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Response prediction to antidepressants using scalp and source-localized loudness dependence of auditory evoked potential (LDAEP) slopes

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Abstract

The loudness-dependence of the auditory evoked potential (LDAEP) slope may be inversely related to serotonin (5-HT) neurotransmission. Thus, steep LDAEPs tend to predict a positive response to selective serotonin reuptake inhibitor (SSRI) antidepressants, which augment 5-HT. However, LDAEPs also predict outcome to antidepressants indirectly altering 5-HT (e.g. bupropion). Hence, the LDAEP's predicative specificity and sensitivity to antidepressant response/outcome remains elusive. Scalp N1, P2 and N1/P2 LDAEP slopes and standardized low resolution brain electromagnetic tomography (sLORETA)-localized N1 and P2 LDAEP slopes were assessed in depressed individuals (N=51) at baseline, 1 and 12 weeks post-treatment with one of three antidepressant regimens [escitalopram (ESC) + bupropion (BUP), ESC or BUP]. Clinical response was greatest with ESC+BUP at week 1. Treatment responders had steep N1 sLORETA-LDAEP baseline slopes while non-responders had shallow ones. P2 sLORETA-LDAEP slope increases at 1 week existed in responders; decreases were noted in non-responders. Exploratory analyses indicated that more BUP and ESC responders versus non-responders had steep baseline N1 sLORETA-LDAEP slopes. Additionally, slight decreases in scalp P2 LDAEP by week 1 existed for ESC treatment, while slope increases existed with ESC+BUP treatment. Only baseline N1 sLORETA-LDAEP discriminated treatment responders/non-responders. This work confirms that certain LDAEP measures are associated with treatment outcome and appear to be differentially modulated with varying antidepressant drug regimens, though this should be confirmed using larger samples.

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Keywords

antidepressants; classification; serotonin; major depressive disorder (MDD); loudness-dependence of auditory evoked potentials (LDAEP)

Introduction

Though many pharmacotherapies exist for treating major depressive disorder (MDD), the majority of patients do not remit with initial treatment (Thase, 2003). Additionally, those who do benefit from antidepressants typically experience weeks-long delays before symptom relief. Although selective serotonin reuptake inhibitors (SSRIs) continue to be the most commonly used antidepressants (Marcus & Olfson, 2010), their therapeutic response variability is high. Some evidence suggests that SSRI efficacy may be enhanced by co-administering other drugs, such as bupropion (Spier, 1998; Lam et al., 2004), and that remission rates can be increased and clinical improvement expedited if drug combinations are given at treatment initiation (Blier et al., 2010). Currently, no established markers exist for predicting response to specific antidepressant pharmacotherapies; such markers would aid in optimizing treatments. One such candidate may be electroencephalogram (EEG)-derived measures to an auditory challenge.

High 5-hydroxytryptamine (5-HT; serotonin) neurotransmission exists in primary sensory cortices, such as the auditory cortex, and is likely implicated in modulating sensory processing (Hegerl et al., 2001). Two EEG-derived auditory evoked potentials (AEPs), the N1 and P2, are generated in auditory cortices; their peak-to-peak amplitude (N1/P2) correlates positively with intensity. By plotting N1/P2 amplitude against intensity, a loudness dependence of the AEP (LDAEP; or intensity-dependent AEP, IDAEP) slope is constructed, which appears to be inversely related to 5-HT activity. As cortical hyper-activation with increasing intensity could be damaging, 5-HT activity may inhibit excess neural firing (Juckel et al., 1999). Thus, low dorsal raphe nucleus 5-HT pre-activation is thought to be reflected by steeper LDAEPs than when 5-HT pre-activation is high, and associated with shallow LDAEP slopes (Mulert et al., 2005).

Though this inverse relationship has been demonstrated pre-clinically (Juckel et al., 1997; 1999; Wutzler et al., 2008), evidence for LDAEP sensitivity to central 5-HT activity in humans is indirect and less consistent. For instance, acute tryptophan depletion (ATD), which lowers 5-HT levels, induced unaltered (Debener et al., 2002; Massey et al., 2004; O'Neill et al., 2008), increased (Norra et al., 2008) and even decreased (Dierks et al., 1999; Kähkönen et al., 2002) intensity-dependent N1/P2 amplitudes or LDAEP slopes. Studies probing acute SSRI effects on the LDAEP in healthy adults have also yielded mixed results, with reports of no LDAEP changes (Uhl et al., 2006; Guille et al., 2008) and the expected slope decreases following both acute and chronic SSRI administration (Nathan et al., 2006; Segrave et al., 2006; Simmons et al., 2011). Further evidence linking the 5-HT system with intensity-dependent AEPs comes from associations between altered LDAEP slopes and polymorphisms of terminal 5-HT_{1B} autoreceptors (Juckel et al., 2008) and 5-HT transporters (Hensch et al., 2006; Lee et al., 2011). Nevertheless, clinical evidence for a strong link between the LDAEP/AEPs and central 5-HT activity is tenuous. Additionally, the purported sensitivity of the LDAEP/AEPs to 5-HT neurotransmission has been questioned, as evidence indicates LDAEP/AEPs alterations with other neurotransmitter system modulations (Juckel et al., 1997; Beucke et al., 2010; Lee et al., 2011, but see O'Neill et al., 2006, 2008; Oliva et al., 2010).

Individuals with aberrant 5-HT system function, as is thought to occur in depression, may be more likely to exhibit altered LDAEPs and intensity-dependent AEPs. Though greater N1/P2 amplitudes with increased intensity and steeper LDAEP slopes have been noted in MDD (Gopal et al., 2004; Manjarrez-Gutierrez et al., 2009), suggesting inefficient 5-HT neurotransmission, others have found no such alterations (Linka et al., 2007; Park et al., 2010). Additionally, LDAEP slope modulations may to be associated with specific MDD subtypes and features (Chen et al., 2005; Fitzgerald et al., 2009; Linka et al., 2009).

Despite these issues, baseline LDAEP slopes appear to be a strong predictor of antidepressant response, especially to 5-HT-targeting drugs. Presumably, individuals with steep pre-treatment LDAEPs have (at least to a certain extent) attenuated 5-HT neurotransmission and may be more likely to respond favorably to drugs that augment it, which indeed seems to be the case (P2 LDAEP: Paige et al., 1994; Gallinat et al., 2000; Mulert et al., 2002; 2007; intensity-dependent N1: Linka et al., 2004; Lee et al., 2005; Park et al., 2011). Conversely, those with shallow LDAEPs may benefit more from treatments indirectly targeting the 5-HT system (N1 LDAEP: Linka et al., 2005; Juckel et al., 2007; Mulert et al., 2007). However, some studies have also found that steep pre-treatment LDAEP slopes predict favorable response to bupropion (Paige et al., 1995) and lithium (Juckel et al., 2004). While both drugs affect 5-HT, their mechanisms of action differ from SSRIs and they substantially alter activity of other monoamines (Blier et al., 1987; Ghanbari et al., 2010). Thus, questions remain regarding the specificity of the LDAEP as predictive measures to particular antidepressant regimens. Furthermore, the predictive utility of LDAEP slopes constructed using the N1, the P2 or the amplitude between the N1 and P2 (N1/P2) has not been systematically probed.

Few studies have also examined whether the LDAEP changes with antidepressant treatment. Previous work noted no LDAEP changes with chronic SSRI or bupropion treatment in depressed adults (Paige et al., 1995; Gallinat et al., 2000), though decreased LDAEP slopes with chronic SSRI administration existed in healthy adults (Simmons et al., 2011). As such, it is unclear if chronic (weeks/months) administration of 5-HT-targeting drugs, in particular, alters LDAEP slopes or whether they are unlikely to be radically influenced by antidepressants (i.e., are trait-like). LDAEP slope changes during the course of treatment, particularly during the early stages, could potentially index whether a drug alters brain activity in a manner associated with eventual therapeutic outcome.

This study aimed to verify and compare the utility of baseline scalp N1, P2, N1/P2 LDAEP and source-localized N1, P2 LDAEP slopes in characterizing and predicting response to chronic treatment (12 weeks) with the SSRI escitalopram (ESC), bupropion (BUP) or ESC +BUP in MDD. We also probed if early LDAEP changes (by 1 week) were associated with treatment response. Scalp- and standardized low-resolution brain electromagnetic tomography (sLORETA)-derived LDAEP slopes were assessed, as evidence suggests that these indices may yield somewhat distinct results and exhibit different sensitivity (Mulert et al., 2002; Hagenmuller et al., 2011). The stability of scalp and sLORETA LDAEP slopes during treatment was also examined; to our knowledge, sLORETA-derived LDAEP slope stability during antidepressant treatment has not yet been probed. Finally, we assessed which baseline LDAEP measure(s) best discriminated antidepressant treatment responders from non-responders. Given that precedent research has noted a main effect of sex on the LDAEP (Hensch et al., 2008; Oliva et al., 2011; Jaworska et al., 2012), sex was used as a covariate in our analyses. We hypothesized that treatment responders (≥50% decrease in baseline Montgomery-Åsberg Depression Rating Scale scores) would be characterized by steeper baseline LDAEPs. Given the putative synergistic effects of drug combinations, we predicted normalization (LDAEP slope decreases) to emerge by 1 week with ESC+BUP; we did not expect slope changes for the monotherapies at this time. Though response evaluation to the

three regimens was not our focus, we nevertheless expected hastened and more pronounced responses with ESC+BUP. Treatment-specific effects were exploratory as samples were small when groups were subdivided by treatment regimens.

Methods

Patients

Fifty-three adults (N=53) with a primary diagnosis of MDD, SCID-IV-I/P-assessed by psychiatrists, were initially recruited; most had previous major depressive episodes (mean duration since illness onset 13.3 years). The 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$; Hamilton, 1960) and Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) were administered. All patients had MADRS scores ≥22 at time of drug randomization (outlined below). Exclusion criteria included: Bipolar disorder (BP-I/II/NOS), psychosis history, current (<6 months) drug/alcohol abuse/dependence, seizure history, unstable (≥3 months) medical condition, history of anorexia/bulimia and significant suicide risk. Participants with hearing loss (using hearing aids and/or unable to hear 60 dB SPL, 1000 Hz, as assessed by an audiometric test) were also excluded. Patients with a secondary diagnosis of some anxiety disorder were included (N=33: no co-morbidity; N=12: sub-threshold anxiety; N=8: secondary diagnosis of some anxiety disorder). At randomization, patients were not taking psychoactive drugs; appropriate drug washout periods were applied for previously medicated patients. Participants were tested pre-, 1 and 12 weeks post-treatment. This study was approved by the Royal Ottawa Health Care Group and University of Ottawa Social Sciences and Humanities Research Ethics Boards; informed consent was obtained from all participants who were compensated $30.00 CDN/session.

Antidepressant Regimens

Patients were recruited from a clinical trial wherein they were randomized to one of three antidepressant regimens (double-blind): escitalopram (ESC) + placebo, bupropion (BUP) + placebo or ESC+BUP. Patients were assessed weekly for the first four weeks and then bi-weekly. Dosing was raised only if tolerated and remission ($HAMD_{17} \leq 7$ over at least two consecutive visits) not reached. Clinical measures of interest were: 1. MDD severity: Assessed by $HAMD_{17}$ and MADRS pre-, 1 and 12 weeks post-treatment and rating changes. 2. Response: ≥50% MADRS reduction from baseline to week 12 (or last session carried forward; ratings were not carried forward if dropout occurred before 6 weeks).

LDAEP Paradigm

Before testing, participants abstained for >3 hr from caffeine and/or smoking/nicotine, as well as from alcohol/non-prescription drugs beginning at midnight. They were seated in a sound- and light-attenuated chamber with their eyes fixated ~1 m in front. Auditory stimuli (1000 Hz, 30 ms, 10 ms rise/fall) were presented (Neurobehavioral Systems Inc, Albany, CA, USA) binaurally through headphones (TDH-49, Northeastern Technologies, Glen Cove, NY, USA). Stimuli at five intensities (60, 70, 80, 90, 100 dB SPL) were presented 80 times each (no identical tones presented back-to-back; inter-stimulus interval: 1200-1800 ms; similar to the paradigm used by Linka et al., 2004; Juckel et al., 2007).

Electrophysiological Recordings & Data Reduction

EEG was recorded (500 Hz) with a cap embedded with 32 Ag/AgCl electrodes (EasyCap, Inning a. Ammersee, Germany) positioned according to the 10-10 system (Chatrian et al., 1985); an AFz electrode was the ground and averaged mastoids ($TP_{9/10}$) were the reference. Electrooculographic activity was also monitored and impedance maintained at ≤5 KΩ (BrainVision Recorder, Gilching, Germany). Signals were filtered (0.1-30 Hz) and ocular-

corrected (Gratton et al., 1983). Data was segmented into 600 ms epochs/intensity (−100-500 ms post-stimulus). Artifact rejection followed, which excluded epochs of +/−75 μV and with faulty channels/drift. Epochs were baseline corrected (mean activity 100 ms pre-stimulus) and averaged for each participant/intensity. >40 epochs/intensity were included in analyses (BrainVision Analyzer, Gilching, Germany).

Auditory Evoked Potentials (AEPs) & LDAEP Extraction

Similarly to procedures outlined elsewhere (Jaworska et al., 2012), N1 and P2 peak time windows were established from grand-averages at Cz (as in Linka et al., 2005; Juckel et al., 2007; Simmons et al., 2011). N1 was the most negative peak at 70-140 ms and P2 was the most positive peak at 110-260 ms post-stimulus. The peak-to-peak amplitude between N1 and P2 (N1/P2) was also calculated at each intensity/participant. A mean slope was constructed for N1, P2 and N1/P2, with intensity being the independent and AEP amplitudes the dependent variables [three scalp loudness-dependence of the auditory potential (LDAEP) slopes were calculated: N1 LDAEP, P2 LDAEP, N1/P2 LDAEP]. Due to faulty channels (specifically Cz), insufficient epochs, patient dropout and/or hearing impairments data was available for N=51 at baseline, N=48 at week 1 and N=46 at week 12 for the scalp LDAEP analyses.

Source Localization

As previously outlined (Jaworska et al., 20120), sLORETA (Pascual-Marqui, 2002) was used to estimate neural activity ($\mu A/mm^2$) in primary auditory cortices [region of interest (ROI); 1500 mm^3 from left (12 voxels), 1375 mm^3 from right (11 voxels) hemispheres] for scalp-derived N1 and P2 AEPs at each intensity/participant (artifact- and ocular-corrected averaged epochs from 28 electrodes) for each session (see Pizzagalli et al., 2001 for assumptions underlying LORETA – sLORETA's precursor). Average current densities at 70-140 ms (N1) and 110-260 ms (P2) per intensity were obtained. These were used to generate mean sLORETA-LDAEP slopes (N1, P2 sLORETA-LDAEP) collapsed across hemispheres; the N1/P2 sLORETA-LDAEP slope was not assessed as preliminary analyses indicated it did not yield unique information (given that it is calculated from mean current densities of the N1 and P2 AEPs). Several more participants were excluded from sLORETA analyses than from the AEP analyses as sLORETA analyses can only be carried out when all subjects have the same channels included in the source-analyses algorithm (N=48 at baseline and week 1, and N=44 at week 12).

Statistical Analyses

A. Antidepressant Response—Chi-square tests were used to assess responder/non-responder proportions (i.e., those with/without a >50% MADRS decrease from baseline to week 12, or last session carried forward) per treatment (ESC+BUP, BUP, ESC). Clinical rating changes [$HAMD_{17}$ and MADRS response rates from baseline to weeks 1 and 12 ((week 1 − baseline)*100/basline; (week 12 − baseline)*100/baseline), reflecting early and late changes, respectively] were assessed between treatments with *t*-tests.

B. N1, P2, N1/P2 LDAEP & N1, P2 sLORETA-LDAEP Slopes—Chi-square tests were carried out on baseline scalp N1, P2, N1/P2 LDAEPs and N1, P2 sLORETA-LDAEPs divided into steep/shallow slopes (median split) to probe if responder/non-responder proportions differed on baseline slope when treatment groups were collapsed. Chi-square tests were also carried out with treatment groups not collapsed (significance set at $p<.01$ for these analyses). Multivariate analyses of covariance (MANCOVAs; sex as covariate) were carried out to assess if steep/shallow baseline scalp N1, P2, N1/P2 LDAEP and N1, P2 sLORETA-LDAEP slopes (entered as separate independent variables per MANCOVA;

treatment was the second independent variable) were associated with early and late clinical symptom changes (i.e., early and late $HAMD_{17}$ and MADRS changes; four dependent variables). Univariate analyses of covariance (ANCOVAs) assessed if early changes in scalp N1, P2, N1/P2 LDAEP and N1, P2 sLORETA-LDAEP slopes [((week 1 − baseline)/ baseline)*100] were associated with response status (responder/non-responder) and altered by treatment (response status, treatment as fixed factors; sex as covariate).

Pearson's correlations were carried out between scalp and sLORETA-derived LDAEP slopes at baseline and respective slopes at weeks 1 and 12; this was further assessed with single-measure intra-class correlations (ICC) using a one-way random effects model (as in Allen et al., 2004) to probe slope stability.

Finally, stepwise discriminant analyses were conducted to probe whether baseline N1, P2 sLORETA- and scalp-derived N1, P2, N1/P2 LDAEP slopes (i.e., 5 predictor variables) differentiated responders/non-responders (treatments collapsed).

All main effects and interactions were Greenhouse-Geisser corrected (for the univariate ANCOVAs); Bonferroni corrections were applied (incorporated within the SPSS syntax) to account for multiple comparisons in all the ANCOVAs. Unless stated otherwise, $p<.05$ was the significance level, means and standard error of the mean (SEMs) are presented.

Results

Patients

Two patients dropped out before week 6 and could not be classified as a responder/non-responder (N=51; Tables 1 and 2). Average ESC or BUP doses at week 12 (assessed by collapsing ESC or BUP doses from the monotherapy and combination regimens) did not differ between responders/non-responders in the current study (responders: BUP=375 mg, ESC=33 mg; non-responders: BUP=418 mg, ESC=35 mg). Eventual treatment responders and non-responders also did not differ on baseline $HAMD_{17}$ and MADRS scores.

Treatment Response & Clinical Ratings

Chi-squared tests revealed no difference in responder/non-responder proportions per treatment (Table 1). *T*-tests indicated no treatment differences in MADRS and $HAMD_{17}$-indexed late symptom changes (baseline to week 12). A difference between ESC+BUP versus BUP existed for $HAMD_{17}$-indexed early symptom changes (baseline to week 1) [$t(32)=2.26$, $p=.031$; ESC+BUP: −26% ± 34; BUP: −2% ± 27]. Clinical scores over the course of treatment (collapsed across treatment regimens) are presented in Table 3.

Scalp N1, P2 & N1/P2 LDAEP

No differences in responder/non-responder proportions emerged when baseline scalp N1, P2 or N1/P2 LDAEPs were split into shallow/steep slopes (treatments collapsed/not collapsed).

MANCOVAs indicated no differences in $HAMD_{17}$ or MADRS early or late response rates (% change from baseline to weeks 1 and 12) when baseline slope (shallow/steep for each of N1, P2 and N1/P2 LDAEP slopes) and treatment were fixed factors.

ANCOVAs indicated no differences in early N1 or N1/P2 LDAEP slope changes (from baseline to week 1) when treatment and response status (responder/non-responder) were the independent variables. A main effect of treatment was noted for P2 LDAEP early slope changes [$F(1,39)=3.96$, $p=.027$], with follow-up comparisons indicating a difference between ESC+BUP versus ESC. ESC+BUP induced early increases in P2 LDAEP slope (135.9% ± 38.6) while ESC induced small P2 LDAEP slope decreases (−6.0% ± 36.2).

Representative baseline LDAEP waveforms (MDD males and females, not collapsed) are presented in Figure 1. The relationship between baseline N1, P2 and N1/P2 LDAEP slopes and late MADRS responses for both responders and non-responders is denoted in Figure 2. Exploratory correlations ($p<.01$) indicated no relationship between baseline scalp LDAEPs and late clinical response (data not shown).

N1, P2 sLORETA-LDAEP Results

When baseline N1 sLORETA-LDAEP was split into shallow/steep slopes (treatments collapsed), a difference in responder/non-responder proportions existed [$\chi^2(1,46)=12.55$, $p=.001$], with more non-responders (77.3%; N=19) than responders (22.7%; N=5) with shallow slopes. More responders (75%; N=18) than non-responders (25%; N=6) had steep N1 sLORETA-LDAEP baseline slopes (Figure 2). When Chi-square analyses were carried out per treatment, more BUP non-responders tended to exhibit shallow baseline N1 sLORETA-LDAEP slopes (80%, N=4) than responders [20%, N=1; $\chi^2(1,12)=5.18$, $p=.02$]; more non-responders had steep baseline slopes (14.3%, N=1) than responders (85.7%, N=6). A similar trend existed for ESC [$\chi^2(1,17)=5.13$, $p=.02$], with more non-responders with shallow baseline slopes (87.5%, N=7) than responders (12.5%, N=1); fewer non-responders had steep baseline slopes (33.3%, N=3) versus responders (66.7%, N=6). No differences in responder/non-responder proportions based on baseline P2 sLORETA-LDAEP slopes (shallow/steep) existed (Figure 3).

MANCOVAs indicated no differences in $HAMD_{17}$ or MADRS early or late response rates (% change from baseline to weeks 1 and 12) when P2 sLORETA-LDAEP baseline slope (shallow/steep) and treatment were fixed factors. MANCOVAs indicated a trend for a main effect of N1 sLORETA-LDAEP baseline slope type (steep/shallow) [Wilks' $\lambda=.80$, $F(4,35)=2.25$, $p=.08$]. Follow-up analyses indicated a main effect of slope type on late $HAMD_{17}$ [$F(1,38)=6.54$, $p=.015$] and MADRS [$F(1,38)=7.98$, $p=.007$] changes, with greater decreases in those with steep ($HAMD_{17}$: −62.1% ± 8.6; MADRS: −65.6 ± 8.6) versus shallow ($HAMD_{17}$: −30.7% ± 8.9; MADRS: −29.8% ± 8.9) baseline N1 sLORETA-LDAEP slopes. The relationship between baseline N1 and P2 sLORETA-LDAEP slopes and late MADRS responses for both responders and non-responders is denoted in Figure 4; no correlations were noted between baseline sLORETA-LDAEPs and late clinical response (exploratory analyses; data not shown).

ANCOVAs indicated no differences in early N1 sLORETA-LDAEP slope changes (% change from baseline to week 1) when treatment and response status (responder/non-responder) were the independent variables. A main effect of responder status was noted for P2 sLORETA-LDAEP early slope changes [$F(1,36)=4.32$, $p=.045$], with follow-up comparisons indicating slope decreases from baseline to week 1 in non-responders (−23.4% ± 16.9) and an slope increase in responders (25.1%, ± 16.11).

Discriminant Analyses

Only N1 sLORETA-LDAEP slopes discriminated responders/non-responders ($\lambda=.78$, $F(1,43)=11.83$, $p=.001$; canonical correlation=.54). Eighty-six percent (86%) of non-responders were correctly classified, while 65% of responders were correctly classified; 76% of cross-validated grouped cases were correctly classified.

LDAEP Stability

Baseline scalp N1 LDAEP correlated with week 1 ($r=.80$, $p<.001$, N=47) and 12 ($r=.61$, $p<.001$, N=45) slopes (ICC=.63). Baseline scalp P2 LDAEP correlated with slopes at weeks 1 ($r=.72$, $p<.001$, N=47) and 12 ($r=.58$, $p<.001$, N=45; ICC=.67). Finally, baseline scalp N1/P2 LDAEP correlated with slopes at weeks 1 ($r=.80$, $p<.001$, N=47) and 12 ($r=.65$, $p<.001$,

N=45; ICC=.69). Baseline N1 sLORETA-LDAEP correlated with slopes at weeks 1 (r=.71, p<.001, N=44) and 12 (r=.46, p=.003, N=40; ICC=.46). Finally, baseline P2 sLORETA-LDAEP correlated only with the week 1 slope (r=.65, p<.001; ICC=.35).

Discussion

This study assessed the relationship between baseline scalp N1, P2, N1/P2 and sLORETA-localized N1, P2 LDAEP slopes, as well as early changes in these slopes, and treatment response to one of three antidepressant pharmacotherapy regimens. The stability of these LDAEP slopes over a 12-week treatment period was also examined. Finally, we probed which baseline scalp and sLORETA-derived LDAEP slopes best discriminated eventual antidepressant treatment responders/non-responders. To the best of our knowledge, this is the first clinical study to probe such issues within one relatively homogenous sample of depressed individuals. No clinical differences existed between treatments at week 12 in our patients, though clinical ratings decreased with treatment. Steeper baseline N1 sLORETA-LDAEP slopes existed in responders while non-responders had shallow slopes. P2 sLORETA-LDAEP slope decreases by week 1 were noted in non-responders, while increases existed in responders. Results were less robust for treatment-specific LDAEP effects, which was likely related to limited power; these analyses were exploratory. Both scalp and sLORETA-LDAEP slopes were stable over a week, but stability decreased over 12 weeks. The interpretation and implications of these results are discussed below.

We evaluated treatment response in order to probe the specificity of the association between baseline and early changes in LDAEPs and treatment outcome. We found comparable regimen efficacy by 12 weeks. However, early $HAMD_{17}$ response rates were greater for ESC+BUP versus ESC (a similar trend was noted versus BUP, data not shown), suggesting that dual treatment may hasten initial response. Though this is consistent with research using other drug combinations (Nelson et al., 2004, Segrave & Nathan, 2005), a recent study did not indicate superior BUP+ESC efficacy to BUP or ESC alone (Rush et al., 2011), contrasting with preliminary work (Leuchter et al., 2008). The results of the clinical trial in which this study was couched within, probing the clinical utility of ESC+BUP versus monotherapy, await publication.

When treatments were collapsed, baseline scalp LDAEP slopes were not related to response, inconsistent with evidence that SSRI (Linka et al., 2004; Lee et al., 2005; Juckel et al., 2007; Mulert et al., 2007) and BUP (Paige et al., 1995) responders exhibit steeper baseline scalp LDAEP slopes than non-responders. While methodological differences may have contributed to this, our protocols were comparable with previous work. We also examined N1 and P2 LDAEP slopes, which may be more sensitive response predictors than the N1/P2 slope (Paige et al., 1994; Linka et al., 2004, 2005). Exploratory analyses indicated that baseline scalp LDAEP slope type (shallow/steep) also did not differentiate responders/non-responders to specific drug regimens.

Steeper baseline N1 sLORETA-LDAEP slopes were noted in treatment responders and were associated with more pronounced late depression rating decreases. Conversely, treatment non-responders exhibited shallow baseline N1 sLORETA-LDAEP slopes, which were also associated with smaller depression rating decreases. Similarly to others' work (Mulert et al., 2002; Park et al., 2011), our results indicate that sLORETA-derived LDAEPs yield comparable results as other source localization methods (Galliant et al., 2000; Juckel et al., 2007; Mulert et al., 2007) in predicting treatment response. Only baseline N1 sLORETA-LDAEP slope was found to associate with antidepressant response, somewhat consistent with previous work indicating superior predictive utility of scalp-derived N1 LDAEPs (Linka et al., 2004; 2005; 2009; but see Paige et al., 1994; Gallinat et al., 2000; Mulert et al.,

2007). Limited rationale exists as to which of the N1, P2 or N1/P2 LDAEPs (scalp or source localized) is most sensitive in predicting eventual response, as predictive utility using all three has been found. Source analysis has localized the N1 to the primary auditory cortex and planum temporale, while P2 sources appear more diffuse (Godey et al., 2001). Thus, the putatively more diverse P2 generators and its more likely influence by cognitive factors may have increased P2 and N1/P2 LDAEP variability and influenced their predictive utility. The specificity regarding the utility of baseline N1 sLORETA-LDAEP slopes in predicting/associating with response was confirmed by the discriminant analyses, which revealed that only baseline N1 sLORETA-LDAEP significantly discriminated antidepressant treatment responders from non-responders.

More BUP and ESC responders tended to exhibit steep baseline N1 sLORETA-LDAEPs while shallow slopes characterized non-responders. The ESC results are consistent with previous work assessing predictive utility of source-localized LDAEPs (Mulert et al, 2007) and scalp-derived N1 LDAEP slopes (Linka et al., 2004; 2005; 2009) to SSRI response. One known study has assessed the predictive utility of scalp LDAEPs to BUP response, and noted findings similar to ours (Paige et al., 1995). If we espouse an inverse relationship between the LDAEP and 5-HT activity, it seems reasonable that steep baseline LDAEPs would predict a positive BUP response, as the drug increases 5-HT neurotransmission (Ghanbari et al., 2010). However, steep baseline N1 sLORETA-LDAEP slopes may index a neurochemical environment responsive to several antidepressant classes that directly or indirectly modulate 5-HT activity, rather than serving solely as an index of 5-HT hypofunction. Although N1 sLORETA-LDAEP baseline slopes did not differentiate ESC +BUP responders/non-responders, it is premature to rule out that they do not predict dual treatment outcome; power issues may have contributed to these null results and treatment-specific results should be treated as preliminary and exploratory findings.

A main effect of response status existed on early (by week 1) P2 sLORETA-LDAEP slopes, with responders exhibiting slope increases and non-responders decreases. This finding is among the first to indicate that early LDAEP slope changes differentiate responders/non-responders and that LDAEPs may be modulated with weeklong treatment, which may subsequently stabilize with chronic treatment. Previous studies on scalp LDAEP changes over the course of antidepressant administration noted no changes with chronic SSRI (Gallinat et al, 2000) and BUP treatment in MDD (Paige et al, 1995), though one group found decreased slopes with chronic SSRI administration in healthy adults (Simmons et al, 2011).

A main effect of treatment was noted for early scalp P2 LDAEP slope changes, with ESC +BUP inducing early slope increases while ESC induced slight slope decreases. Short-term/acute SSRI treatment does not enhance 5-HT neurotransmission, as compensatory/homeostatic mechanisms buffer against 5-HT surges (i.e., 5-HT_{1A} autoreceptor desensitization; Blier et al., 1987). Thus, the relatively modest P2 LDAEP slope decrease with ESC may reflect this initial homeostatic response to increased 5-HT availability. ESC +BUP treatment has been shown to induce greater 5-HT increases than SSRI monotherapy (Ghanbari et al., 2010). Thus, early P2 LDAEP slope increases may reflect more robust homeostatic/compensatory mechanisms following combination treatment. Furthermore, ESC +BUP induces more robust central neurochemical modulations, affecting DA, 5-HT and NA systems (Blier et al., 2010), and likely others, than the monotherapy regimens, as such, ESC +BUP treatment may induce more pronounced early LDAEP modulations (i.e., large P2 LDAEP slope increase). However, these inferences must be verified with larger sample sizes.

Only a handful of studies have examined if LDAEPs change with antidepressants and none, to our knowledge, have assessed sLORETA-LDAEP stability. Baseline scalp LDAEP slopes correlated with their respective slopes at later time points and moderate scalp LDAEP stability existed; the same was true for the N1 sLORETA-LDAEP. Baseline P2 sLORETA-LDAEP slopes only correlated with its respective slopes at week 1 and relatively weak slope stability existed. Given that sLORETA-derived LDAEP slopes were calculated from average current source density value in the primary auditory cortex over a time window corresponding to a particular AEP (versus a discrete time point), increased variability may have contributed to the diminished P2 sLORETA-LDAEP slope stability. It is difficult to speculate if chronic antidepressant treatment destabilized LDAEP slopes or whether LDAEPs, particularly sLORETA-derived slopes, are somewhat unstable electrophysiological measures. LDAEP stability assessments in healthy, unmedicated controls are required to resolve this.

Several study limitations must be acknowledged. First, once divided into responders/non-responders per treatment, samples were reduced and analyses became problematic. Thus, the treatment-specific results are preliminary, and interpretations/conclusions should be treated with caution. Second, sLORETA source-localization was used rather than dipole source analyses, which may limit our findings' generalizability. Future sLORETA work should also employ larger electrode montages, which would increase source-localization accuracy. Finally, factors such as MDD subtype (though our sample was relatively homogenous) and psychiatric co-morbidity should be better controlled for in similar work.

Future work should replicate this study using a larger sample size of responders/non-responders following single and combination antidepressant pharmacotherapy. Additionally, the contribution of individual AEPs in predicting response should be explored. Previous work suggests that the auditory N1 is associated with treatment/intervention outcome (Danos et al., 1994; Spronk et al., 2011). Future research should also investigate mid-latency AEPs (MAEPs) in the context of depression and antidepressant response. As evident in Figure 1, MAEPs (i.e., Na, Pa, Nb, and Pb/P1, peaking at ~15-25, 25-40, 40-50 and 50-80 ms, respectively) were evoked using our LDAEP paradigm. To out knowledge, no one has yet inspected whether these pre-conscious AEPs are associated with MDD and/or treatment response. Other methodological aspects that should be considered in comparable future work include presenting standard deviations (SD; versus SEMs) to more accurately reflect a sample's LDAEP slope value distributions, as well as indicating outlier presence. In the current study, three outliers in baseline LDAEP slopes measures were identified (2.5 SDs above the mean); their exclusion did not alter the results and they were thus included in the analyses (data not shown).

Finally, future work should further explore the putative utility of several electrophysiological markers in predicting treatment response within the same study, as certain markers may be better suited in predicting response to a particular class of antidepressants. The construction of a composite electrophysiological index may ultimately prove to be most sensitive in predicating response, however, large, methods-focused studies are required before this is possible.

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Relevant Abbreviations

LDAEP	loudness dependence of the auditory evoked potentials
MDD	major depressive disorder (MDD)
AEP	auditory evoked potentials
5-HT	5-hydroxytryptamine/serotonin
$HAMD_{17}$	Hamilton rating scale for depression
MADRS	Montgomery-Åsberg Depression Rating Scale

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Research Highlights

- Antidepressant responders had steep baseline N1 source localized-LDAEP (loudness dependence of the auditory evoked potential) slopes; non-responders had shallow ones.
- Responders had P2 source localized-LDAEP slope increases by week 1 post-treatment; decreases existed in non-responders.
- Slight decreases in scalp P2 LDAEP slopes existed with escitalopram treatment by week 1; increases existed with escitalopram+bupropion treatment.
- Only baseline N1 sLORETA-LDAEP discriminated treatment responders/ non-responders.

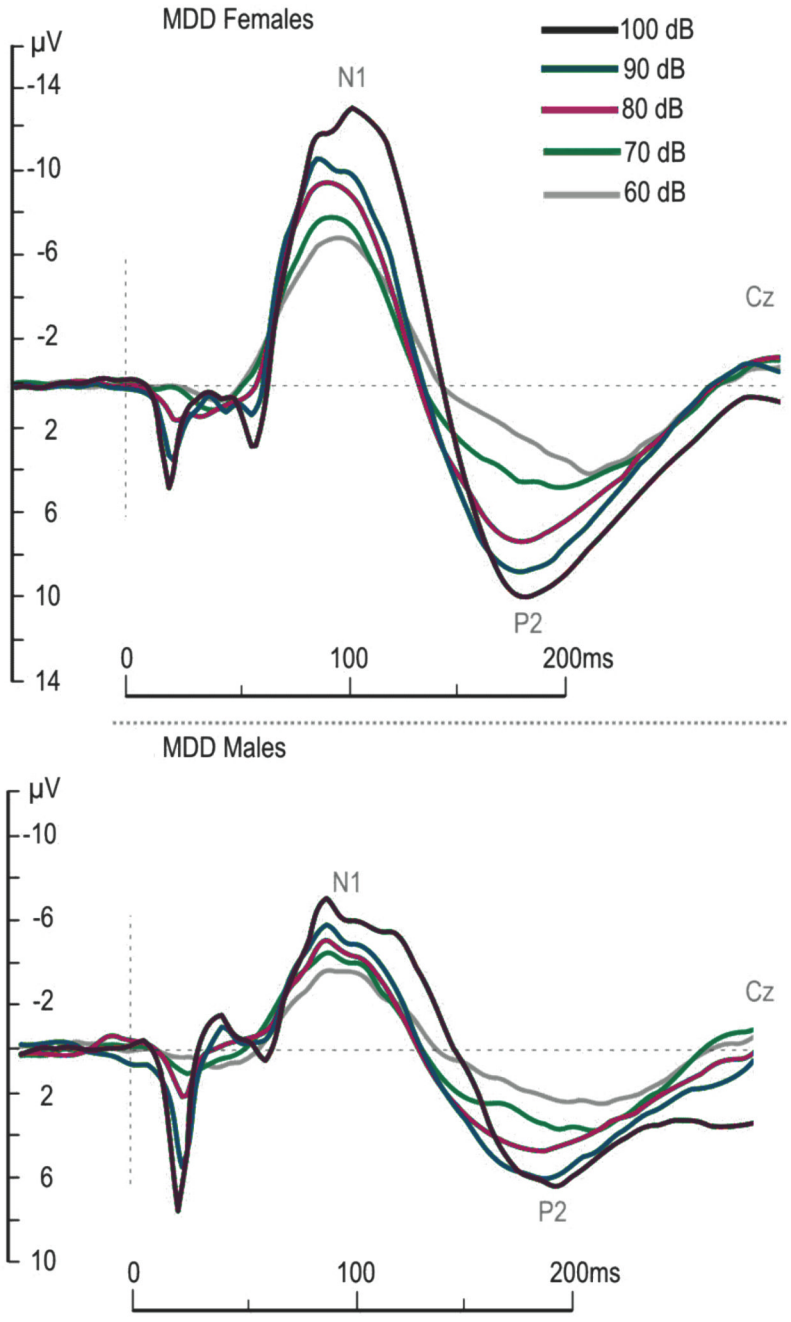

Figure 1.
Mean auditory evoked potentials (at Cz) in males and females with Major Depressive Disorder (MDD) at baseline to increasing sound intensities

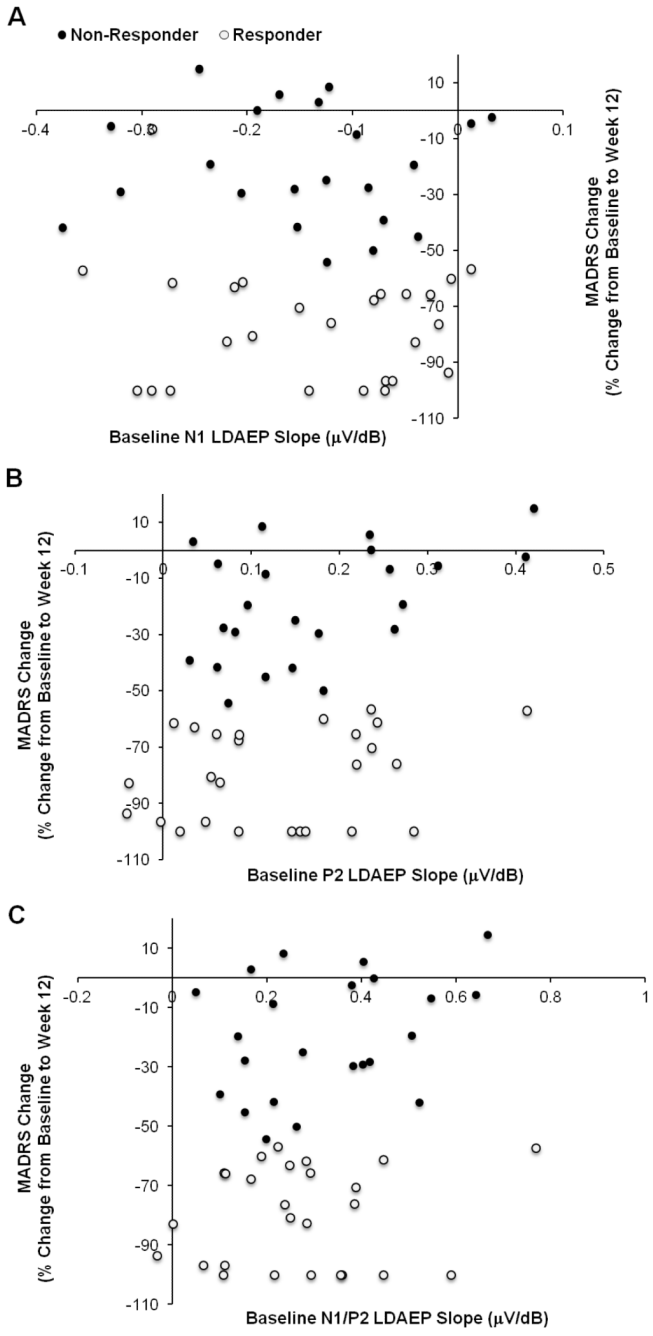

Figure 2.
Relationship between baseline scalp N1 (A), P2 (B) and N1/P2 (C) LDAEP slopes and MADRS response rates (%) from baseline to week 12; a greater decrease indicates a more pronounced antidepressant response. Treatment responders and non-responders are presented.

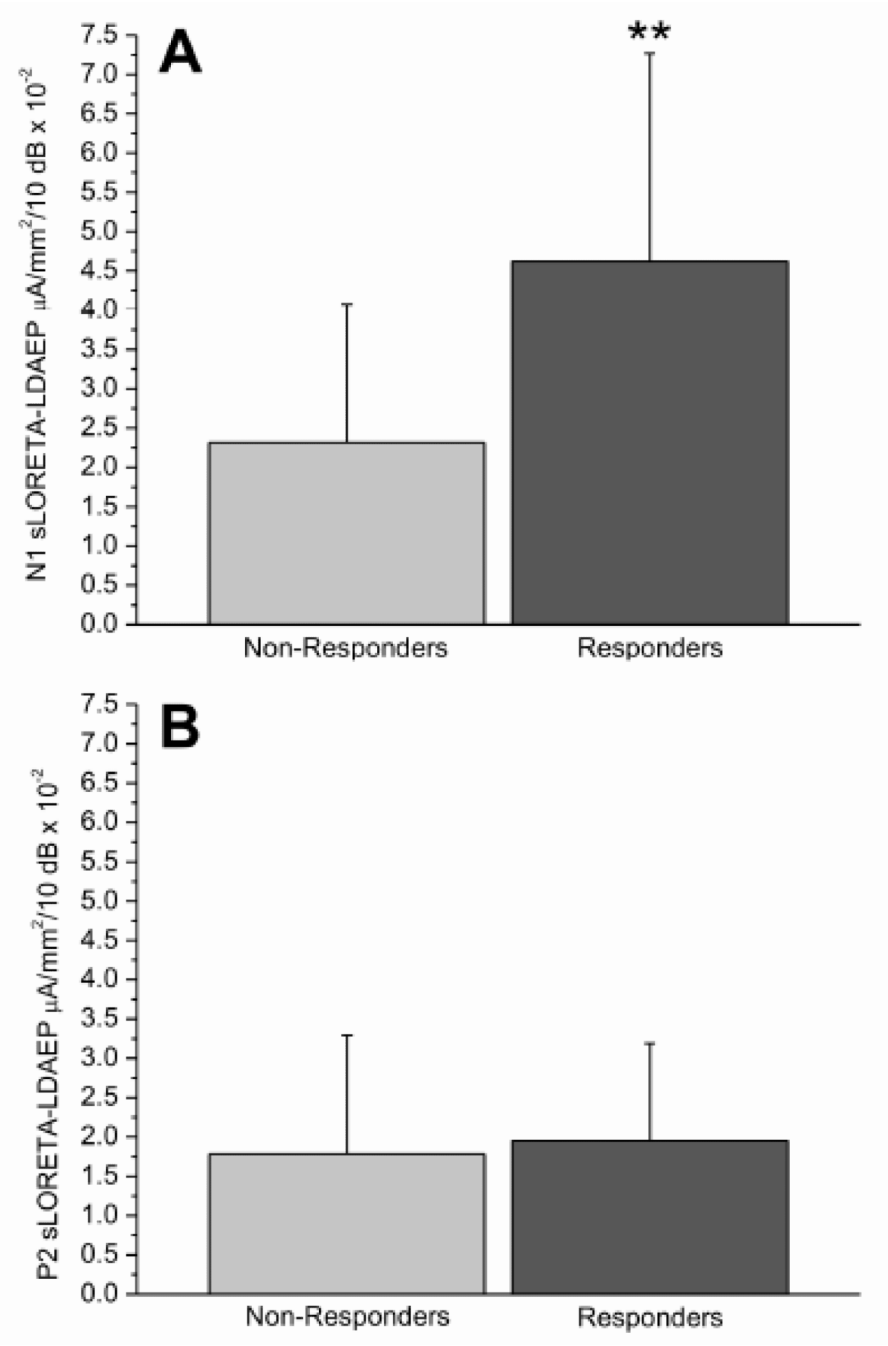

Figure 3.

Mean (+/− S.D) baseline N1 (A) and P2 (B) sLORETA-LDAEP slope values in eventual treatment responders (N=23) and non-responders (N=25) (treatment groups and sex collapsed; ** $p<0.01$)

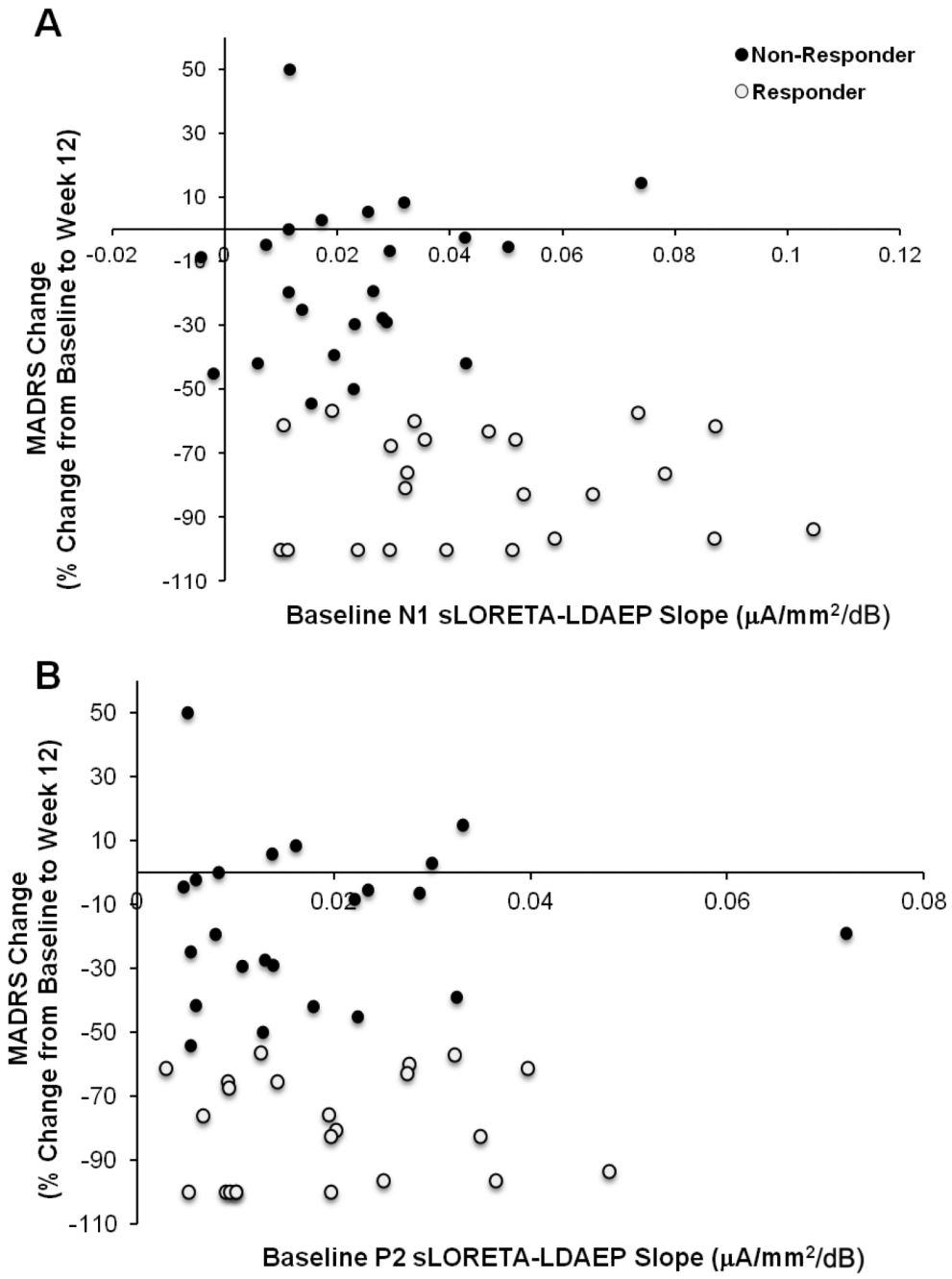

Figure 4.

Relationship between N1 (A) and P2 (B) sLORETA-LDAEP slopes and MADRS response rates (%) from baseline to week 12; a greater decrease indicates a more pronounced antidepressant response. Treatment responders and non-responders are presented.

Table 1

Baseline characteristics of individuals with major depressive disorder (MDD; means ± S.D.)

	MDD (Total N=51)
Sex (Females/Males)	28/23
Age (years)	30.4 ± 11.8
Education (years)	16.0 ± 2.4
Smoker (N)	10
Ethnicity (N)	45 Caucasian; 3 Asian; 1 South Asian; 1 African
Depression Type (N)	23 melancholic; 18 atypical; 11 neither/not catatonic

Table 2

Number of responders/non-responders per treatment group

	ESC+BUP	BUP	ESC
N = Total	17	16	18
N = Responders/ Non-Responders	12/5	7/9	7/11

ESC: escitalopram; BUP: bupropion

Table 3

Clinical ratings in individuals with Major Depressive Disorder (MDD) at baseline, weeks 1 and 12 post-treatment, collapsed across treatments (means ± S.D.)

Clinical Measures	Baseline	Week 1	Week 12*
	Overall (N=51)		
$HAMD_{17}$	20.6 ± 4.9	17.7 ± 7.1	11.0 ± 8.4
MADRS	30.5 ± 5.2	26.2 ± 8.7	15.9 ± 12.5
	Responder (N=26)		
$HAMD_{17}$	19.6 ± 5.9	14.7 ± 5.6	4.4 ± 3.2
MADRS	29.4 ± 4.5	22.9 ± 8.0	5.8 ± 4.9
	Non-Responder (N=24)		
$HAMD_{17}$	21.6 ± 3.4	20.8 ± 7.3	17.8 ± 6.3
MADRS	31.7 ± 5.7	29.8 ± 8.0	26.4 ± 8.7

$HAMD_{17}$: Hamilton Rating Scale for Depression, 17 item version

MADRS: Montgomery- Åsberg Depression Rating Scale

*Scores are obtained at week 12 or last session carried forward (sessions <6 weeks were not carried forward)