnancy.

Four patients dropped out due to the following reasons: change of diagnosis to bipolar disorder (mixed episode) during the 4-week observation period (n = 1), abnormal thyroid test (assessed after the first EEG, n = 1), accidental cMRI finding of a brain abnormality (n = 1), and refusal to participate in follow-up assessments (n = 1).

The final sample consisted of 45 participants (29 women, 16 men; mean age 39.9 ± 10.9 years), of whom 33 patients were classified as nonresponders and 12 as responders based on the reduction in MADRS scores from baseline to week 4, that is, response ≥50%, nonresponse <50%.

Participants' demographic and clinical data are presented in Table 1. Participants in the nonresponder group were significantly older than those in the responder group. There were no relevant differences in the key clinical characteristics. Most patients had experienced previous major depressive episodes. Nine individuals (nonresponders, 18%; responders, 25%) were diagnosed with their first episode. Antidepressant medication at baseline and after the first EEG was heterogeneous due to the naturalistic design of the study (see online suppl. material: 1.1 Psychiatric Medication; for all online suppl. material, see www.karger.com/doi/10.1159/000517860), similar to other studies [12, 20]. About 55% of the nonresponder and 58% of the responder group did not receive any antidepressants at baseline. The other participants were on a single antidepressant (nonresponders 36%/responders 25%) or received a combination of 2 antidepressants (nonresponders 9%/responders 17%). Treatment strate-

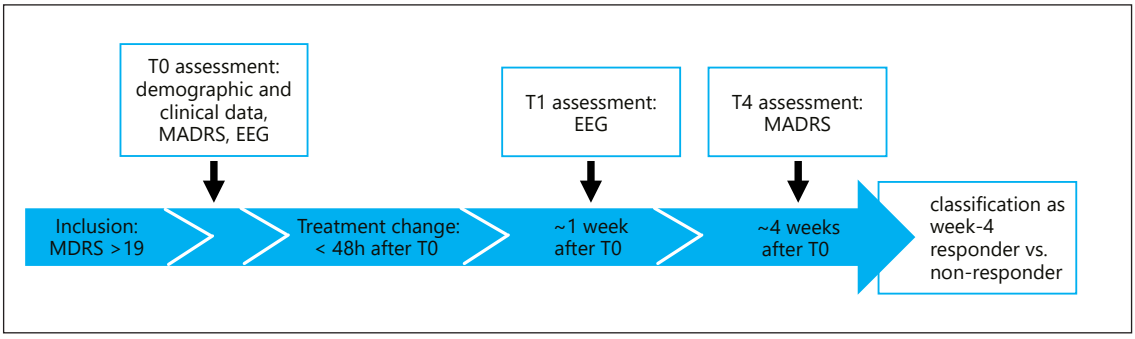

Fig. 1. Timeline of the study. MADRS, Montgomery-Asberg Depression Rating Scale.

gies established after T0 included switches to a different antidepressant or combination with other antidepressants, augmentation, or dose escalation.

Procedure

The study followed a naturalistic design and assessed patients treated in the in- and outpatient clinics of the Charité – Universitätmedizin Berlin, Campus Mitte. The study team had no influence on treatment plan decisions.

EEG was recorded before (baseline, T0) and about 1 week (T1) after the changes in or initiation of psychopharmacological treatment (days between T0 and T1, responders: 6.8 ± 0.83, min – max: 6–8 days; nonresponders: 7.5 ± 1.48, 6–10 days, $p = 1.24$, $t[43] = 1.57$). The time of the day for the assessments did not differ significantly between the 2 groups (T0: $t[43] = 1.31$, $p = 0.2$; T1: $t[43] = 0.763$, $p = 0.45$; data not shown) and within the 2 time points (responders: $t[11] = 0.58$, $p = 0.58$; nonresponders: $t[32] = 0.20$, $p = 0.84$; data not shown).

At baseline, all participants completed a self-report questionnaire on demographic data, the Edinburgh Handedness Inventory [37], and the German Multiple Choice Vocabulary Test (MWT) [38] as an estimate for premorbid verbal IQ. For baseline (T0) and follow-up (T1, T4), depressive symptoms were assessed using the MADRS. To assess melancholic features, the Mini-International Neuropsychiatric Interview [39] was used. Questionnaires and interviews were administered before the EEG recording. Antidepressant treatment changes were initiated after the T0 recording. The time line of the study is depicted in Figure 1.

Tasks and Stimuli

The study task (also described in [40]) consisted of alternating trials of a randomized consecutive series of face stimuli depicting sad or happy facial expressions [41]. Stimuli were presented on a CRT monitor positioned in front of the participants. EEG was recorded continuously during stimulus presentation. Each trial consisted of 5–8 consecutive faces displaying one emotion (e.g., happy) followed by the next trial of 5–8 consecutive faces displaying the other emotion (e.g., sad). The duration of face stimuli presentation was 1,000 ms. Trials were intercepted by short breaks (duration of about 10 s, in which participants were asked to indicate how they felt) and one long break (about 20 s, in which participants were prompted to also indicate how far they were able to emphasize with the face stimuli). To enhance attention, participants were instructed to press a button when they noticed a switch in emotional expressions. In sum, there were 12 trials of sad and 12 trials of happy facial stimuli intercepted by 4 short and one long break (see online suppl. material: 1.2 Experimental Task). Resting-state EEG was not assessed.

EEG Data Collection and Analysis

The EEG procedure was identical for both measurements (T0, T1). Participants were seated in a comfortable chair with a headrest in a sound and light-attenuated, not-electrically shielded room adjacent to the recording apparatus and the experimenter. The EEG was recorded continuously during visual stimulus presentation.

A BrainAmp amplifier with BrainVision Recorder software was used to record the scalp EEG signal (sampling rate 500 Hz, low-cut filter 0.016 Hz [i.e., time constant 9.947 s], high-cut filter 250 Hz, amplifier gain 5,000; Brain Products GmbH, Gilching, Germany). An EASYCAP-EEG cap (EASYCAP GmbH, Herrsching, Germany) with 33 Ag/AgCl electrodes (i.e., Fp1, Fp2, F3, F4, F5, F6, F7, F8, FC1, FC2, FC5, FC6, C3, C4, CP1, CP2, CP5, CP6, P3, P4, P7, P8, T7, T8, O1, O2, PO9, PO10, AFz, Fz, Cz, Pz, and POz) arranged according to the extended 10/20 system was used to capture the signal. The FCz electrode served as online reference, and the FPz electrode served as ground. Impedance at all electrodes was less than 10 kOhm.

Offline EEG analysis was performed using BrainVision Analyzer version 2.1 (Brain Products GmbH, Gilching, Germany) and EEGlab version v13.1.1 [42]. Following offline filtering of the continuous EEG signal (infinite impulse response zero-phase shift Butterworth filter; low cutoff: 0.5 Hz [i.e., time constant 0.318], 12 dB/octave; high cutoff: 70 Hz, 12 dB/octave; notch filter: 50 Hz with a symmetrical bandwidth of 5 Hz, 24 dB/octave), artifacts (e.g., ocular movements, electrocardiac artifacts, and muscle artifacts) were automatically corrected using the EEGLAB plugins Artifact Subspace Reconstruction version 0.13 [43] (EEGlab code: clean_asr(EEG, 20) and Automatic Artifact Removal version 1.3 [44] (EEGlab code: pop_autobsseog(EEG, [EEG.xmax], [EEG.xmax], EFICA, {'eigratio', [1000000]}, 'eog_fd', {'range', [1 3]})). In some instances, artifacts could not be corrected by these automatic procedures. In these cases, ICA-based correction was performed by manual elimination of the independent components corresponding to the artifact.

Before current source density transformation (order of splines: 4, maximum degree of Legendre polynomials: 10, approximation

Table 2. Self-rating scores of emotional state and empathy toward sad and happy faces

Time	Nonresponders (n = 33)		Responders (n = 12)		Responders versus nonresponders: Z, p value
	mean ± SD	T0 versus T1: Z, p value	mean ± SD	T0 versus T1: Z, p value	
Emotional state[1]					
T0	2.21±0.53	−0.97, 0.33	1.92±0.58	−0.96, 0.34	−1.36, 0.17
T1	2.10±0.45		1.85±0.55		−1.46, 0.14
Empathy happy faces[2]					
T0	2.39±0.63	−1.63, 0.10	2.42±0.51	−1.58, 0.11	−0.18, 0.86
T1	2.25±0.55		2.12±0.53		−0.63, 0.52
Empathy sad faces[2]					
T0	2.24±0.72	−0.74, 0.46	2.33±0.49	−1.18, 0.24	−0.33, 0.74
T1	2.15±0.57		2.12±0.53		−0.04, 0.96

Paired test: Wilcoxon-W test. Unpaired test: Mann-Whitney U test. Note: higher values indicate lower ratings of self-rated emotional state and empathy toward the face stimuli. [1] Self-reports of emotional state during EEG recording ("How do you feel?"). [2] Self-rated empathy toward faces ("To what extent were you able to empathize with the faces?").

parameter Lambda: 1.0e−005; unit: $\mu V/m^2$), voltage activity ±50 μV (artifact criterion) was flagged for later rejection. The continuous EEG signal was segmented from stimulus onset to 1,000 ms after stimulus onset and fast Fourier transformed (frequency resolution: 0.977 Hz) after the data had been weighted with a Hamming window that tapered the distal 5% of each segment (Hamming window with variance correction and symmetric window borders). As the result of the weighting functions, both ends of any 1,000-ms segment were weighted less. All segments that were not flagged as artifacts (see above) were averaged without overlap separately for the happy and the sad stimulus conditions. After averaging, power for alpha-1 (8–10 Hz) and alpha-2 (11–13 Hz) frequency bands was extracted separately for happy and sad face stimuli for frontal (left: mean of F3 and F5; right: mean of F4 and F6 electrodes) and occipital regions (left: O1; right: O2). Power for the theta band (4–7 Hz) was extracted for the frontal midline electrode AFz. All power values were ln-transformed. Alpha asymmetry scores were calculated as follows: $\ln(\text{alpha power}_{right}) - \ln(\text{alpha power}_{left})$. Processing and analysis were conducted blind to group assignment.

Analysis of Artifacts

To estimate differences in data quality, we compared the number of segments after artifact rejection, the number of eliminated independent components due to the artifact correction procedure, and the number of eye blinks before any correction procedure between groups and sessions. There were no significant group differences in these parameters (see online suppl. material: 1.3 Artifact Analysis).

Statistical Analyses

Statistical analyses were performed using the "Statistical Package for Social Sciences" (SPSS version 23, Chicago, SPSS Inc.). Normal distribution of EEG measures was inspected and is reported in the Results section. Normal distribution was tested with the Kolmogorov-Smirnov test with Lilliefors correction ($p > 0.05$), homogeneity of the error variances with Levene's test ($p > 0.05$), and homogeneity of covariances with Box's test ($p > 0.05$). Demographic data were compared using t tests and χ^2 tests as indicated. Variables that differed between groups were added as covariates as a control to the following analyses. As gender-specific effects have been reported regarding the assessed EEG parameters, gender was also included as a covariate.

To investigate changes in EEG parameters from baseline (T0) to week 1 (T1) between responders and nonresponders, we conducted 2 × 2 × 2 three-way mixed analyses of covariance (ANCOVAs) with group (responders and nonresponders) as the between-subject factor and the within-subject factors time (T0, T1) and emotion (happy, sad) for each frequency band of interest (i.e., frontal and occipital alpha-1 asymmetry, frontal and occipital alpha-2 asymmetry, and frontal midline theta).

Due to the exploratory nature of our study, ANCOVAs were conducted without adjustments for multiple comparisons. Significant interaction effects were broken down by simple effect analyses and interpretation of graphical plots. Significant main effects were further analyzed with post hoc paired t tests.

In a further exploratory analysis, we conducted a post hoc linear regression analysis to investigate the relations between the clinical treatment outcome (MADRS score) and EEG parameter(s) of interest. EEG parameter(s) of interest were those parameters that differed between responders and nonresponders. In these analyses, the percentage changes in the MADRS scores ($MADRS_{T1}/MADRS_{T0} \times 100$) served as the dependent variable. The EEG parameter change across assessments served as the independent variable, while age and gender served as further covariates. Note that ln-transformations of the EEG parameters were done after calculating the change scores, for example, $\ln(\text{alpha power}_{T0} - \text{alpha power}_{T1})$, as ln-transformation was only used for normalization of data.

Statistical significance was defined as $p < 0.05$ for all analyses.

Table 3. Frontal theta power, and frontal and occipital alpha asymmetry

	Nonresponse (n = 33)		Response (n = 12)	
	T0 (mean ± SD)	T1 (mean ± SD)	T0 (mean ± SD)	T1 (mean ± SD)
Frontal theta power, $\mu V/m^2$				
Happy	2.678±0.593	2.508±0.540	3.093±0.453	2.698±0.841
Sad	2.681±0.581	2.527±0.562	3.057±0.388	2.760±0.966
Frontal alpha asymmetry				
Alpha-1				
Happy	−0.083±0.354	0.046±0.257	−0.206±0.469	0.067±0.508
Sad	−0.073±0.325	0.039±0.252	−0.106±0.421	−0.027±0.468
Alpha-2				
Happy	−0.031±0.442	0.150±0.521	−0.046±0.454	0.096±0.584
Sad	−0.028±0.443	0.155±0.486	−0.049±0.378	0.106±0.579
Occipital alpha symmetry				
Alpha-1				
Happy	−0.050±0.658	−0.006±0.620	0.267±0.720	0.188±0.892
Sad	−0.014±0.687	−0.027±0.604	0.294±0.714	0.128±0.939
Alpha-2				
Happy	−0.126±0.724	−0.125±0.589	0.202±0.692	0.172±0.792
Sad	−0.157±0.735	−0.173±0.528	0.251±0.631	0.121±0.899

Shown are means and standard deviations for each group. Asymmetry was calculated: $\ln(\text{alpha}_{right}) - \ln(\text{alpha}_{left})$. T0, baseline EEG before changing of treatment; T1, EEG about 1 week after changing treatment.

Results

Behavioral Data

As shown in Table 2, there were no statistically significant between- and within-group differences in self-rating scores of emotional state and empathy toward sad and happy faces.

Electrophysiological Data

Table 3 shows asymmetry scores for alpha-1 and alpha-2 sub-bands, and frontal midline theta power for each group and condition. EEG power spectra for all electrodes and conditions (for both groups) are presented in the online suppl. material: 2.1 Results.

Frontal Alpha-1 Asymmetry

Frontal alpha-1 asymmetry scores were normally distributed for both groups. There was homogeneity of the error variances and homogeneity of covariances.

The mixed model three-way ANCOVA for frontal alpha-1 asymmetry showed a significant main effect of time ($F[1, 41] = 7.258$, $p = 0.010$), while there was no significant main effect of emotion ($F[1, 41] = 0.696$, $p = 0.409$), group ($F[1, 41] = 2.712$, $p = 0.107$), time × emotion ($F[1, 41] = 1.927$ $p = 0.173$), time × group ($F[1, 41] = 0.143$, $p = 0.708$), or group × emotion ($F[1, 41] = 0.114$, $p = 0.737$). There was a statistically significant three-way interaction effect of time × emotion × group ($F[1, 41] = 4.529$, $p = 0.039$). This effect indicates that the frontal alpha-1 asymmetry score differed in relation to emotions (happy or sad condition) and time in the two groups.

To break down the three-way interaction, we conducted simple effect analyses. In responders, the effect of emotion in alpha-1 asymmetry was statistically significant for T0 ($F[1, 41] = 4.320$, $p = 0.044$) but only showed a trend for T1 ($F[1, 41] = 2.928$, $p = 0.095$). In nonresponders, the effect of emotion in alpha-1 asymmetry was not statistically significant at T0 ($F[1, 41] = 0.007$, $p = 0.934$) and T1 ($F[1, 41] = 0.275$, $p = 0.603$).

Interpretation of the interaction graph (shown in Fig. 2) suggests that responders' mean alpha-1 asymmetry was higher for the sad than the happy condition at T0 with an opposite direction at T1, while in nonresponders, such differences were not apparent; mean alpha-1 asymmetry was largely similar for the happy and sad conditions at both sessions.

We repeated the analysis of our main result with only those participants who did not receive any psychiatric

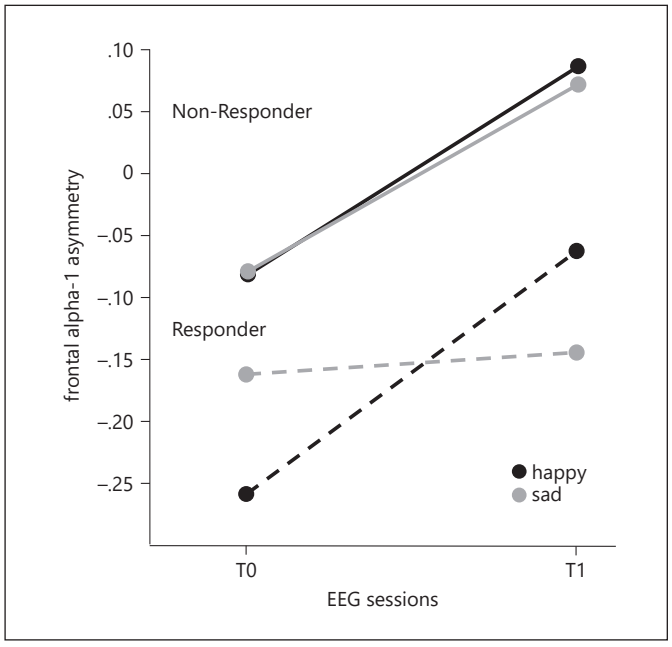

Fig. 2. Interaction graph for frontal alpha-1 asymmetry for responders and nonresponders at T0 and T1.

medication at T0 (nonresponders, $n = 18$; responders, $n = 7$). Again, the interaction emotion × time × response was significant ($F[1, 21] = 4.66$, $p < 0.043$).

The exploratory post hoc regression analysis showed that changes in the MADRS score ($MADRS_{T1/T0x100}$) were significantly predicted by the combination of changes in alpha-1 asymmetry from T0 to T1 (i.e., alpha-1 $asymmetry_{T0\text{-}T1,happy}$ and alpha-1 $asymmetry_{T0\text{-}T1,sad}$), age, and gender ($F[4, 44] = 4.62$, $p < 0.004$; $R^2 = 0.32$). The beta weights suggested that a decrease in the $MADRS_{T1/T0x100}$ score (i.e., symptom improvement) was significantly associated with an increase in the alpha-1 $asymmetry_{T0\text{-}T1,sad}$ score (i.e., lower asymmetry at T1 compared to T0; beta = −0.99, $T = 3.85$, $p < 0.001$; $R^2 = 0.27$) and with a decrease in the alpha-1 $asymmetry_{T0\text{-}T1,happy}$ score (i.e., higher asymmetry at T1 compared to T0, beta = 0.89, $T = 3.38$, $p < 0.002$; $R^2 = 0.22$). The beta weights for age and gender were not significant.

Frontal Alpha-2 Asymmetry

Alpha-2 frontal asymmetry scores were normally distributed for both groups, except for alpha-2 at T1 in the sad face condition. There was homogeneity of the error variances for all variables, except for alpha-2 asymmetry in the happy face condition at T1. There was homogeneity of covariances.

The mixed model ANCOVA showed a significant main effect of time ($F[1, 41] = 9.003$, $p = 0.005$). There were no further significant main or interaction effects (emotion: $F[1, 41] = 0.670$, $p = 0.418$; group: $F[1, 41] = 0.809$, $p = 0.210$; time × emotion: $F[1, 41] = 0.148$ $p = 0.702$; time × group: $F[1, 41] = 1.015$, $p = 0.320$; group × emotion: $F[1, 41] = 0.101$, $p = 0.752$; time × emotion × group: $F[1, 41] = 0.001$, $p = 0.974$).

Occipital Alpha-1 Asymmetry

Alpha-1 occipital asymmetry scores were normally distributed for all groups except for the happy face condition at T0 in the nonresponder group. There were homogeneity of the error variances and homogeneity of covariances.

The mixed model ANCOVA did not reveal any significant main or interaction effects (time: $F[1, 41] = 0.476$, $p = 0.494$; emotion: $F[1, 41] = 0.996$, $p = 0.324$; group: $F[1, 41] = 1.016$, $p = 0.319$; time × emotion: $F[1, 41] = 0.014$, $p = 0.907$; time × group: $F[1, 41] = 0.048$, $p = 0.827$; group × emotion: $F[1, 41] < 0.001$, $p = 0.998$; time × emotion × group: $F[1, 41] = 0.258$, $p = 0.614$).

Occipital Alpha-2 Asymmetry

Alpha-2 occipital asymmetry scores were normally distributed for the happy face condition. In the sad face condition, asymmetry scores were not normally distributed in the nonresponder group at T0 and at T1, and at T1 in the responder group. There were homogeneity of the error variances and homogeneity of covariances.

The mixed model ANCOVA showed a trend for a main group effect ($F[1, 41] = 3.416$, $p = 0.072$). There were no further significant main or interaction effects (time: $F[1, 41] = 0.053$, $p = 0.820$; emotion: $F[1, 41] = 0.204$, $p = 0.654$; time × emotion: $F[1, 41] = 2.935$, $p = 0.094$; time × group: $F[1, 41] = 0.042$, $p = 0.839$; group × emotion: $F[1, 41] = 0.513$, $p = 0.478$; time × emotion × group: $F[1, 41] = 0.099$, $p = 0.754$).

Frontal Midline Theta Power

Theta values were normally distributed for all groups except for the happy face condition at baseline in the nonresponder group. There was homogeneity of the error variances for theta at T0, but not at T1, and there was homogeneity of covariances.

The mixed model ANCOVA for the theta band showed no significant main or interaction effects (time: $F[1, 41] = 3.444$, $p = 0.071$; emotion: $F[1, 41] = 0.706$, $p = 0.406$; group: $F[1, 41] = 1.52$, $p = 0.225$; time × emotion: $F[1, 41] = 2.975$, $p = 0.092$; time × group: $F[1, 41] = 0.149$, $p = 0.701$; group × emotion: $F[1, 41] = 0.034$, $p = 0.854$; time × emotion × group: $F[1, 41] = 0.571$, $p = 0.454$).

Discussion

We compared early changes in alpha asymmetry and frontal midline theta power while presenting affective stimuli to responders and nonresponders to 4-week antidepressant treatment. Unexpectedly, only 27% of participants in our sample showed a treatment response, which is a lower percentage than in our former [45] and in other studies [46].

Our results showed a differential change in frontal alpha-1 asymmetry in the first week of treatment depending on the presented stimuli valence (happy vs. sad facial expressions) in responders compared to nonresponders. While asymmetry in the happy face condition was lower than that in the sad face condition at baseline, we found a different pattern 1 week after the initiation of treatment in the responder group. In contrast, we did not find such a pattern in nonresponders; frontal alpha-1 asymmetry was virtually identical for both stimulus conditions at both assessments. Reduction of depressive symptoms was generally associated with an increase in alpha-1 asymmetry in the happy face condition and with a decrease in the sad face condition across groups. These results fall in line with previous work demonstrating that early changes in EEG were associated with antidepressant response [12, 20, 21] and that particular differences in responders and nonresponders become more evident in change parameters as opposed to a single measurement at baseline only [20, 21].

However, in contrast to other studies, we did not find statistically significant group differences in occipital alpha-1 and alpha-2 asymmetry or frontal midline theta activity at baseline, nor were group differences observed regarding changes of these parameters from T0 to T1.

Our results on frontal alpha-1 asymmetry are in line with studies showing an early increase in the relative processing of positive versus negative affective stimuli after intake of antidepressants [31] and the relation of this differential processing to clinical outcome [34] and treatment response [33, 47]. The results of these and our study underline the importance of emotional processing in the course of depression and may point to a relation in the mechanisms of antidepressant action to the reactivity to emotional stimuli [47].

Frontal alpha asymmetry has also been interpreted in the light of tendencies to approach- and withdrawal-oriented motivational processes. It is discussed to reflect the individual motivational direction related to a given stimulus or an experimental situation [48]. Relative higher frontal alpha asymmetry scores, calculated as ln(alpha $power_{right}$) – ln(alpha $power_{left}$), have been associated with approach-oriented motivational processes. In comparison, relative lower frontal alpha asymmetry scores have been linked to avoidance/withdrawal-oriented motivational processes. In this framework, higher frontal alpha-1-asymmetry scores in response to sad compared to happy faces, as seen in the responder group at baseline in our study, may be interpreted as higher approach tendencies toward sad faces relative to happy faces. This may also be interpreted as a bias toward negative stimuli in the responder group at baseline, which is a finding that has been previously described for depressed patients [49, 50]. The changes to an opposite pattern 1 week later, that is, lower asymmetry to sad than happy faces, may indicate an alleviation of the negative response bias in the responder group due to initiation of antidepressant treatment [51]. This interpretation finds some support by our regression analysis across groups which found that an increase in asymmetry in the happy condition from T0 to T1, that is, an increase in approach to happy faces, together with a decrease in asymmetry in the sad condition from T0 to T1, that is, increase in withdrawal or decrease in approach to sad faces, was related to the 4-week reduction in depressive symptoms.

Apart from the approach/withdrawal interpretation of frontal alpha asymmetry, our results may indicate that early neurochemical effects of antidepressants relate to changes in the processing of emotional stimuli in those patients who showed a response at week 4 [32, 51]. Despite several findings, the neurobiology of frontal alpha asymmetry still remains unclear (see [52] for review).

Our results on frontal midline theta power differ from previous results on resting-state activity. We did not find significant group differences at baseline nor changes in theta activity associated with treatment response as reported in other studies (e.g., [23–25]). However, the mentioned studies investigated frontal theta cordance instead of simple frontal midline theta power. For the occipital alpha-2 asymmetry, we found a group difference similar to the one reported by Bruder et al. [19] for resting total alpha asymmetry; the mean asymmetry score was higher for the responder than the nonresponder group. However, for this main group effect, we found a statistical trend only. We did not find a significant difference in T0–T1 changes of occipital alpha-2 asymmetry, as was reported by Bares et al. [20] for resting asymmetry. Jaworska et al. [21] and Tenke et al. [22] investigated resting posterior alpha asymmetry, which was calculated across parietal and occipital electrodes. Both studies did not find differences in posterior alpha asymmetry between respond-

ers and nonresponders, neither at baseline [21, 22] nor in the 1-week changes in asymmetry between groups [21].

However, it is difficult to compare our results with those of other studies on alpha asymmetry and frontal theta power. The sample size of our study was relatively small, and our treatment responder rate was low. Moreover, the mentioned studies investigated resting-state activity instead of brain activity related to affective stimuli, as in our study. Different mechanisms may be at play during the resting state and emotional challenge. Further methodological differences exist in study design and analysis of the EEG parameters, limiting comparability of the results.

Several relevant limitations may reduce the impact of our study. A key limitation is the small sample size and the low rate of responders. As this was a naturalistic study, this may reflect current clinical challenges and potentially low response rates in pharmacological treatment in clinical practice. A further important limitation was that patients received different medication types. Another limitation due to the naturalistic study design is that we were also not able to include patients receiving a placebo, which would provide further information on whether effects are medication specific. A further limitation was the use of only 33 electrodes for the used CSD reference method and that the assessments did not take place in an electrically shielded room. The lack of mastoid electrodes precluded the use of these as a reference.

Taken together, our results of different patterns in alpha-1 asymmetry in response to sad and happy face stimuli in responders versus nonresponders suggest the usefulness of multiple assessments early in the treatment process during emotional challenge for predicting treatment response. Changes in the way emotional stimuli are being processed might be one of the early detectable indicators for a response. However, further studies are needed to shed light on these assumptions. To our best knowledge, this is one of the first studies comparing early changes in electric brain responses to affective stimuli in antidepressant responders and nonresponders. Large randomized controlled studies with assignment to different treatment regimens are needed to shed light on the specific effects and underlying mechanisms. Moreover, future research should expand the scope to other frequency bands.

Statement of Ethics

As indicated in the Methods section, this research was conducted ethically and in accordance with the World Medical Association Declaration of Helsinki as revised in 1989. The study protocol was approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin (Ethikkommission der Charité; reference No. EA1/080/10). Participants gave their written informed consent before enrollment in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.K.-S. and J.R. led the investigation, project administration, acquisition, analysis, interpretation of data, and visualization. K.K.-S. wrote the original draft. J.R. was responsible for supervision, software, and methodology. A.S. substantially contributed to the conception of the work and revised the work for important intellectual content. J.B. substantially contributed to the interpretation of data and revised the work for important intellectual content. E.B. substantially contributed to the acquisition of data and revised the work for important intellectual content.

All authors approved of the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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