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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.

1. 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 and 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 (Lam et al., 2004; Spier, 1998), 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

Abbreviations: LDAEP: loudness dependence of the auditory evoked potentials; MDD: major depressive disorder; 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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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 preclinically (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 (Guille et al., 2008; Uhl et al., 2006) 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 (Beucke et al., 2010; Juckel et al., 1997; Lee et al., 2011, but see Oliva et al., 2010; O'Neill et al., 2006, 2008).

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: Gallinat et al., 2000; Mulert et al., 2002, 2007; Paige et al., 1994; 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: Juckel et al., 2007; Linka et al., 2005; 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 (Gallinat et al., 2000; Paige et al., 1995), 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 (Hagenmuller et al., 2011; Mulert et al., 2002). 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; Jaworska et al., 2012; Oliva et al., 2011), 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.

2. Methods

2.1. 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 and 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.

2.2. 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 ($\text{HAMD}_{17} \leq 7$ 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