

# Current Source Density Measures of Electroencephalographic Alpha Predict Antidepressant Treatment Response

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**Background:** Despite recent success in pharmacologic treatment of depression, the inability to predict individual treatment response remains a liability. This study replicates and extends findings relating pretreatment electroencephalographic (EEG) alpha to treatment outcomes for serotonergic medications.

**Methods:** Resting EEG (eyes-open and eyes-closed) was recorded from a 67-electrode montage in 41 unmedicated depressed patients and 41 healthy control subjects. Patients were tested before receiving antidepressants including a serotonergic mode of action (selective serotonin reuptake inhibitor [SSRI], serotonin and norepinephrine reuptake inhibitor, or SSRI plus norepinephrine and dopamine reuptake inhibitor). EEG was quantified by frequency principal components analysis of spectra derived from reference-free current source density (CSD) waveforms, which sharpens and simplifies EEG topographies, disentangles them from artifact, and yields measures that more closely represent underlying neuronal current generators.

**Results:** Patients who did not respond to treatment had significantly less alpha CSD compared with responders or healthy control subjects, localizable to well-defined posterior generators. The alpha difference between responders and nonresponders was greater for eyes-closed than eyes-open conditions and was present across alpha subbands. A classification criterion based on the median alpha for healthy control subjects showed good positive predictive value (93.3) and specificity (92.3). There was no evidence of differential value for predicting response to an SSRI alone or dual treatment targeting serotonergic plus other monoamine neurotransmitters.

**Conclusions:** Findings confirm the value of EEG alpha amplitude as a viable predictor of antidepressant response and suggest that personalized treatments for depression may be identified using simple electrophysiologic CSD measures.

**Key Words:** Alpha rhythm, antidepressant treatment response, current source density (CSD), depression, principal components analysis, quantitative EEG (qEEG)

Pharmacologic treatments for major depressive disorder (MDD) have long focused on monoamine mechanisms, with the early success of tricyclic and monoamine oxidase inhibitor antidepressants and marked by the advent of selective serotonin reuptake inhibitors (SSRIs). Despite these advances, the failure rate for any specific treatment imposes formidable delays in relief from depression in patients for whom hopelessness and discouragement are already a concern. Without objective tests indicating the likelihood of an individual's response to treatment, the risks to the patient grow with each failure. A reliable, objective, and readily available measure capable of differentiating between those who may or may not respond to specific treatments would find a much-needed place in clinical practice.

The alpha rhythm of the electroencephalogram (EEG) is a non-invasive and cost-effective index of the tonic state of the brain. The classical view of resting EEG alpha is of a posterior,<sup>1</sup> 8 Hz to 13 Hz idling rhythm characteristic of a relaxed, wakeful state, which is blocked (desynchronized) when the individual is alert or when vi-

sual processes are engaged by opening the eyes. An inverse association has been reported between scalp-recorded EEG alpha and local positron-emission tomography perfusion (3). Feige *et al.* (4) also reported an inverse association between posterior alpha (quantified by Independent Components Analysis) and the functional magnetic resonance imaging blood oxygenation level-dependent response in cortical visual regions, but not in subcortical visual or reticular thalamic nuclei, which have also been implicated in the generation and synchronization of alpha (5–8). Alpha is also generated within the ventral visual stream, although its laminar organization differs considerably across cortical regions (9).

Electroencephalographic alpha has found extensive use as an index of relative cortical deactivation (i.e., greater alpha, less activation) in studies of depressive disorders. In early studies, patients having a depressive disorder and elderly adults having a prior depressive disorder showed greater EEG alpha power than healthy control subjects (10,11). A number of additional studies have reported abnormal regional hemispheric asymmetries of alpha in individuals having a depressive disorder, with relatively less activity in left frontal (12–15) and right parietal regions (16–19).

There is evidence that EEG alpha may differentiate patients who clinically respond to pharmacologic treatment from those who do not. Ulrich *et al.* (20) found increased posterior alpha in depressed patients who subsequently responded to amitriptyline. More recently, Bruder *et al.* (21) reported encouraging findings for predicting response to fluoxetine. Responders had greater alpha than nonresponders, with differences being topographically and functionally consistent with the classic alpha rhythm, i.e., evidence of reduced cortical activity in responders over posterior regions. They

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<sup>1</sup>Additional alpha rhythms include sensorimotor  $\mu$ , a temporal third rhythm (1), and sleep spindles (2).

**Table 1.** Antidepressant Treatments

	Responders		Nonresponders	
	<i>n</i>	Dosage <sup>a</sup>	<i>n</i>	Dosage <sup>a</sup>
<b>Monotherapy</b>				
Escitalopram (SSRI)	7	20 (10–40)	6	25 (20–40)
Fluoxetine (SSRI)	0	—	2	60
Sertraline (SSRI)	1	50	0	—
<b>Dual Therapy</b>				
Escitalopram (SSRI)	12	40 (7.5–40)	3	40 (20–40)
Plus Bupropion (NDRI)		350 (150–450)		450 (400–450)
Duloxetine (SNRI)	5	60 (30–120)	1	90
Venlafaxine (SNRI)	3	375 (125–375)	1	375

NDRI, norepinephrine and dopamine reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

<sup>a</sup>Median dosage in milligrams (range).

also found SSRI responders to differ from nonresponders in alpha symmetry, with responders showing relatively less cortical activity over right posterior regions. Neither alpha power nor asymmetry changed following treatment, which is consistent with alpha being a stable trait characteristic (22–24).

The present study was designed to confirm the predictive value of EEG alpha amplitude and asymmetry in a larger, independent sample of patients having a depressive disorder, and to extend the prior study in the following ways: First, we examined the predictive value not only for patients receiving an SSRI alone but also for those receiving dual treatment with an SSRI plus bupropion (i.e., a noradrenaline/dopamine reuptake inhibitor) or an antidepressant with a dual mechanism of action (duloxetine or venlafaxine, both serotonin/noradrenaline reuptake inhibitors). Second, to better identify and describe spectral topographic differences of interest, a dense recording montage (67 channels) and high-resolution EEG methods were used. Specifically, we used current source density (CSD) measures (25,26), which reduce volume conduction from distal sites, sharpen spatial resolution, and avoid problems associated with the recording reference (27,28). In contrast to re-referencing approaches to the ubiquitous reference problem for EEG recordings, CSD measures are unique (i.e., identical waveforms for any reference) and are more closely related to neuronal activity, indicating the strength of underlying current generators as radial (transcranial) current flow (25,26,29,30). Consequently, CSD measures are less likely to mislocalize activity than their reference-dependent counterparts. Third, CSD measures were quantified using frequency principal components analysis (fPCA) to obtain measures for empirically derived frequency bands. Using this technique, Tenke and Kayser (29) identified factors with peaks corresponding to alpha subbands, including a high-frequency factor and a low-alpha/theta factor that included activity typically classified as theta (i.e., between 4 Hz and 8 Hz). Based on prior findings, we predicted that patients who responded to a serotonin reuptake inhibitor would show greater global alpha than nonresponders and also differ in their alpha asymmetry. Moreover, given evidence that pretreatment EEG theta also predicts antidepressant response (31–34), we examined whether the predicted differences between responders and nonresponders would be most prominent for the low-alpha/theta factor.

## Methods and Materials

### Participants

Outpatients (*n* = 41; 17 male patients) from the Depression Evaluation Service at the New York State Psychiatric Institute and

healthy control subjects (*n* = 41; 17 male subjects) with no history of psychopathology were recruited from the New York metropolitan area. Participants were right-handed, as indicated by their Laterality Quotient (LQ > 0) on the Edinburgh Inventory (35). Participants were excluded for any of the following reasons: serious suicide risk, current substance use disorders (including alcohol abuse), psychotic disorders, seizure disorder, a history of head trauma, or other neurological disorder. Control participants were screened using the Structured Clinical Interview for DSM-IV Axis I Disorders, Nonpatient Edition (36) to exclude those with current or past psychopathology. The diagnostic assessment and treatment of patients was carried out by research psychiatrists. Patients met DSM-IV criteria for MDD (*n* = 22), dysthymia (*n* = 7), both disorders (*n* = 10), or depression not otherwise specified (*n* = 2). Five patients had a comorbid anxiety disorder. Beck Depression Inventory (37) scores of patients ranged from 13 to 55 (mean = 24.0 ± 8.3; *n* = 39). All participants were paid \$15 per hour. The study was approved by the institutional review board, and all participants signed an informed consent form.

Patients were tested after being unmedicated for a minimum of 7 days (6 weeks for two patients receiving fluoxetine), but most patients had been drug-free for considerably longer or had not previously been treated with an antidepressant. Patients then received one of six treatments listed in Table 1, all of which included a serotonin reuptake inhibitor. A total of 16 patients received an SSRI alone, 15 received an SSRI plus a noradrenaline/dopamine reuptake inhibitor, and 10 received a serotonin/noradrenaline reuptake inhibitor. After 8 to 12 weeks of treatment, clinical response was assessed using the Clinical Global Impression Improvement scale (38) by a rater who was blind to the EEG data. Patients who had a Clinical Global Impression Improvement scale rating of “much improved” or “very much improved” were considered responders (*n* = 28) and all other patients were considered nonresponders (*n* = 13). The final dosage levels for each antidepressant were comparable in responders and nonresponders (Table 1), who also did not differ from each other or from healthy control subjects in gender, age, education, or handedness (Table 2). There was no significant difference between responders and nonresponders in severity of depression on Beck Depression Inventory (BDI) or Hamilton Depression Rating Scale (HAM-D) (39) before treatment, but responders had

**Table 2.** Characteristics of Treatment Responders, Nonresponders, and Control Subjects

	Responders	Nonresponders	Control Subjects
Gender (F/M)	16/12	8/5	24/17
Age (Years) <sup>a</sup>	34.9 ± 10.8	36.4 ± 9.8	33.1 ± 11.6
Education (Years) <sup>a</sup>	16.4 ± 1.7	15.9 ± 4.8	15.9 ± 2.7
Handedness (Laterality Quotient) <sup>a</sup>	76.8 ± 20.2	79.9 ± 21.7	86.0 ± 18.4
Beck Depression Inventory <sup>a,b</sup>	23.0 ± 9.0	26.0 ± 6.3	2.1 ± 2.9
Pretreatment HAM-D <sup>a</sup>	14.8 ± 4.1	17.4 ± 5.4	
Posttreatment HAM-D <sup>a,c</sup>	4.0 ± 2.6	14.8 ± 5.7	

BDI, Beck Depression Inventory; F, female; HAM-D, Hamilton Depression Rating Scale; M, male.

<sup>a</sup>Mean ± SD.

<sup>b</sup>Control subjects (*n* = 38) had significantly lower BDI than responders (*n* = 27) and nonresponders (*n* = 12) [*F*(2,74) = 120.6, *p* < .001] but the patient groups did not differ from each other.

<sup>c</sup>Responders (*n* = 22) had significantly lower HAM-D scores than nonresponders (*n* = 13) posttreatment [*t*(33) = 6.49, *p* < .001].

significantly lower HAM-D scores than nonresponders posttreatment.

### EEG Recordings

The EEG was recorded from 67 expanded 10-20 system locations (40) with a Lycra stretch electrode cap (ActiveTwo EEG system) (41) using an active reference at sites PO1 (common mode sense) and PO2 (driven right leg). Along with 11 midline sites, the montage consisted of 28 homologous pairs over the left and right hemispheres, extending laterally to include the inferior temporal lobes (cf. [42]). Electrode placement was optimized by direct measurement of landmarks (nasion,inion, auditory meatus, vertex). The scalp placements were prepared using a conventional water-soluble electrolyte gel and the interface verified (ActiView) (41). Additional electrodes above and below the right eye and at the left and right outer canthi provided bipolar electro-oculogram recordings for identification and rejection of blinks and eye movements.

### EEG Acquisition and Artifact Procedures

Resting EEG was recorded while subjects sat quietly in a sound-attenuated booth during four 2-minute resting EEG periods (eyes-closed [C] and eyes-open [O] counterbalanced across blocks: COOC or OCCO; order alternated across subjects in each group). Subjects were instructed to remain still and inhibit blinks or eye movements during each recording period. During the eyes-open condition, subjects fixated on a central cross. Continuous EEG was acquired at 256 samples/second using the 24-bit Biosemi system (Biosemi, Amsterdam) and nose-referenced data were exported into 16-bit Neuroscan format using Polyrex (43) to remove offsets, optimize scaling, and re-reference the EEG.

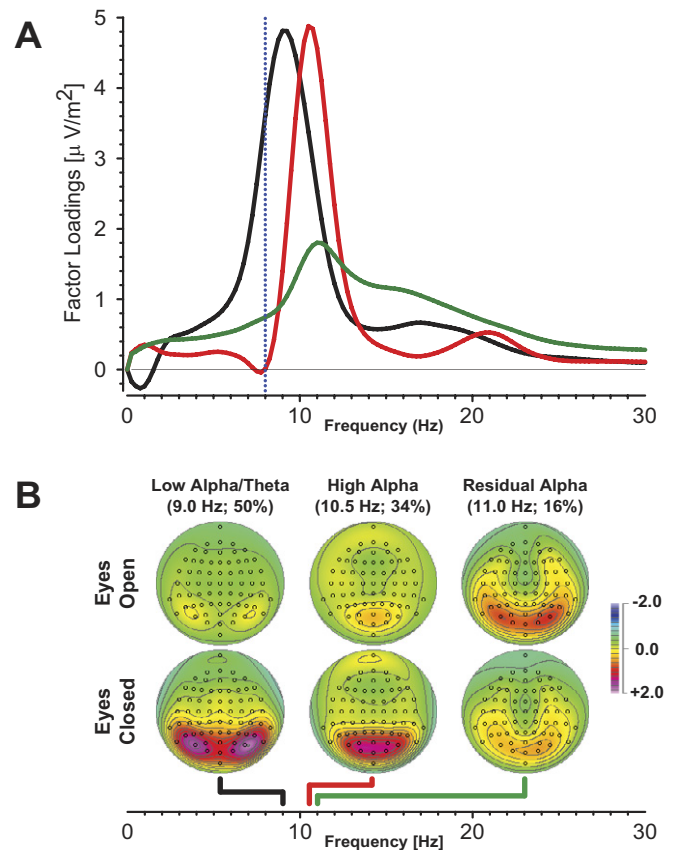
Continuous data were segmented into 1-second epochs every .5 seconds (50% overlap). After rejection of epochs contaminated by blink or eye movement ( $\pm 100 \mu\text{V}$  threshold, followed by interactive rejection), a reference-free approach identified isolated EEG channels containing amplifier drift, residual eye activity, muscle, or movement-related artifacts (44), which were then replaced by spherical spline interpolations (45) from artifact-free channels whenever possible (i.e., fewer than 25% affected channels). Artifact detection and electrode interpolation were verified interactively and accepted epochs were screened for electrolyte bridges (46).

### CSD Amplitude Spectra

Artifactual EEG epochs for each subject were transformed into reference-free current source density estimates ( $\mu\text{V}/\text{cm}^2$  units; 10 cm head radius; 50 iterations;  $m = 4$ ;  $\lambda = 10^{-5}$ ) (29) using a spherical spline surface Laplacian (26,45; MATLAB-based CSD toolbox and tutorial: 47). The mean offset of each epoch was eliminated, a 50% Hanning taper window was applied, and zeros were added to the beginning and end of each epoch to yield power spectra with a resolution of .25 Hz (i.e., 4 seconds at 1024 points/epoch). Averaged power spectra were then computed (48) for each condition (closed/open) and converted to amplitude spectra by square root transformation (i.e., root mean square). After eliminating the first (direct current) point, the next 299 points were used in subsequent analyses (i.e., .25–74.75 Hz).

### Frequency Principal Components Analysis (fPCA) of CSD

Averaged CSD amplitude spectra (299 frequency points = variables) were submitted to unrestricted, covariance-based fPCA (29), with 67 electrodes, 2 conditions, and 82 participants (i.e., 10,988 cases), followed by varimax rotation of the covariance loadings ([49]; also see [50,51]). CSD-fPCA yields meaningful, physiologically identifiable spectral components that conform to the underlying data, while isolating and removing artifact (e.g., electromyogram

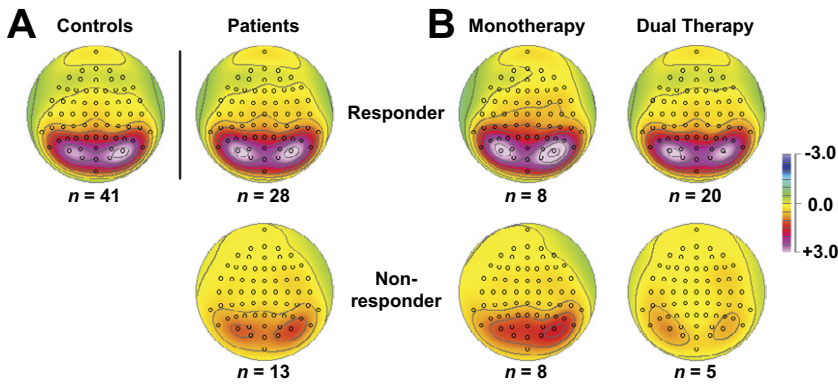


**Figure 1.** (A) Rotated CSD-fPCA factor loading waveforms for filtered spectra consisted of low-alpha/theta (black), high-alpha (red), and residual-alpha (green). The rising slope of the low-alpha/theta waveform includes frequencies below 8 Hz (conventional theta band, left of the dotted blue line), while the residual-alpha component includes low-beta. (B) Corresponding factor score topographies show that all three alpha factors were greatest at posterior sites, as previously described (29). Low-alpha/theta and high-alpha were greater for eyes-closed but residual alpha was not. Dots indicate the spherical positions of electrodes (nose at top). Colored lines below maps point to the peak frequencies of corresponding factor loadings on the common abscissa (colors as shown in [A]).

and electro-oculogram activity extracted as distinct components), thereby reducing noise and eliminating reference-related errors. Six factors accounted for 95% of the variance of amplitude spectra (cf. Section S1 in Supplement 1), three of which (48% total variance) had clear peaks in alpha (low-alpha/theta, high-alpha, and residual alpha, cf. [29]) and had posterior maxima for eyes-closed.<sup>2</sup>

Although preliminary results for these three alpha factors revealed significant group differences (52), a comparison of corresponding factor loading waveforms extracted separately for control subjects and patients indicated variability in the residual alpha factor loadings for patients that was eliminated by using these three factors as a spectral filter (Section S2 in Supplement 1). This approach exploits the capacity of fPCA to isolate and remove overlapping broadband activity (cf. Figure S1 in Supplement 1). A varimax-fPCA of these data led to highly consistent alpha factors. As shown in Figure 1A and 1B, these included low-alpha/theta (black lines, 9 Hz peak, 50% variance of filtered waveforms; waveform rise below 8 Hz) and high-alpha (red lines, 10.5 Hz, 34% variance) fac-

<sup>2</sup>We analyzed only alpha components, noting that their orthogonality allows them to be analyzed separately or in combination, without concern about the shared variance of nonorthogonal methods.



**Figure 2.** (A) Condition-dependent (eyes-closed minus eyes-open) difference topographies, averaged across high-alpha and low-alpha/theta factors for control subjects, responders, and nonresponders. Alpha reduction was pronounced for nonresponders. (B) Corresponding condition-dependent topographies for patients treated with a monotherapy or dual therapy. Both nonresponder groups showed a marked alpha reduction compared with responders.

tors, with characteristic lateral and midline posterior maxima, respectively, for eyes-closed. The residual alpha factor (green lines, 11 Hz, 16% variance) will not be further considered, because it included a substantial low-beta contribution (12–20 Hz) and a maximum for eyes-open (i.e., a reversed condition effect), neither of which are characteristic of alpha activity.

### Statistical Analyses

By virtue of the spatial sharpening and removal of ambiguity with CSD, low-alpha/theta and high-alpha may be concisely quantified as means across sites spanning these well-defined maxima: P9/10, P7/8, P5/6, PO7/8, PO3/4, O1/2 for low-alpha/theta; PO7/8, PO3/4, O1/2, POz, Oz for high-alpha. Neither the overall topographies of posterior condition-dependent alpha nor repeated measures analysis of variance (ANOVA), including hemisphere (left, right) as a within-subject factor, suggested differential alpha asymmetries between groups. Consequently, regional alpha means were subjected to a simpler repeated measures ANOVA (GLM procedure) (53) for *Alpha Frequency* (low-alpha/theta, high-alpha) and *Condition* (eyes-closed, eyes-open), with *Group* (control, responder, nonresponder; or responder, nonresponder for patients only) and *Gender* (male, female) as between-subjects factors and *Age* as a covariate. An exploratory analysis was also conducted using *Treatment* (monotherapy, dual therapy) and *Response Group* (responder, nonresponder) as between-subjects factors, excluding *Gender* because of insufficient cell sizes.

Based on our prior study (21), we predicted that patients with greater alpha than expected for control subjects would respond well to serotonin reuptake inhibitor treatment, whereas those with less alpha than expected for control subjects would not. This prediction was tested using the median of condition-dependent alpha for healthy control subjects (eyes-closed minus eyes-open, averaged across low-alpha and high-alpha factors) to classify patients as having greater alpha (predicted to be responders) or less alpha (predicted nonresponders) than healthy control subjects. The capacity of condition-dependent alpha to predict treatment outcome was also explored using logistic regression. The association between condition-dependent alpha and measures related to depression (e.g., BDI and HAM-D) were examined using product-moment correlations.

### Results

Alpha topographies were consistent across the three groups, but nonresponders showed substantially less alpha than responders and control subjects, particularly in the eyes-closed condition. The smaller condition-dependent alpha in nonresponders is illustrated in Figure 2A, and this group difference was supported by a significant *Condition*  $\times$  *Group* interaction,  $F(2, 75) = 3.56, p = .033$ .

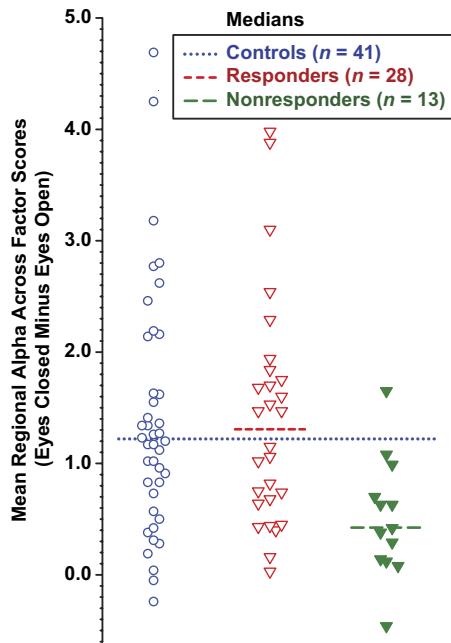
No additional *Group* effects attained significance, and there were no significant *Gender* interactions.<sup>3</sup> An *Age* (covariate) effect [ $F(1,75) = 12.0, p = .001$ ; corresponding Pearson  $r = -.41, p < .001$  for grand mean] indicating alpha decreases with age and a *Condition*  $\times$  *Age* interaction [ $F(1,75) = 10.9, p = .001$ ; corresponding Pearson  $r = -.38, p < .001$  for mean closed-minus-open difference] were also observed, but they did not interact with *Group*. Aside from the defining *Condition* effect [ $F(1,75) = 36.4, p < .001$ ; cf. Figure 1], there were no additional significant effects.

When the ANOVA model was restricted to patients (i.e., responders vs. nonresponders), the *Condition*  $\times$  *Response Group* effect was prominent [ $F(1,36) = 7.86, p = .008$ ], and a *Response Group* effect attained significance [ $F(1,36) = 4.71, p = .037$ ] but the *Age* effects did not. *Response Group* did not interact with *Alpha Frequency* (low vs. high), and no significant *Condition*  $\times$  *Response Group* effect was observed for separate ANOVA models for low-alpha and high-alpha factors, suggesting that the alpha reduction in nonresponders is a shared property that is maximal for eyes-closed and cuts broadly across alpha subbands (Section S3 in Supplement 1).

The marked difference in alpha between nonresponders and responders contrasts with the lack of differentiation between monotherapy and dual therapy, evident in Figure 2B. The exploratory ANOVA in patients (i.e., *Response Group* and *Treatment* as between-group factors; *Age* covariate) replicated the *Condition*  $\times$  *Response Group* effect,  $F(1,36) = 7.23; p = .011$ , but revealed no significant effects or interactions involving *Treatment*.

The value of these alpha scores for predicting treatment response was examined by classifying patients as to whether they had prominent alpha above the median for control subjects (dotted line in Figure 3; predicted responders) or less alpha than the control median (predicted nonresponders). By this classification, 14 of the 15 patients with prominent alpha responded to treatment, whereas only 14 of 26 patients with less alpha were responders (Fisher's exact test, two-tail  $p = .014$ ). This indicates that prominent alpha had a high positive predictive value of 93.3 (response rate for those predicted to be responders) and specificity of 92.3 (percentage of nonresponders predicted to be nonresponders). In contrast, sensitivity was only 50.0, and negative predictive value was 46.1, with an overall predictive value of 63.4. Eyes-closed minus eyes-open alpha was also significantly correlated with posttreatment HAM-D ( $r = -.35, n = 35, p = .04$ ) but not with pretreatment HAM-D ( $r = -.14, n = 41, ns$ ) or BDI ( $r = -.12, n = 39, ns$ ). Logistic regression also indicated that posterior condition-dependent alpha was predictive of treatment response (Wald test = 6.183,  $df = 1, p = .013$ ).

<sup>3</sup>However, the *Condition*  $\times$  *Group* interaction was present for female subjects [ $n = 48; F(2,44) = 4.27, p = .02$ ] but not for male subjects [ $n = 34; F(2,60) = .95, ns$ ].



**Figure 3.** Scatterplot of mean condition-dependent (eyes-closed minus eyes-open) posterior alpha, averaged across factors for control subjects, responders, and nonresponders. The median for control subjects (dotted line) was comparable with that for responders (short dashes) but differed markedly from that for nonresponders (long dashes).

#### Supplementary Analyses: Conventional EEG Measures and Low-Density CSD

Even though high-resolution CSD measures were crucial for the present study, we also submitted a reduced-electrode CSD montage to fPCA, resulting in significant findings (Section S4 in Supplement 1). In addition, nose-referenced EEG power spectra were analyzed at standard 10-20 system sites to provide a bridge to the literature using conventional low-resolution EEG in alpha and theta bands. Although group differences in alpha showed trends consistent with those reported for CSD measures, they were not statistically significant and alpha asymmetry did not differ between groups (Section S5 in Supplement 1). However, an ANOVA of EEG theta revealed one significant group effect: a *Group × Condition × Electrode* interaction in which the slope of the anterior-to-posterior increase in power for eyes-closed (i.e., also seen in maps at low-alpha/theta frequencies; Figure S5 in Supplement 1) was flatter in nonresponders (Figure S6 in Supplement 1).

#### Discussion

These findings replicate, extend, and formalize the previous finding (21) that depressed patients with prominent (large amplitude) EEG alpha benefit from treatment with a serotonin reuptake inhibitor. Patients who failed to respond to these antidepressants had markedly less alpha than responders and healthy control subjects. The present study was based on independent and considerably larger samples of depressed patients and healthy adults. Additionally, the EEG was recorded at a higher spatial resolution and further enhanced by CSD measures, yielding reference-independent topographies that clearly implicate posterior anatomical regions in the generation of these condition-dependent alpha effects. A simple classification scheme, based on median alpha for healthy control subjects, yielded predictions of treatment outcome with a surprisingly high positive predictive value and specificity.

There was no evidence to support a differential value for predicting response to SSRI monotherapy as opposed to dual therapy targeting both serotonergic and nonserotonergic neurotransmitters. These results are consistent with the view of alpha as a marker for serotonin reuptake inhibitor responsiveness. In contrast to our previous findings (21), treatment response was not related to hemispheric asymmetry of posterior alpha. Although the reason for the lack of replication of the alpha asymmetry findings is unclear, alpha asymmetry is known to be less reliable than alpha power (21–24) and may be influenced by a number of moderator or mediator variables (18).

#### Advantages, Caveats, and Constraints

The findings on the value of alpha as a predictor of treatment outcome are quite encouraging, but additional study is required with diverse treatments (e.g., nonserotonergic antidepressants, cognitive behavioral therapy, or placebo) to determine whether the prediction uniquely reflects a serotonergic response. Using alpha levels in healthy control subjects as the threshold cutoff (cf. (21) proved again to be successful for predicting treatment response. Positive predictive value and specificity were very high (>90%), the clinical implication being that depressed patients having prominent alpha can be predicted to be responsive with a high degree of confidence. However, sensitivity was low (50%); about half of the responders had alpha below the control median and were therefore not predicted to be responders. It is not known how many responders may have been placebo responders, shown spontaneous remission, or otherwise not been true drug responders. Further studies should explore other alpha thresholds, as well as combining alpha with other electrophysiologic (32,54) or neurocognitive (55) measures to improve prediction of treatment response. Also, despite evidence that EEG alpha has high reliability and heritability (21–24), few studies have directly examined whether acute or chronic administration of an SSRI alters alpha in depressed patients. A multisite study is now underway assessing neuroimaging, electrophysiologic, and neurocognitive measures before and after 1 week of SSRI or placebo to further examine their differential predictive value.

The observed differences in alpha were robust and used methods that unambiguously localized the effect to posterior EEG generators. Another fundamental advantage of CSD-fPCA is that it improves the quality of the data by separating and removing sources of artifact. For example, electromyogram and residual electro-oculogram, which are broadly distributed and vary with the recording reference, are isolated as separate CSD factors (cf. Figure S1 in Supplement 1). Although the generators of these factors may largely be outside the braincase and might otherwise obscure the effects reported here, they nevertheless represent physiological activity that could be separately explored by CSD-fPCA.<sup>4</sup>

#### Relationship to Activity in the Theta Band

As previously observed (29), the spectral loadings of the low-alpha/theta factor extend below the conventional 8 Hz border into theta. Consequently, conventional quantitative EEG measures based on standard frequency band cutoffs would unjustifiably split the factor in two, just below its peak (Figure 1A; Figures S4 and S5 in Supplement 1). Therefore, some differences reported here between treatment responders and nonresponders might have previously been attributed to theta activity.

Using imipramine, Knott *et al.* (31) reported a trend for greater

<sup>4</sup>Preliminary analysis of the remaining components identified in Figure S1 in Supplement 1 suggested no additional differences related to the treatment response.

alpha, but significantly less theta, in treatment responders. For fluoxetine, Cook *et al.* (56) reported differences in theta band cordance, a measure related to the local Laplacian but derived from a complex combination of relative and absolute power. Additional quantitative EEG studies of treatment response have focused on midline frontal theta as identified by low resolution electromagnetic tomography (LORETA). Greater theta current density, localized by LORETA to the anterior cingulate cortex, has been reported for patients who responded to treatment with nortriptyline (33), citalopram, or reboxetine (32). Korb *et al.* (34) also reported greater theta current density for responders than nonresponders treated with fluoxetine or venlafaxine but not between placebo responders and nonresponders. Given the secondary midline topography of our low-alpha/theta factor, midline findings might be anticipated<sup>5</sup> but differences between responders and nonresponders were not supported in analyses (Section S3 in Supplement 1). Moreover, both low-alpha/theta and high-alpha were required to reliably differentiate between responders and nonresponders. Conventional EEG analysis did show a reduction in anterior-to-posterior gradient of condition-dependent theta power in nonresponders (Section S5 in Supplement 1). We conclude that the observed group differences in the low-alpha/theta factor do not reflect theta or midline frontal theta, in particular, but rather are specific to classic posterior alpha.

The identified alpha subbands and an absence of a distinct theta are consistent with the findings of Shackman *et al.* (57), based on a spectral factor analysis of common-average EEG. These investigators suggested that alpha subbands provide no advantage over the broader alpha band in describing differences related to temperament or task demands. Although the two CSD-fPCA factors likewise do not differentially predict treatment response, there is no a priori rationale for generalizing to other clinical or physiological classifications. It should also be noted that these findings discount the possibility that a simple shift between two distinct spectral components is involved (e.g., alpha-slowness).

### Alpha and Treatment Response

Previous work suggests that resting alpha is a stable trait characteristic (22–24) and alpha differences between depressed patients and control subjects (10) or between treatment response groups (21) persist following treatment. Condition-dependent posterior alpha was also found to be greatest in individuals with a strong familial risk for depression (i.e., both parents having MDD) (58). Consequently, prominent alpha in patients may be a trait marker for a form of depression that is responsive to serotonergic agents. The correspondence between serotonergic activity and behavioral arousal (59) and the inverse relationship between posterior alpha and physiological or emotional arousal (60) may both have implications for depression and serotonin reuptake inhibitor response. Further study is, however, needed to identify their relevance for different forms of depression.

The present study exploited the tonic nature of posterior EEG alpha and the capacity of high-resolution CSD-fPCA to identify and quantify neuronal generator patterns to produce a promising predictor of antidepressant response. The factor score topographies suggest that a considerably smaller array of electrodes may provide a sufficient predictor, which is supported by exploratory findings (Section S4 in Supplement 1). It is also hoped that the judicious choice of additional, phasic electrophysiologic measures (e.g., loudness dependency of auditory evoked potential) (32,54) may provide a complementary source of information on serotonergic function to further improve outcome predictions for a range of treatments.

<sup>5</sup>Phase-locking of midline with posterior activity is also possible (cf. [29]).

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Supplementary material cited in this article is available online.

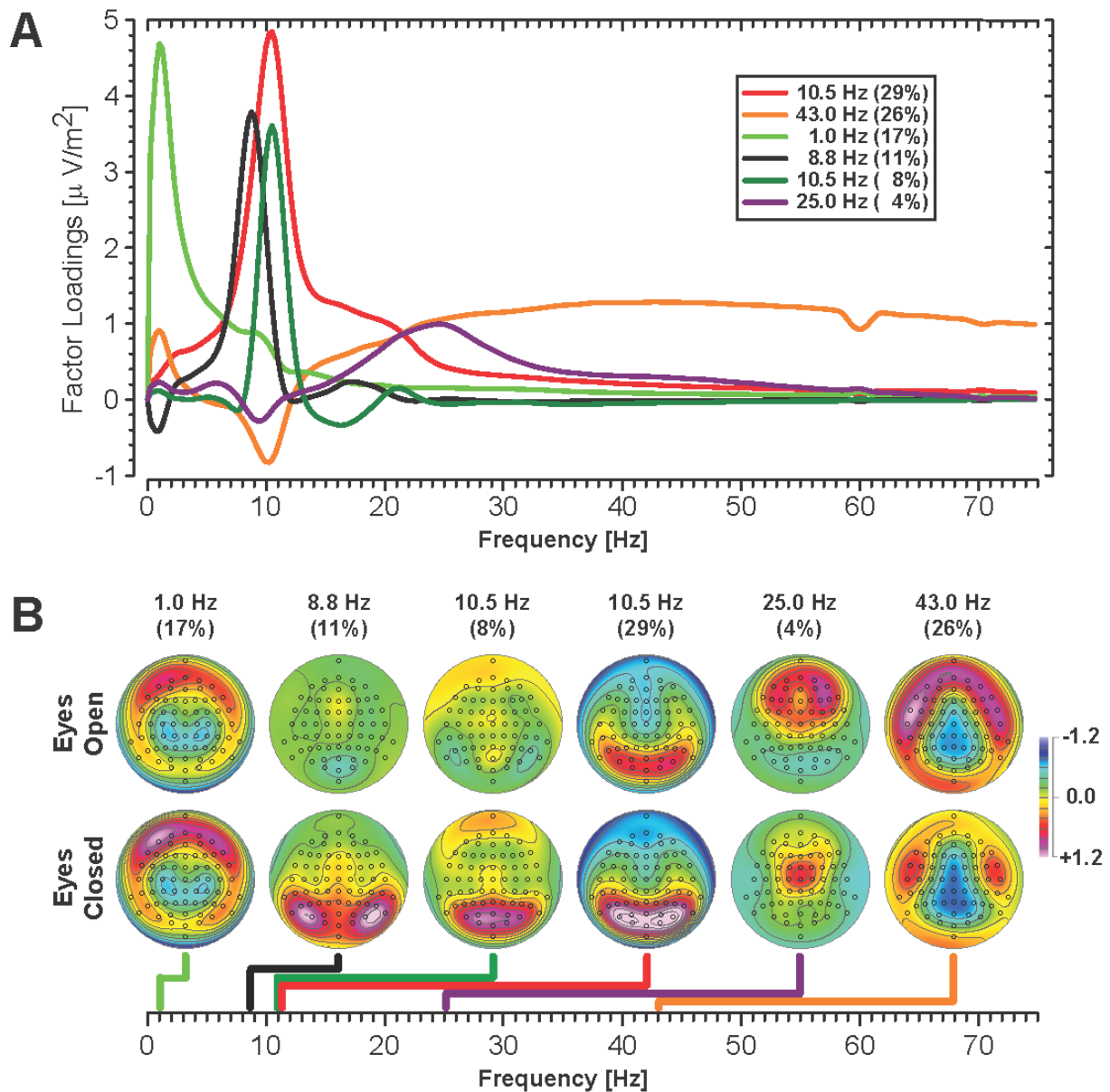
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## Supplementary Material

## Supplement S1: Overall CSD-fPCA Solution

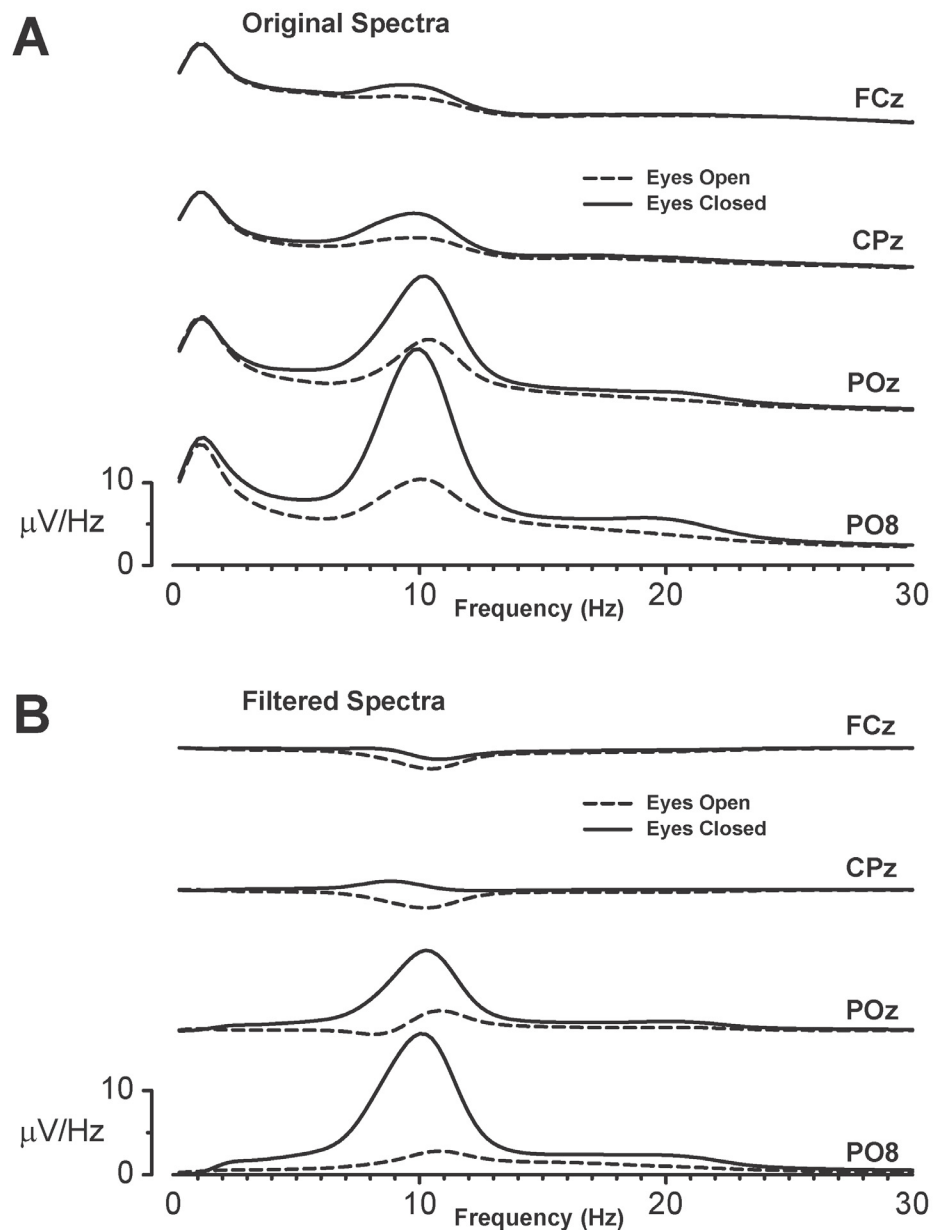
Averaged CSD amplitude spectra (299 frequency points = variables) were submitted to unrestricted, covariance-based fPCA, with 67 electrodes, 2 conditions, and 82 participants (i.e., 10988 cases), followed by Varimax rotation of the covariance loadings. As shown in Fig. S1, six factors accounted for 95% of the variance of amplitude spectra, three of which (48% total variance) had clear peaks in alpha (low-alpha/theta, high-alpha and residual alpha; cf. 29), and had posterior maxima for eyes-closed.



**Figure S1.** **A.** Rotated factor loadings waveforms for the first six CSD-fPCA components derived from the original (unfiltered) data. **B.** Corresponding mean factor score topographies for eyes-open and eyes-closed conditions, arranged by loadings peak frequency (coded by line color; e.g., black line: 8.8 Hz peak, 11% amplitude spectrum variance, lateral-posterior eyes-closed topography). Alpha activity was summarized by three factors with 8.8-10.5 Hz peaks. Dots indicate the spherical positions of electrodes (nose at top). Colored lines below maps point to the peak frequencies of corresponding factor loadings waveforms on the common abscissa.

*Supplement S2: Reconstruction of Amplitude Spectra from CSD-fPCA Alpha Factors*

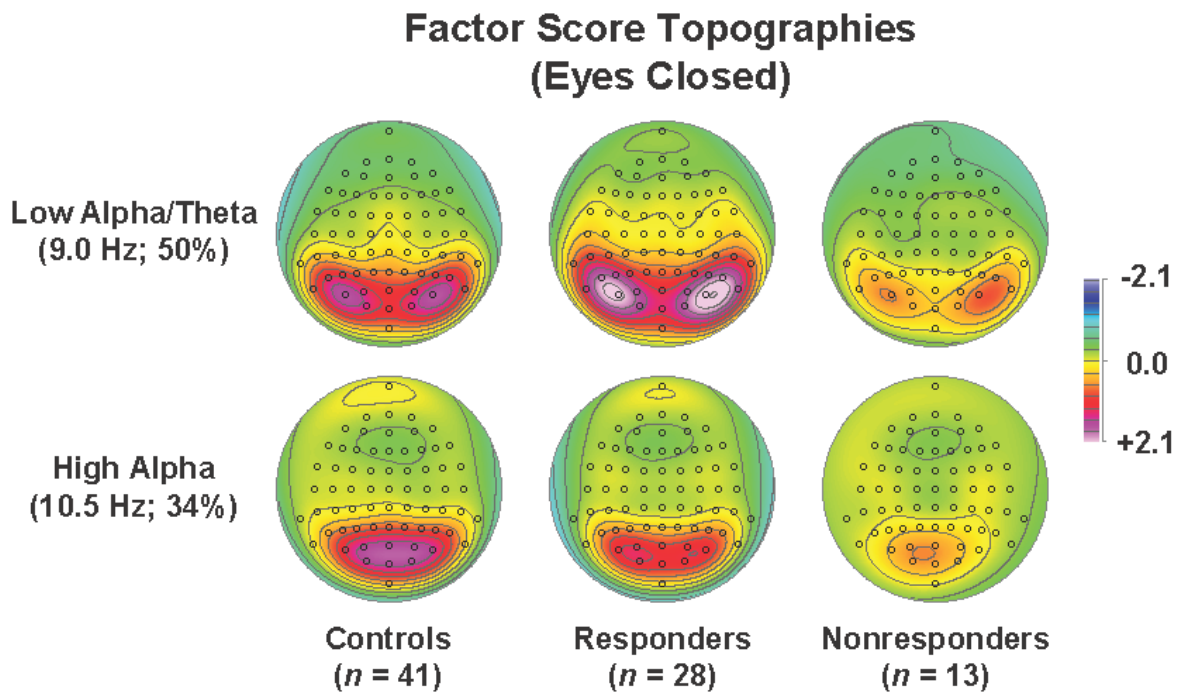
Preliminary comparisons of the CSD-fPCA factor loadings waveforms for the three alpha factors in Fig. S1 (8-12 Hz peaks) with those extracted separately for controls and patients indicated variability in the residual alpha factor loadings for patients (i.e., correlation between overall and patient residual alpha waveforms was  $< .7$ , compared to  $> .95$  for all others). This inconsistency was eliminated by using these three factors as a spectral filter (correlation of alpha factor loadings all  $> .994$ ), resulting in reconstructed amplitude spectra (summation of the products of factor scores and loadings waveforms across the three alpha factors) for each subject and condition. This approach serves as an effective alpha-pass filter that exploits the capacity of fPCA to remove overlapping broadband components (e.g., eye and muscle artifact) from the analysis. The final fPCA factors are reminiscent of those observed for factors produced by band-limiting the original, unfiltered spectra to 5-15 Hz (i.e., others set to zero).



**Figure S2.** **A.** Grand averaged CSD spectra showing greater alpha amplitude for eyes-closed (solid lines) than eyes-open (dashed lines) conditions at midline (FCz, CPz, POz) and right posterolateral (PO8) sites. **B.** Corresponding filtered amplitude spectra show preserved alpha, but activity and artifact at lower and higher frequencies is eliminated

## Supplement S3: Separate Contributions of Low-alpha/Theta and High Alpha

Low-alpha/theta and high-alpha were both maximal for the eyes-closed condition in posterior regions, but the topographic maximum of high-alpha was at the midline, and the maximum of low-alpha/theta was posterolateral, with a shallow anterior midline secondary topography (Fig. S3). Although Group trends were evident for the averaged factor score topographies of both factors, the main ANOVA model showed no significant Group interaction with Alpha Frequency (maximum effect is Condition x Alpha Frequency x Group:  $F[2,75] = .613$ ;  $p > .5$ ). However, an exploratory analysis indicated a statistical trend for condition-dependent low-alpha/theta (Group x Condition:  $F[2,75] = 2.47$ ;  $p = .083$ ), but not for high-alpha (Group x Condition:  $F[2,75] = 1.93$ ,  $p > .3$ ). A separate model for anterior midline low-alpha/theta (Fz, FCz) showed no Group effects (maximal Group effect or interaction was Group:  $F[1,75] = .93$ ,  $p = .4$ ).

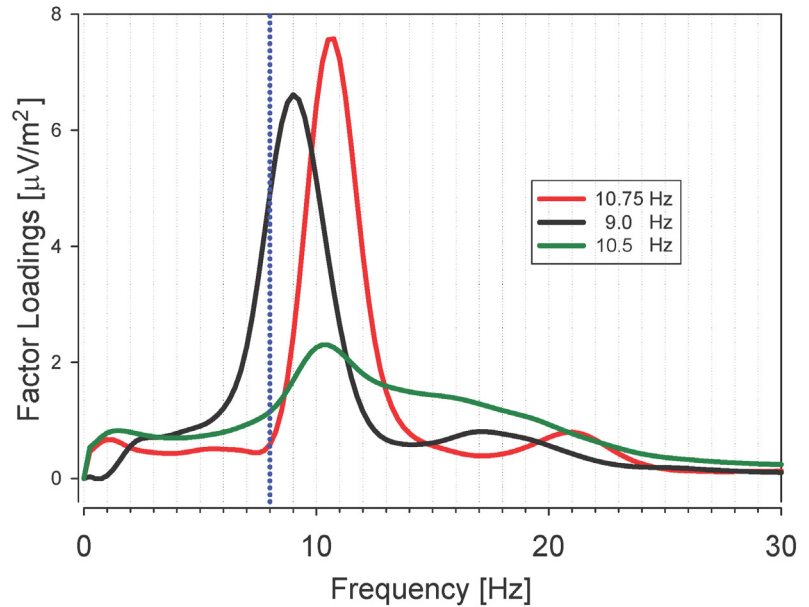


**Figure S3.** Averaged eyes-closed factor score topographies of low alpha/theta and high-alpha factors for control, responder and nonresponder groups. Both alpha factors showed marked attenuation for nonresponders, despite comparable topographies across groups.

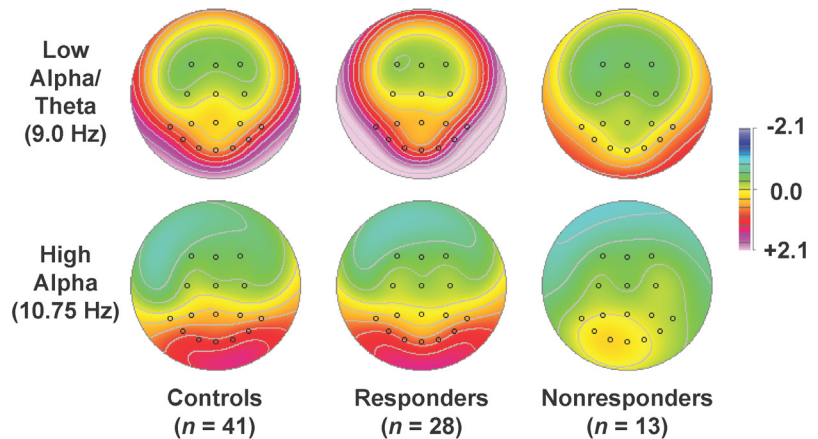
Supplement S4: fPCA of Low-density CSD Montage

Although the high-density electrode montage and CSD-fPCA methods provide an advantage for describing and characterizing differences in posterior condition-dependent alpha between responders and nonresponders, a montage consisting of considerably fewer than 67 electrodes should provide acceptable results. We evaluated this possibility by selecting a subset of 16 channels from the full CSD montage, consisting of standard 10-20 sites (F3,Fz,F4; C3,Cz,C4; P7,P3,Pz,P4,P8; O1,Oz,O2), but also including a pair of interpolated sites (PO7/8) to better reflect the posterolateral topography of low-alpha/theta. Data were otherwise processed as indicated in the main analyses. The resulting fPCA factor loadings and eyes-closed topographies are shown in Fig. S4.

An ANOVA of CSD-fPCA factor score averages across the available posterior sites (P7/8, PO7/8, O1/2, Oz), reproduced the critical Group x Condition (3-groups:  $F[2, 75] = 4.09$ ;  $p = .021$ ) and Response Group x Condition (2-groups:  $F[1, 36] = 7.47$ ;  $p = .01$ ) seen for the full montage. These data also provided a comparable prediction of treatment response, identifying 15 of the 17 patients with prominent alpha (greater than control median) as responders, but only 13 of 24 with less alpha were responders (Fisher's exact test, 2-tail  $p = .022$ ; positive predictive value = 88.2; specificity = 84.6). The results of the low-density fPCA were therefore comparable with that provided by the complete montage. A necessary caveat is that the spectra for this fPCA were extracted from the complete CSD montage. The adequacy of CSD estimates must also be verified for impoverished montages, which will require additional piloting to validate or optimize the minimal montage required to predict treatment response from posterior, condition-dependent alpha.



Factor Score Topographies  
(Eyes Closed)



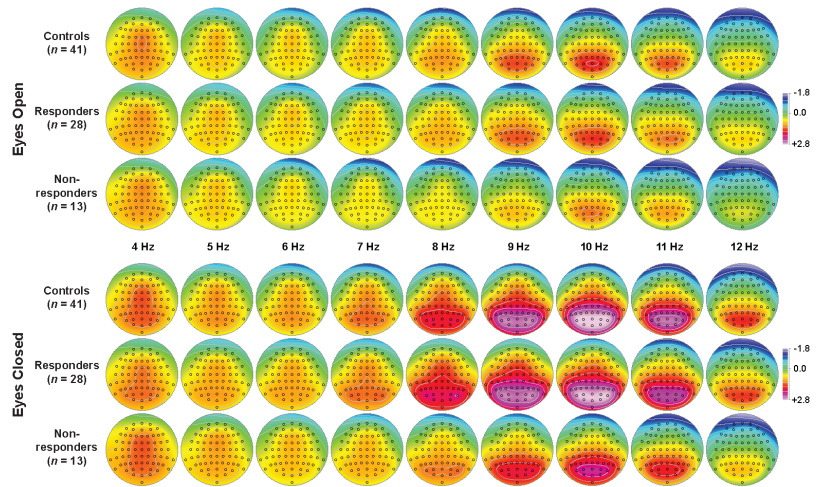
**Figure S4. A.** The resulting three CSD-fPCA alpha factor loadings are comparable to those derived from the complete montage (cf. Fig. 1A). **B.** Even though the diminished resolution resulted in topographic inaccuracies (cf. Fig. S3), the eyes-closed factor score topographies replicated the reduced alpha in nonresponders.

Supplement S5: Findings for Conventional EEG Analyses

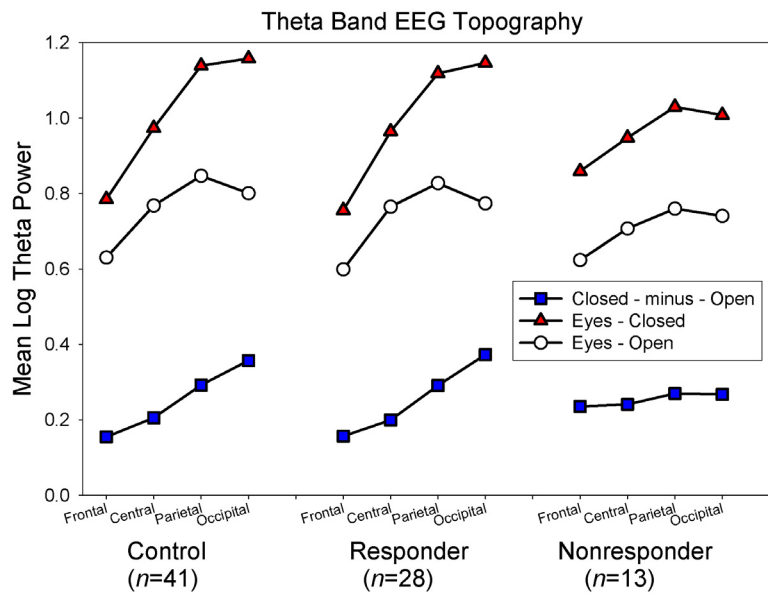
To examine conventional EEG measures, nose-referenced EEG power spectra were computed directly from EEG epochs (1 s, unpadded; 1 Hz FFT resolution), averaged across epochs for each condition, log-transformed, and averaged across subjects in each group (41 controls, 28 responders, 13 nonresponders). The spectral topographies shown in Fig. S5 therefore represent conventional log power comparisons common to the literature, and consistent with our prior study (e.g., Bruder et al, 2008). Of importance for the present study, controls and responders showed greater eyes-closed alpha than nonresponders throughout the entire 8-12 Hz classic alpha band. However, it should also be noted that this difference is not limited to the alpha band, but starts to build up at 6-8 Hz. Moreover, the anterior midline contribution and posterolateral maximum builds up below 8 Hz, while the high-alpha (e.g. 10 Hz) draw toward the posterior midline. These properties are most prominent for eyes-closed, and are characteristic of low-alpha/theta and high-alpha CSD-fPCA factors (cf. Fig. 1).

Band-averaged EEG power spectra were also log-transformed and subjected to a conventional repeated measures ANOVA for alpha (8-12 Hz) and theta (4-7 Hz) bands at the medial 10-20 sites (F3/4, C3/4, P3/4, O1/2; cf. Bruder et al., 2008), with Group (control, nonresponder, responder) as a between-subjects factor and within-subject factors of Condition (eyes-open, eyes-closed), site (frontal, central, parietal, occipital), and Hemisphere (left, right). In contrast to the CSD-fPCA findings, no statistically significant Group (control, responder, nonresponder) effects were observed for the alpha; there was no statistical support for an overall difference between groups (maximal Group effect or interaction was Group:  $F[2,79]=1.90, p=.16$ ). A statistical trend was also absent when analyses were restricted to patients (i.e., using Response Group as a between-subjects factor).

When the same ANOVA model was repeated for the theta band (4-7 Hz spectra in Fig. S5), there was no significant Group effect, but a Condition x Site x Group interaction ( $F[6, 237] = 2.93, p = .038, p = .484$ ) was found. As shown in Fig. S6, the anterior-to-posterior gradient for condition-dependent theta was more evident in responders and controls than in nonresponders. These topographic and functional properties are similar to those seen for alpha, which strengthens our contention that the EEG differences between SRI responders and nonresponders reflect classic, posterior, condition-dependent (i.e., “visual”) alpha (cf. Fig. 1 and Fig. S5), which can be measured on either side of the conventional 8 Hz border, and which originates from two distinct spectral components: low-alpha/theta and high-alpha.



**Figure S5.** Averaged spectral topographies (nose at top) of eyes-open (top rows) and eyes-closed log EEG power for controls, responders and nonresponders. Columns are unique frequencies ranging from 4-12 Hz.



**Figure S6.** The condition-dependent (eyes-closed minus eyes-open) topography of theta-band activity is consistent with posterior condition-dependent alpha (cf. Fig. S5). Both responders and controls showed a monotonic increase in eyes-closed minus eyes-open theta from frontal to occipital sites, which was reduced in nonresponders.

**Supplemental References**

1. Tenke CE, Kayser J (2005): Reference-free quantification of EEG spectra: combining current source density (CSD) and frequency principal components analysis (fPCA). *Clin Neurophysiol* 116:2826-2846.
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