Electrophysiological Predictors of Clinical Response to Antidepressants

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Introduction

Electrophysiological measures are important tools for assessing brain function, which have found their main clinical use in Neurology for assessment of epilepsy, coma, and integrity of neural circuits. They include the electroencephalogram (EEG) and evoked or event-related potentials (ERPs). Electrophysiological measures have the advantage of being noninvasive (i.e., no radioactive or magnetic field exposure), economical, and provide continuous millisecond by millisecond recordings of brain electrical activity. Although their temporal resolution far exceeds that of fMRI and PET, electrophysiological measures have more limited spatial resolution. The use of electrophysiological measures in Psychiatry has largely been in the research domain or to measure and document seizure activity during electroconvulsive therapy (ECT). Promising findings reviewed in this chapter point to a potential wider clinical role in mood disorders and their treatment.

The EEG is typically measured using electrodes placed on the scalp (e.g., using an elastic electrode cap). Clinical EEG recordings have traditionally been used in Psychiatry to screen for brain disorders or to monitor cortical activity during ECT or sleep. A description of the neural basis of the EEG and applications of clinical EEG is available in the textbook by Niedermeyer and Lopes Da Silva (2004). Digital recording and analysis of EEG has made possible quantitative measures, which usually involves doing a Fast Fourier Transform (FFT) to measure the amplitude (power) of the EEG spectrum within frequency ranges in the classical delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz) bands. Although quantitative EEG measures may have some value for the differential diagnosis of dementia and depression (Hughes and John, 1999), their clinical

utility as an adjunct for psychiatric diagnosis has not been demonstrated. There is, however, a growing literature suggesting that quantitative EEG measures in the theta and alpha bands, obtained prior to treatment of mood disorders or soon after it begins, predict subsequent clinical response to antidepressants.

Evoked potentials or ERPs, which are averaged EEG epochs time-locked to the onset of stimuli or other discrete events, have been widely used in clinical and research settings. For instance, evoked potentials that occur in the first 12 milliseconds after onset of clicks are used clinically to assess hearing in infants and for assessment of brainstem lesions and multiple sclerosis. ERPs occurring about 100-200 milliseconds after the onset of tones (N1 and P2 potentials) are indicative of early sensory or attentional processing, and later ERPs (most notably the P3 potential) provide neurophysiologic correlates of cognitive processing. Numerous studies have found a reduction of the P3 potential in depressed patients, which is consistent with evidence of cognitive deficits in depression (see Bruder et al., 2012, for a review of ERP studies in depression). This reduction is greatest in patients having a melancholic or psychotic depression, and clinical improvement is accompanied by an increase in P3 amplitude. P3 reduction is not, however, specific to depression, but occurs in other neuropsychiatric disorders, and is therefore not of value for diagnostic purposes. A more promising finding from a clinical perspective has been evidence of a relationship between early auditory ERPs (N1, P2) and response to SSRI antidepressants.

This chapter focuses selectively on EEG and ERP findings that have raised hopes for the application of electrophysiological measures as clinical aides for selecting the most appropriate course of treatment for depressed patients.

EEG Alpha Power and Asymmetry in Depression

The alpha rhythm (8-13 Hz) is an oscillatory EEG pattern that is maximal when an individual is in a relaxed, wakeful state with eyes closed, but is reduced (blocked) when the individual becomes alert or when visual processes are engaged by opening the eyes (see Figure 1). Alpha is thought of as an idling rhythm and is inversely related cortical activity as indexed by PET measures of cerebral blood flow (Cook et al., 1998) or fMRI measures of blood-oxygen level dependent (BOLD) signal in posterior regions where alpha is greatest (Feige et al., 2005). EEG alpha has been used as an index of relative cortical deactivation, with greater alpha (less activation) being found in depressed patients than healthy controls (Polack & Schneider, 1990; Debener et al., 2000; Grin-Yatsenko et al., 2010; Kemp et al., 2010). Studies have also reported abnormal regional hemispheric asymmetry of alpha, with depressed patients showing relatively less activity over left frontal (Gotlib et al., 1998; Henriques & Davidson, 1991; Kemp et al., 2010; Stewart et al., 2010) or right parietal regions (Bruder et al., 1997; Kemp et al., 2010; Kentgen et al., 2000; Reid et al., 1998; Stewart et al., 2011).

Insert Figure 1 about here

There have, however, been conflicting alpha asymmetry findings for depressed patients. Thibodeau et al. (2006) reviewed findings of frontal alpha asymmetry in depression and examined a number of possible moderator variables that could help account for inconsistent findings. The moderate effect size for frontal alpha asymmetry differences between depressed patients and controls (Cohen's *d*=.54) and low test-retest

reliability of frontal alpha asymmetry in depressed patients (Debener et al., 2000) might also contribute to inconsistencies. While Debener et al. found higher test-retest reliability of parietal asymmetry in depressed patients, their study and others (e.g., Henriques & Davidson, 1991; Schaffer et al., 1983) did not find reduced right parietal activity in depression. Heller et al. (1995) suggested that this may be due to the opposing effects of anxiety or anxious arousal on parietal alpha asymmetry. They hypothesized that anxious arousal, such as seen in panic disorders, is associated with right parietotemporal hyperactivation, whereas depression is associated with right parietotemporal hypoactivation. Evidence supporting this hypothesis was found in a study examining the effect of comorbidity of depressive and anxiety disorders on regional alpha asymmetry (Bruder et al., 1997). Patients having a major depressive disorder (MDD) and comorbid anxiety disorders, primarily panic disorder or social phobia, showed an alpha asymmetry indicative of relatively greater activity over right frontal and parietal sites, whereas patients having "pure" major depression showed less activity over right than left parietal sites, but no frontal asymmetry. Thus, comorbidity of depressive and anxiety disorders may heighten abnormal frontal alpha asymmetry favoring right over left hemisphere activity, but counteract the tendency for depressed patients to show reduced right posterior activity.

As part of a multigenerational study (Weissman et al., 2005), offspring of depressed probands who are at risk for depressive disorders also showed an EEG alpha asymmetry indicative of relatively less right posterior activity (Bruder et al., 2005). Moreover, anatomical MRI findings in this high risk study revealed an association between risk for depression and cortical thinning across lateral parietal, posterior

temporal and frontal cortices of the right hemisphere (Peterson et al., 2009). Alpha power was found to correlate inversely with cortical thickness among individuals in this study, particularly over the right posterior region, suggesting that EEG evidence of reduced cortical activity was associated with increased cortical thinning (Bruder et al., in press). Self-ratings of depression severity in adults having a MDD also correlated inversely with PET measures of glucose metabolism in dorsal areas of prefrontal, occipital, temporal and parietal cortex, predominantly in the right hemisphere (Milak et al., 2010).

In summary, abnormalities of EEG alpha power and asymmetry have been found in depressed patients. Although there have been conflicting findings, alpha asymmetry abnormalities may represent biological traits associated with risk for developing a depressive disorder.

Alpha Power and Asymmetry in Antidepressant Responders and Nonresponders

A likely contributor to inconsistent alpha asymmetry findings is the clinical and biological heterogeneity of depression. One approach for reducing this heterogeneity is to divide a sample of unmedicated depressed patients into those who subsequently respond favorably to a specific antidepressant and those who do not respond. Patients who respond to an antidepressant with a specific mode of action, e.g., an SSRI, may share a common biological substrate not present in nonresponders. Findings of pretreatment EEG differences between responders and nonresponders also have potential clinical utility for identifying predictors of clinical response, and personalizing treatment for individual patients.

There is good agreement that pretreatment EEG alpha may differentiate patients who respond to antidepressants from those who do not. Ulrich et al. (1986) found

increased alpha over occipital sites in depressed patients who eventually responded to amitriptyline and they suggested that there are two subtypes of depression having different pathophysiology and response to antidepressants. Prichep et al. (1993), using cluster analysis of neurometric EEG features to identify clusters of patients having distinctive EEG profiles, similarly found evidence for two subgroups among 27 patients having an obsessive-compulsive disorder. About 82% of members of a subgroup with increased relative alpha power in frontal and temporal regions responded well to an SSRI antidepressant, while only 20% of members of a second cluster with increased relative theta power were treatment responders. This neurometric technique was also used by Suffin and Emory (1995) in a study of 54 depressed patients treated with an SSRI or tricyclic antidepressant and they found 86% of treatment responders to have increased relative alpha power in frontal and occipital regions. In a study of 29 patients having a unipolar depressive disorder who were treated with a tricyclic antidepressant, Knott et al. (1996) found that greater pretreatment relative alpha in responders than nonresponders did not reach a conventional level of statistical significance. In summary, these early studies suggest that increased alpha power, which was originally identified in depressed patients by Polack & Schneider (1990), is particularly likely to be found among depressed patients who respond to an SSRI or tricyclic antidepressant, although the predictive value of this measure needs further study to make it clinically useful.

We confirmed the value of alpha power in predicting clinical response to an SSRI and also found a difference in posterior alpha asymmetry between responders and nonresponders (Bruder et al., 2008). Resting EEG scalp potentials were measured from 28 electrodes (nose reference) in 18 depressed patients before and after about 12 weeks of

treatment with fluoxetine, and 18 matched healthy controls were also tested. Treatment responders (n=11) showed significantly greater alpha power when compared to nonresponders (n=7) and controls, with the largest difference at occipital sites where alpha was greatest. As shown in Figure 2, greater alpha power in responders than

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Insert Figure 2 about here

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nonresponders was present across the pre-treatment and post-treatment sessions and there was no change in alpha following SSRI treatment. Test-retest reliability of alpha power was high at both frontal and posterior sites ($r \geq .92$), and is comparable to that found for healthy adults for retest periods over one year (Smit et al., 2005). Elevated alpha has also been found in depressed patients in a euthymic state (Pollock & Schneider, 1989), which suggests that it reflects a stable biological trait in patients who respond favorably to antidepressants. Responders in our study also differed from nonresponders in alpha asymmetry at occipital sites, with responders having greater alpha (less activation) over right than left occipital cortex and nonresponders showing the opposite asymmetry. The difference in alpha asymmetry between SSRI responders and nonresponders is consistent with our prior findings (Bruder et al., 2001), and did not change following treatment (Figure 2). Test-retest correlations were, however, lower for alpha asymmetry ($r \geq .63$ at frontal and posterior sites), which agrees with the lower test-retest correlations of alpha asymmetry for healthy adults (Hagemann et al., 2005). To examine the value of alpha power and asymmetry at occipital sites for predicting clinical response to an SSRI, the average scores for healthy adults were used as a cutoff for dividing patients into those

who were greater or less than normal. Both alpha power and asymmetry showed reasonable positive predictive value (i.e., response rate ≥ 72% for patients predicted to be responders), but lower negative predictive value (i.e., nonresponse rate ≥ 56% for those predicted to be nonresponders).

A recent study (Tenke et al., 2011) was designed to confirm the predictive value of EEG alpha amplitude and asymmetry in an independent sample of patients. Resting EEG was recorded with eyes open and eyes closed prior to treatment in a larger sample of depressed patients (n=41) and in healthy controls (n=41). This study extended our prior study in several respects. First, the predictive value of alpha was examined not only for patients receiving an SSRI, but also those receiving dual treatment with an SSRI plus a noradrenaline/dopamine reuptake inhibitor (NDRI; bupropion) or a serotonin/noradrenaline reuptake inhibitor (SNRI; duloxetine or venlafaxine). Second, to improve the spatial resolution of spectral topographies, EEG was recorded from a dense array of recording electrodes (67 channels) and current source density (CSD) measures were used to reduce volume conduction from distal sites, and avoid problems associated with selection of a reference electrode. CSD measures are reference-free and indicate the strength of underlying radial current generators (Nunez & Srinivasan, 2006; Kayser & Tenke, 2006; Tenke & Kayser, 2005). Third, CSD measures were quantified using frequency principal components analysis (fPCA) to derive empirically-based frequency bands. Two factors corresponding to alpha sub-bands were examined: a high-alpha factor (10.5 Hz peak) and a low alpha/theta (9.0 Hz peak), which included activity usually classified as theta (4-8 Hz).

Significant differences in alpha were found between treatment responders (n=28) and nonresponders (n=13), which were particularly evident for the eyes-closed condition and were seen broadly across the low and high alpha bands. Figure 3A shows the condition-dependent topographies, averaged across the low and high alpha bands, for patients who responded to treatment (Clinical Global Improvement rating of "much or very much improved"), nonresponders and healthy controls. Nonresponders had significantly less alpha than responders and controls over posterior regions where alpha was maximal for each group. The marked difference in alpha between responders and nonresponders was present for patients who received monotherapy with an SSRI or dual therapy (Figure 3B). It was seen at posterior sites over each hemisphere and there was no significant difference in alpha asymmetry among groups.

Insert Figure 3 about here

The value of alpha for predicting treatment response was examined by classifying patients as to whether they had alpha above the median for healthy controls (predicted to be responders) or less than the median for controls (predicted to be nonresponders). As shown in Figure 4, alpha had high positive predictive value of 93.3 with 14 of 15 patients with alpha above median for controls responding to treatment, and high specificity of 92.3 (percent of nonresponders predicted to be nonresponders), but lower sensitivity of 50.0 (percent of responders who were predicted to be responders) and negative predictive value of 46.1. Thus, depressed patients who have prominent condition-dependent posterior alpha are predicted to respond to serotonergic antidepressants with a high

degree of confidence. However, half of responders had alpha below the median for controls and were not predicted to be responders. It is possible that a sizable portion of these responders may be placebo responders or not true drug responders. There was also no evidence for differential prediction of clinical response to an SSRI as opposed to dual therapy targeting both serotonergic and nonsertonergic neurotransmitters. Moreover, the early studies reviewed above suggest that alpha is not be specific for predicting response to a SSRI but also predicts response to a tricyclic antidepressant. In contrast to our prior study (Bruder et al., 2008), treatment response was not related to hemispheric asymmetry of alpha. Although the reason for this lack of replication is unknown, alpha asymmetry is less reliable than alpha power and may be more influenced by a number of moderator variables.

Insert Figure 4 about here

In summary, EEG alpha power may be useful when it predicts good response because about 90% of those cases with prominent alpha will indeed be medication responders, but about half of cases where poor response is predicted will actually turn of to be medication responders.

Theta Power in Responders and Nonresponders

Several studies have reported EEG differences between antidepressant responders and nonresponders in the lower frequency theta band (4-8 Hz). Knott et al. (1996) examined the value of both pretreatment EEG and changes during acute treatment for predicting response to imipramine. EEG from 16 electrodes was recorded in 29 depressed

patients with eyes closed while they pressed a hand-held button. Response to 4 weeks of treatment with imipramine was defined as greater than 50% reduction in HAM-D ratings. Relative theta power, i.e., the percentage of theta relative to total absolute power across the delta, theta, alpha and beta bands, was less in responders than nonresponders prior to treatment and responders exhibited greater increase in theta 3 hours after the first dose and after 2 weeks. Thus, both baseline theta and changes during acute treatment may predict subsequent clinical response. In studies using the neurometric EEG approach (Prichep et al., 1993; Suffin & Emory, 1995), patients having either a depressive disorder or OCD with increased relative theta power were nonresponders to antidepressants. More recently, Iosifescu et al. (2009) measured EEG from fronto-temporal electrodes (F7, F8, A1, A2 referenced to Fpz) in depressed patients before and 1 week after starting 8 weeks of open treatment with an SSRI or venlafaxine. EEG was recorded while patients counted backwards from 1000 to keep them alert. Relative theta power was lower in treatment responders (HAM-D reduction ≥ 50%) than in nonresponders and predicted response with an accuracy of 63% (64% sensitivity and 62% specificity). Relative theta after 1 week of treatment showed comparable differences between responders and nonresponders. The unusual electrode montage used by Iosifescu et al. (2009), however, makes their findings difficult to interpret and compare with conventional EEG studies. In contrast to the above studies, Spronk et al. (2011) reported that *higher* absolute theta power at a midline frontal site (Fz; linked-mastoids reference) predicted improvement of depression after 8 weeks of open-label treatment with predominantly SSRI or SNRI antidepressants. Among 25 patients having a MDD, higher theta power was associated with greater decrease in HAM-D ratings.

In summary, there is conflicting evidence as to whether lower or higher theta power predicts favorable response to an SSRI or other antidepressants. Differences in study procedures (e.g., EEG recording site or reference electrode), medication, or EEG analyses (e.g., use of relative as opposed to absolute theta measures) might account for the difference in theta findings. The use of low resolution electromagnetic tomography analysis (LORETA; Pascual-Marqui et al., 1994) to measure theta activity localized to the region of the anterior cingulate cortex (ACC) has yielded more consistent predictions of treatment response.

LORETA Measures of Theta and Treatment Response

Mayberg et al. (1997) were first to report that PET measures of glucose metabolism in the rostral ACC predicted response to antidepressants. Pizzagalli (2011) recently reviewed studies using neuroimaging (PET, fMRI, SPECT) or EEG measures supporting the hypothesis that increased activity or metabolism in rostral ACC predicts response to a wide range of treatments for depression (including various antidepressants, sleep deprivation and rTMS). EEG evidence comes from three studies using the LORETA source localization technique to infer the distributed current density attributable by this model to the region of the rACC. Pizzagalli et al. (2001) recorded resting EEG from 28 electrodes in 18 patients having a MDD and 18 healthy controls. Clinical response to 4-6 months of treatment with nortriptyline was assessed using the Beck Depression Inventory (BDI). Although most patients (n=16) were responders, they used a median split of BDI ratings to compare patients having better or worse response to treatment. Patients having a better response showed greater theta (6.5-8.0 Hz; eyes closed), localized by LORETA to the region of the rACC. There was a significant

correlation between pretreatment theta activity and BDI scores, consistent with the hypothesis that higher rACC activity is associated with greater improvement in depression. A subsequent study by Mulert et al. (2007) compared resting EEG (eyes closed) of responders (≥50% reduction in HAM-D) and nonresponders to 4 weeks of treatment with either citalopram (7 reponders, 4 nonresponders) or reboxetine (3 responders, 6 nonresponders). Responders had greater pretreatment theta activity (6.5-8 Hz), again localized by LORETA to the rACC when compared to nonresponders and there was a significant correlation of pretreatment theta and improvement in depression after treatment, which replicates the findings of Pizzagalli et al. (2001). In the first double-blind, placebo controlled study to examine the relationship of pretreatment EEG and antidepressant response, Korb et al. (2009) used LORETA to localize theta activity (4-7 Hz) to the same rACC region as specified by Pizzagalli et al. (2001). Patients who responded to either fluoxetine or venlafaxine (n=22) had greater theta than nonresponders (n=15), whereas there was no difference between placebo responders (n=15) and nonresponders. They report that rACC activity had a sensitivity of 64% and a specificity of 67% for predicting treatment response. Results for midline frontal theta using conventional EEG measures were consistent with the above findings, but did not attain statistical significance.

In summary, EEG measures of resting midline frontal theta, as quantified by LORETA, predict clinical response to a variety of antidepressants, but the sensitivity and specificity may be too modest at this stage to be of use to the clinician. Also, the LORETA technique involves a number of assumptions and localizing generators

underlying surface potentials is difficult and subject to problems because an infinite number of theoretical generators in the brain can yield the same scalp potentials.

Cordance and Antidepressant Response Index

Cook et al. (1999) did not find pretreatment differences in relative theta power between responders and nonresponders to 8 weeks of treatment with fluoxetine, but did find differences in "cordance", a measure that integrates relative and absolute theta power. Although the biophysical basis of cordance is not clear (Tenke & Kayser, 2005), it has been reported to be positively correlated with PET scan measures of cortical perfusion (Leuchter et al., 1999). Based on pretreatment measures of EEG cordance, 24 patients were retrospectively divided into concordant or discordant groups depending on the type of association of absolute and relative power in theta band. Patients in the concordant group had a robust response to fluoxetine, while the discordant group did not. In a subsequent study (Cook et al., 2002), they did not, however, find a significant difference in the numeral value of cordance at baseline between responders (HAM-D $\leq$ 10 after 8 weeks of treatment) and nonresponders to fluoxetine or venlafaxine. They did find a difference in the change of prefrontal cordance after 1 week of treatment, with responders showing a decrease in cordance not seen in nonresponders or placebo responders. The decreased cordance predicted treatment response with a sensitivity of 69% and a specificity of 75%. Independent studies (Bares et al., 2007, 2008) replicated this relationship between early change in prefrontal cordance and clinical response in patients treated with a variety of antidepressants. Also, among 18 treatment-resistant depressed patients who received 4 weeks of treatment with bupropion, responders ($\geq$50% reduction of MADRS) differed from nonresponders in showing higher baseline prefrontal

cordance and a decrease after one week of treatment (Bares et al., 2010). In summary, studies indicate that a reduction of cordance after one week of treatment is predictive of clinical response to SSRI, SNRI, or NDRI antidepressants. However, there is less agreement as to the value of pretreatment cordance for predicting treatment response, and the biophysical basis of cordance remains unknown.

Iosifescu et al. (2009) developed an Antidepressant Treatment Response (ATR) index, which is derived from a weighted combination of theta and alpha power at baseline and after 1 week of treatment, and is recorded from fronto-temporal sites (Fpz, FT7, FT8, A1, A2). Initial studies showed promise of the ATR index for predicting response to an SSRI or venlafaxine, but not placebo (Hunter et al., 2011; Iosifescu et al., 2009). In a multi-site BRITE-MD study (Leuchter et al., 2009a,b), resting EEG of patients having a MDD was recorded at baseline and after 1 week of treatment with escitalopram. Patients were then randomly assigned to continue on escitalopram, switch to bupropion or a combination of both antidepressants. Responders to escitalopram had significantly higher ATR index than nonresponders. A threshold value selected to maximize classification of responders and nonresponders predicted response with 58% sensitivity and 91% specificity. These values are comparable to those reported by Tenke et al. (2011) for alpha power, and indicate that about half of escitalopram responders would not be predicted to be responders. Escitalopram responders differed from bupropion responders in ATR index. Patients with high ATR values were more likely to respond to escitalopram than those with low ATR values, whereas patients with low ATR values who were switched to bupropion were more likely to respond to bupropion alone than those who remained on escitalopram. While the ATR index may be of value in

differential prediction of response to antidepressants, a replication using the same ATR algorithm and threshold cutoff is needed to independently confirm these findings. Also, since the ATR index is based on an atypical electrode montage and a complex proprietary algorithm, it is not clear what high or low ATR scores mean or what their relation is to standard EEG measures of theta or alpha. While the limited electrode montage may be an advantage for clinical applications, the frontal sites (Fpz, FT7, FT8) could be problematic because they are near known sources of artifact from the eyes and facial musculature.

In summary, both cordance and ATR measures, based on baseline EEG and changes after one week of treatment, show promise as predictors of clinical response to SSRI, SNRI, or NDRI antidepressants. These are, however, complex proprietary measures, which makes it difficult to independently replicate findings and limits their value as biomarkers of treatment response.

Clinical and Theoretical Implications of EEG findings in Depression

Resting EEG measures of alpha and theta have potential for clinical application because they are relatively easy to measure and have high reliability. Two measures obtained *before* treatment appear to have particular potential for predicting response to antidepressants. Alpha over posterior brain regions and midline frontal theta, localized using LORETA inverse model to rACC, were found to be greater in antidepressant responders than nonresponders. Pizzagalli (2011) suggested that the default mode network may explain the relation between resting rACC activity and treatment response. Activity in the default network, including rACC, posterior cingulate, lateral parietal and temporal cortex, and other structures, is greatest during resting states and decreases during processing of external stimuli. Pizzagalli postulated that increased resting rACC

activity in treatment responders may be linked to introspective or adaptive self-referential processing, which is thought to involve the default network. This hypothesis also suggests a possible interpretation of increased resting alpha in responders. Greater alpha in responders is more evident with eyes closed than open and is maximal over lateral parietal cortex (Tenke et al., 2011), which is a region in the default mode network. Moreover, Tenke et al. found a trend for the difference between responders and nonresponders to be greatest for a "low alpha factor" having a bandwidth that overlaps the theta band typically used in LORETA measures of rACC activity (6.5-8 Hz). Increased resting alpha and rACC theta activity in treatment responders could therefore both be related to default network activity. A study is now underway to test this hypothesis.

A reduction of frontal cordance in theta band after one week of antidepressant treatment also appears to be predictive of antidepressant response. Most recently, an ATR index, which uses theta and alpha measures at baseline and after one week of antidepressant, was developed to maximize predictions. The ATR index shows promise not only for predicting response to an SSRI or SNRI, but also differential response to an SSRI versus NDRI antidepressant. A critical problem with the ATR index is that its algorithm and cutoffs were derived in studies to maximize predictions and it is therefore in need of independent replications. Further research using multiple EEG measures, i.e., resting alpha, theta, LORETA rACC, cordance, ATR index, is needed to evaluate their relative merits as predictors of treatment response, and to determine how these measures relate to each other. Of greatest clinical value would be measures that can make

differential prediction of response to antidepressants with different mechanisms of action or to non-pharmacological treatments, e.g., cognitive behavioral therapy.

Auditory Evoked Potentials and Treatment Response

Although there are reports relating amplitude of auditory ERPs (e.g., N1, P2) and antidepressant response (Bruder et al., 2012; Spronk et al., 2011; Vandoolaeghe et al., 1998), the most replicated finding has come for loudness dependency of auditory evoked potentials (LDAEPs). Increases in tone intensity from 60 to 100 dB are known to result in a monotonic increase in N1 and P2 amplitude. In an ongoing study, we measured ERPs of 64 healthy adults to 1000 Hz tones (40 ms duration; 1600-2000 ms ISI) while they sat quietly with eyes fixed on a cross. Figure 5 shows CSD waveforms with peaks corresponding to N1 and P2 potentials. N1, which was maximal at central electrode sites (C3/C4), showed the expected monotonic increase in amplitude with increasing tone intensity from 60 to 100 dB.

Hegerl and Juckel (1993) reviewed evidence suggesting that the slope of the function relating tone loudness and N1-P2 amplitude provides a noninvasive indicator of seotonergic activity. They suggest that serotonergic neurons originating in dorsal raphé modulate activity in auditory cortex by providing a stable, tonic firing rate. Low firing rate of serotonergic neurons is related to strong loudness dependency, i.e., a steep increase in N1-P1 amplitude with increasing tone loudness, whereas high firing rate is related to weak loudness dependency, i.e., only a small increase in N1-P2 with increasing loudness (Hegerl et al., 2001). Direct evidence of an inverse relationship between serotonergic activity in dorsal raphé and LDAEP was found in recordings from primary auditory cortex of cats (Juckel et al., 1999). A recent review did not find strong support

for the utility of LDAEP as a marker of central serotonin function, but did conclude that LDAEP shows promise as a predictor of response to antidepressants (O'Neill et al., 2008a).

Depressed patients with low serotonergic activity, as evidenced by pronounced LDAEP prior to treatment, respond better to SSRI antidepressants compared to patients with high serotonergic activity, as evidenced by weak LDAEP (Gallinat et al., 2000; Hegerl et al., 2001; Lee et al., 2005; Paige et al., 1994). Although Paige et al. (1995) found a similar difference in LDAEP between a small sample of responders (n=4) versus nonresponders (n=4) to an NDRI antidepressant (bupropion), more recent studies suggest that LDAEP may differentially predict clinical response to serotonergic and noradrenergic antidepressants. Among 16 patients having a MDD, stronger pretreatment loudness dependency of N1 was associated with greater reduction in depression following 3-4 weeks of treatment with the SSRI citalopram (Linka et al., 2004). In contrast, in 14 patients tested before treatment with a noradrenaline reuptake inhibitor (NRI) reboxetine, *smaller* loudness dependency of N1 was associated with greater improvement in depression (Linka et al., 2005). In the first study in which depressed patients were randomly assigned to treatment with either the citalopram or reboxetine, Mulert et al. (2007) measured LDAEP for current source distribution (latency window of 60-240 ms) localized using LORETA to primary auditory cortex. SSRI responders (n=7) showed significantly stronger LDAEP when compared to SSRI nonresponders (n=4), whereas NRI responders (n=3) did not differ significantly from NRI nonresponders (n=6). Stronger LDAEP was associated with greater improvement in depression

following citalopram treatment (r=.71), whereas weaker LDAEP tended to be associated with greater improvement in depression following reboxetine treatment (r= -.54).

LDAEP has not, however, been associated with the clinical state of depressed patients or levels of central serotonergic neurotransmission. Thus, studies have *not* found a change in LDAEP following treatment with SSRI or other antidepressants (Gallinat et al., 2000; Linka et al., 2009; Paige et al., 1994, 1995). Also, acute enhancement of serotonin levels by administrating an SSRI to healthy adults has not yielded consistent findings. A double-blind placebo controlled study in healthy adults found a decrease in LDAEP during acute administration of a single dose of the SSRI citalopram, which would be expected given an increase in central serotonin (Nathan et al., 2006). This change in LDAEP was not replicated in a study in which healthy females received an intravenous infusion of citalopram or placebo (Uhl et al., 2006) or in a study measuring LDAEP during administration of sertraline or escitalopram (Guille et al., 2008). Moreover, acute depletion of serotonin in healthy adults during administration of tryptophan did not alter LDAEP (Debener et al., 2002; Dierks et al., 1999; O'Neill et al., 2008b).

In summary, studies have found that LDAEP predicts clinical response to an SSRI and may be of value for differential prediction of response to an NRI antidepressant. LDAEP may represent a stable trait that is not readily altered by changes clinical state or serotonin levels.

Conclusions

The findings reviewed in this chapter indicate that certain electrophysiologic measures of brain activity are predictive of clinical response to antidepressants. The most

promising EEG predictors are resting alpha and theta with eyes closed. Specific measures derived from the EEG, e.g., current source density, cordance, LORETA, ATR index, have all shown value as predictors, but further research is needed to compare their physiological interpretability and relative merits. Auditory evoked potential measures of loudness dependency (LDAEP) also predict response to antidepressants. A variety of different measures have been used to assess LDAEP, including scalp potentials, LORETA, and dipole source analyses of N1, P2 or N1-P2 differences. To the extent that EEG and LDAEP measures are uncorrelated and separately predictive, their combined use could lead to models with clinically relevant predictive power.

Several points are important for developing and evaluating electrophysiological predictors of treatment response. First, measures that are stable indicators with good test-retest reliability are likely to be of most value for predicting clinical response in individual patients. Resting EEG alpha and theta potentials have demonstrated high test-retest reliability (generally $\geq .90$) in both healthy adults (Smit et al., 2005) and depressed patients (Allen et al., 2004; Bruder et al., 2008). Auditory evoked potentials likewise have high reliability in healthy adults and depressed patients. Hensch et al. (2008), in reviewing prior studies and their study of 166 healthy adults, reported reliability of the LDAEP function to generally be in region of .70 to .80. Comparable LDAEP reliabilities have been found for depressed patients retested after antidepressant treatment (Gallinat et al., 2000; Linka et al., 2009). Less in known, however, about the test-retest reliability of EEG cordance, LORETA rACC, or ATR measures, which are derived from alpha and theta scalp potentials. Assessment of reliability is particularly important for measures, such as ATR index, that depend on assessing changes in EEG between baseline and one

week of treatment. Second, to be of clinical value measures should have high sensitivity and specificity for predicting treatment response. The EEG measures reviewed in this chapter generally had only moderate sensitivity (50 to 70% of responders correctly predicted to be responders) and somewhat higher specificity (60 to 90% of nonresponders correctly predicted to be nonresponders). Studies of LDAEP have generally reported average data for small samples with no indication of sensitivity or specificity. Third, the typical procedure for determining the predictive value of a measure is to choose a cutoff or threshold value above which patients are predicted to be a responder. There are quantitative procedures available to aid in choosing a cutoff, e.g., receiver operating characteristic (ROC) curve, but there is no guarantee that a cutoff established in a given study will work for a new sample of patients. Another approach is to use the median value for healthy adults as the cutoff, for example, with the rationale being that responders have higher than normal values and nonresponders lower values (e.g., Tenke et al., 2011). Normative data for a large sample of healthy adults could then be developed for a given population. Fourth, electrophysiologic measures would ideally be predictive of treatment response to a specific class of antidepressants with known pharmacologic profile, e.g., SSRI, and be of value for differential prediction of treatment response. Some EEG measures, e.g., LORETA measures of rACC activity, are clearly not specific, but predict response to a wide range of treatments. There are, however, preliminary indications that the ATR index and LDAEP may differentially predict response to SSRI and NDRI or NARI antidepressants. Fifth, ease of application of predictors in clinical settings is a critical issue. For instance, it would not be efficient to use a large array of electrodes in the clinic. It should, however, be possible to record resting EEG or LDAEP

with a small number of well targeted electrodes and use computer algorithms to predict response for individual patients. A multi-site BRITE-MD study (Leuchter et al., 2009b) using the ATR index was conducted with this in mind, but further studies to replicate their findings are needed before it could be recommended for clinical use.

Lastly, it may be too optimistic to expect any one electrophysiologic measure to provide sufficiently accurate predictions of clinical response. A recent review by Alhaj et al. (2011) referred to evidence that combining various EEG or ERP measures may improve prediction. For instance, Mulert et al. (2007) suggested that a resting EEG measure, using LORETA to infer rACC activity, might be useful as a first step to identify a subgroup of depressed patients who are *not* likely to respond to standard antidepressants and, if response is likely, LDAEP could be used for differential prediction of response to a SSRI or NRI antidepressant. Moreover, neuropsychological tests and neuroimaging measures (PET or MRI scans) may also contribute to prediction of treatment response. An ongoing NIMH initiative "Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care" (EMBARC; M. Trivedi & P. McGrath, Principal Investigators) is a multi-site, double-blind study examining the value of resting EEG, LDAEP, MRI (structural and functional), and neurocognitive tests for differential prediction of clinical response to an SSRI versus placebo. The aim is to begin to evaluate whether combined use of the best predictors in these domains could ultimately serve as biosignatures for personalizing antidepressant treatment.

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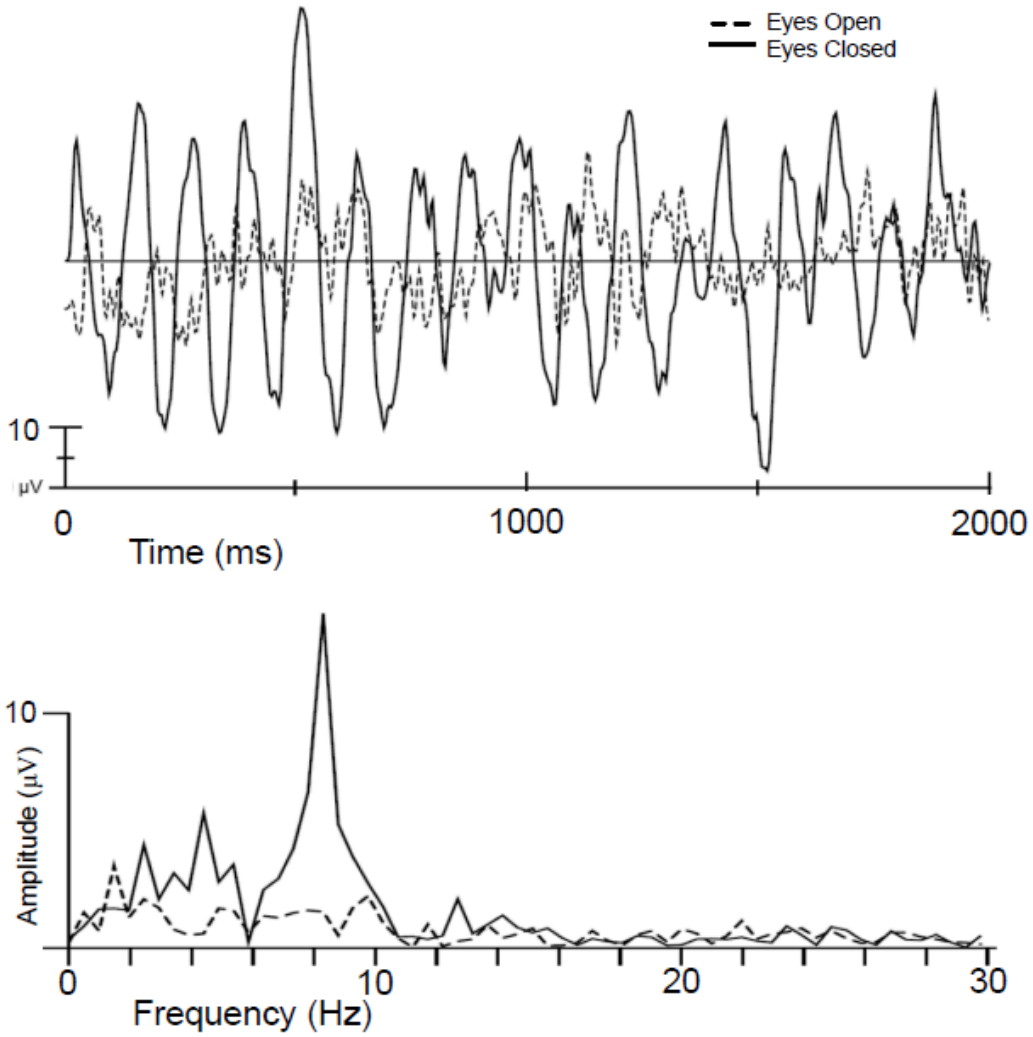

Figure 1. Top portion shows alpha oscillations during 2 second sample of Eyes Closed EEG (solid lines) and alpha blocking with Eyes Open (dashed lines). Bottom portion gives the corresponding frequency spectra with peak amplitude in alpha band in the Eyes Closed condition, but not in the Eyes Open condition.

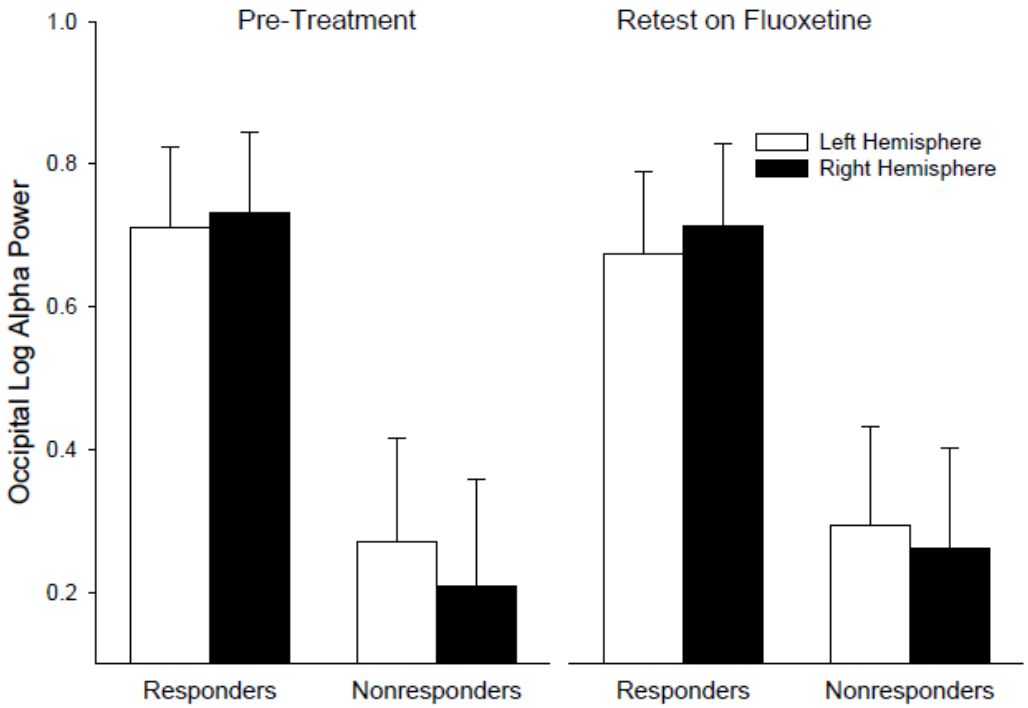

Figure 2. Mean log alpha power (± SEM) over right and left posterior sites for responders and nonresponders before treatment and after 12 weeks of treatment on fluoxetine (nose-referenced EEG).

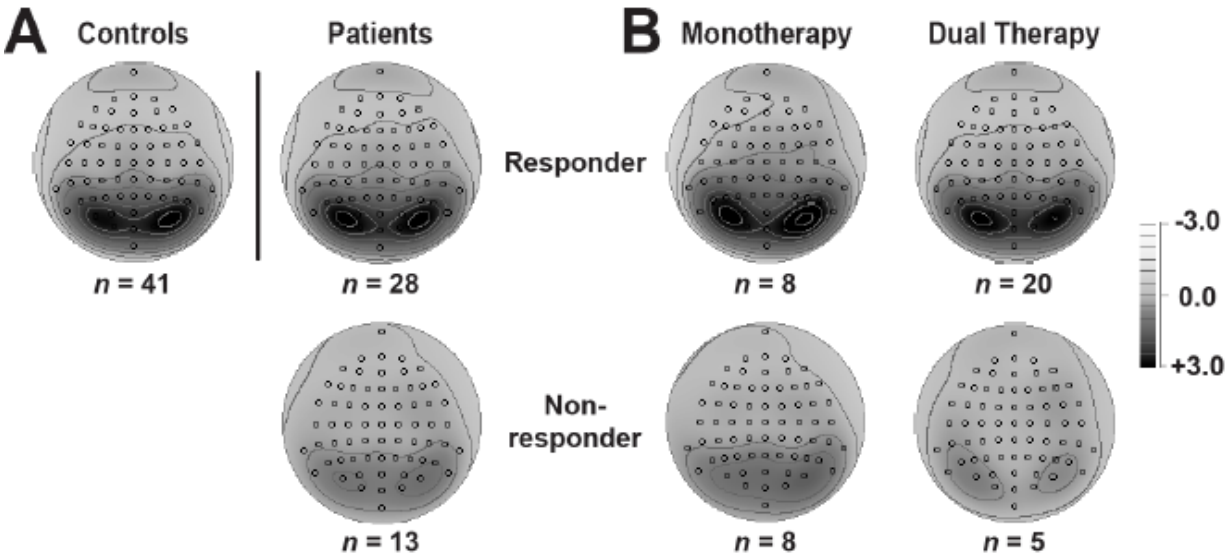

Figure 3. A. Condition-dependent (eyes closed minus eyes open) topographies of alpha (average across high and low alpha factors using CSD-transformed EEG) for controls, responders and nonresponders. Alpha reduction in nonresponders is most marked over posterior sites (bottom of maps). B. Corresponding condition-dependent alpha topographies for patients treated with a monotherapy or dual therapy. Both nonresponder groups showed marked alpha reduction compared to responders.

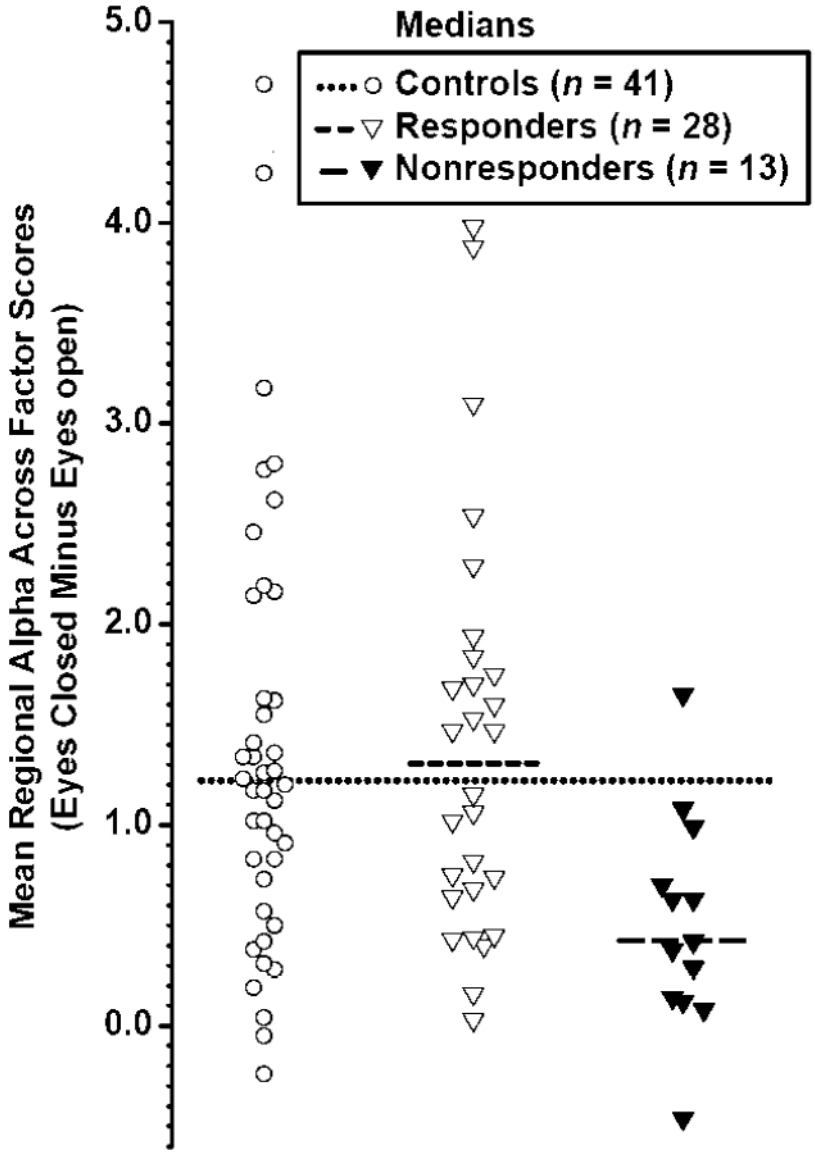

Figure 4. Scatterplot of mean condition-dependent (eyes closed minus eyes open) posterior alpha for controls, responders and nonresponders. The median for healthy controls (dotted line) was used as the cutoff for predicting treatment response.

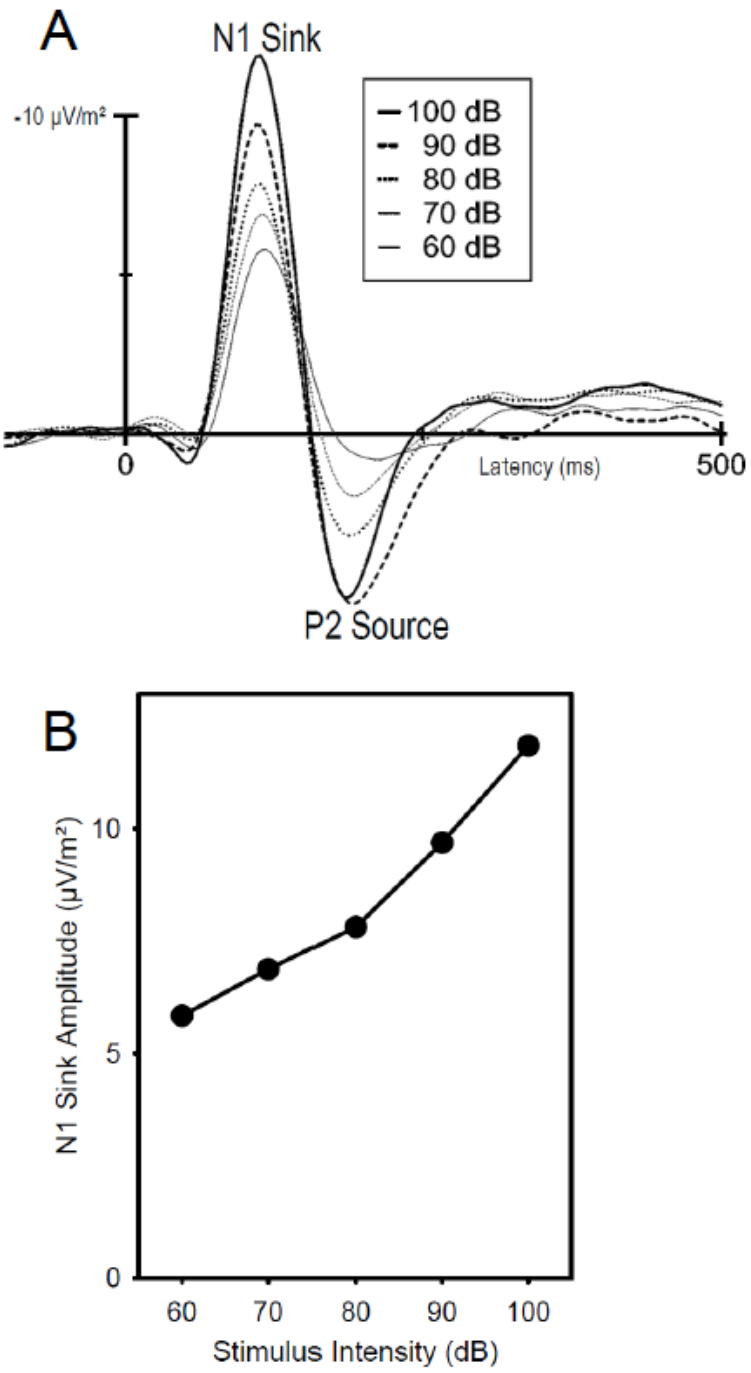

Figure 5. A. Average current source density waveforms at C3/C4 sites for 64 healthy adults showing peaks corresponding to N1 and P2. B. LDAEP function showing increase in tangential N1 with increasing intensity of tones.