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The Antidepressant Treatment Response Index as a Predictor of Reboxetine Treatment Outcome in Major Depressive Disorder

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Abstract

Biomarkers to predict clinical outcomes early during the treatment of major depressive disorder (MDD) could reduce suffering and improve outcomes. A quantitative electroencephalogram (qEEG) biomarker, the Antidepressant Treatment Response (ATR) index, has been associated with outcomes of treatment with selective serotonin reuptake inhibitor antidepressants in patients with MDD. Here, we report the results of a post hoc analysis initiated to evaluate whether the ATR index may also be associated with reboxetine treatment outcome, given that its putative mechanism of action is via norepinephrine reuptake inhibition (NRI). Twenty-five adults with MDD underwent qEEG studies during open-label treatment with reboxetine at doses of 8 to 10 mg daily for 8 weeks. The ATR index calculated after 1 week of reboxetine treatment was significantly associated with overall Hamilton Depression Rating Scale (HAM-D) improvement at week 8 ($r = 0.605$, $P = .001$), even after controlling for baseline depression severity ($P = .002$). The ATR index predicted response (≥50% reduction in HAM-D) with 70.6% sensitivity and 87.5% specificity, and remission (final HAM-D ≤7) with 87.5% sensitivity and 64.7% specificity. These results suggest that the ATR index may be a useful biomarker of clinical response during NRI treatment of adults with MDD. Future studies are warranted to investigate further the potential utility of the ATR index as a predictor of noradrenergic antidepressant treatment response.

Keywords

adult, biomarker, reboxetine, quantitative EEG, antidepressant treatment response (ATR) index, treatment outcome, major depressive disorder

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Introduction

Major depressive disorder (MDD) is estimated to affect 1 in 6 people in their lifetime.[1] MDD ranks as the leading cause of disability in terms of life years affected by disability, and its economic burden is predicted to rise in coming years.[2,3] Prompt and effective treatment of MDD therefore is a high priority goal for clinicians, patients, and society at large.

Despite the numerous antidepressant options available, predicting response to treatment remains a challenge. The current standard of care calls for a 2- to 3-month trial to determine if a patient will achieve remission with a given antidepressant medication.[4] Large studies indicate that only approximately one-third of patients remit during the first 8 to 12 weeks of treatment with a given medication.[5] Hence remission may be delayed in the majority of cases by the need to change antidepressant treatment. Clinically useful biomarkers to predict treatment-specific outcomes before or early in the course of treatment are, therefore, a crucial area of psychiatric research.

Prior research has identified several potential biomarkers of treatment response. These biomarkers include changes observed in brain imaging,[6-8] inflammatory markers,[9-14] genetic polymorphisms,[13-16] and various qEEG measurements (reviewed in Alhaj et al[17] and Hunter et al[18]). qEEG biomarkers are clinically appealing because they can be measured noninvasively, at low cost, and frequently during the course of antidepressant treatment. Several qEEG measures have been examined for their relationship to antidepressant response. These include current density in the rostral anterior cingulate cortex assessed using low-resolution electromagnetic tomography (LORETA)[19,20] and the loudness-dependent auditory evoked potential (LDAEP).[21,22] In addition, studies have examined the predictive value of absolute and relative power,

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using various methods and with different results. Bruder et al[23] examined absolute alpha and theta power in frontal, central, parietal, and occipital regions at baseline and after 12 weeks of fluoxetine treatment. They found a trend for increased absolute alpha power in occipital regions of responders versus nonresponders to fluoxetine, and also observed an effect of laterality, with responders showing significantly greater alpha power on the right than the left. This finding was not replicated in other studies of subjects treated with fluoxetine.[24,25] Knott et al[26] looked at relative alpha, beta, delta, and theta power before and after 4 weeks of treatment with imipramine using whole-head EEG and found only relative theta power was decreased in responders compared with nonresponders. Of interest to our study, this group reported that after 2 weeks of drug therapy, responders had significantly greater anterior (FPz, FP1, FP2, F3, and F4) relative theta power than nonresponders. Another study examined relative non-alpha power in subjects treated with clomiprimine (a serotonin reuptake inhibitor) or maprotiline (an NRI) and found that responders had higher frequencies than nonresponders at baseline, but the values were so close as to have limited clinical utility in predicting individual responses.[27] More recent studies have examined regional measures of cordance, a metric that incorporates both absolute and relative power, and has been shown to associate with brain perfusion.[18,24,25,28,29] In a study examining cordance, medication responders (fluoxetine or venlafaxine) demonstrated significant differences in cordance of prefrontal regions at 1 week of treatment.[25] Several other qEEG results indicate that electrodes from the prefrontal regions may yield the most useful information regarding medication response, possibly because activity in this brain region reflects activity of the anterior cingulate cortex and dorsolateral prefrontal cortex (DLPFC)[18,20,25,28,30-33] and may reflect abnormalities associated with MDD.[34] Prefrontal electrodes have the advantage that they can be easily and reliably applied outside the hairline, and are well tolerated by patients. Therefore, our group and others have pursued a focused frontal qEEG array as a clinically useful tool to predict response in MDD.[35-40]

A recently refined frontal qEEG marker, the Antidepressant Treatment Response index (hereafter referred to as "ATR"; Covidien plc; Boulder, CO), has been shown to have a strong relationship to clinical response to escitalopram[38] and fluoxetine[39] selective serotonin reuptake inhibitor (SSRI) medications, as well as bupropion,[40] a medication whose mechanism of action is not clearly established.[40] In a large-scale trial, this measure, calculated after one week of treatment, was found to be highly predictive of escitalopram treatment outcome at 7 weeks[38] as well as sustained remission over 13 weeks.[41] ATR also appears to be a specific predictor of treatment outcome as it is not associated with response to placebo.[39] From previous results, it is unclear to what extent the putative neurochemical target of an antidepressant medication affects the performance accuracy of ATR. In the present study, we therefore examined retrospectively whether ATR might also correlate with outcome in MDD subjects treated with reboxetine, a selective NRI.

Methods and Materials

Study Design

This study was conducted in the Laboratory of Brain, Behavior, and Pharmacology at University of California, Los Angeles. The institutional review board approved the methods of the study, and all subjects gave written informed consent prior to any experimental procedures. On day 1, subjects were screened with the 17-item HAM-D and a baseline QEEG was obtained. To be eligible for the study, subjects were required to have a score higher than 16 on the HAM-D, with a score of 2 or greater on the depressed mood item. After 1 week of single-blinded treatment with placebo, the HAM-D was repeated. Subjects who had a >50% reduction in their baseline HAM-D score or had a score of 16 or lower at the end of the placebo lead-in were withdrawn from the study. Eight weeks of open-label reboxetine treatment was then initiated, with a dose of 4 mg per os (orally) twice a day. Response was defined as a HAM-D score reduction of ≥50% and remission was defined as a HAM-D score of ≤7. At day 29, those subjects who had not met response criteria (ie, those with HAM-D >50% of baseline) were eligible for a dose increase to 4 mg per os every day before noon and 6 mg per os every night at bedtime for the duration of the study. Clinical symptoms were assessed weekly during treatment using the HAM-D. EEGs were obtained at baseline (day 1) and after 7 days of treatment with reboxetine. Clinical outcome was assessed at the end of 8 weeks of treatment.

Subjects

Thirty-four adults, aged 23 to 60 years, participated in this study. Inclusion required a diagnosis of current, unipolar, nonpsychotic MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria.[42(p943)] Exclusion criteria included (*a*) any history of hypomania or mania; (*b*) history of MDDs associated with endocrine disorders; (*c*) positive pregnancy test (or planned or expected pregnancy); (*d*) females who were breastfeeding or refused to use an accepted means of birth control; (*e*) concomitant use of psychotropic medications or use of psychotropic medications within 1 week (or use of fluoxetine within 4 weeks) prior to enrollment; (*f*) history or presence of gastrointestinal, liver, kidney, or other disease known to interfere with absorption, distribution, metabolism, and excretion of drugs; (*g*) history of seizures or brain injury, current evidence of clinically important hematopoietic, respiratory, or cardiovascular diseases, or current evidence of urinary retention or glaucoma; (*h*) any important clinical illness in the 2 weeks preceding the study that might interfere with the conduct of the trial; and (*i*) clinically relevant abnormal findings in the physical examination, laboratory tests, and electrocardiography at screen.

Electroencephalogram Biomarker Methods

qEEG recordings for this analysis were obtained at pretreatment baseline and after 1 week of reboxetine treatment.

Recordings were made with the QND System (Neurodata, Inc, Pasadena, CA), using procedures employed in our previous reports,[25,29,43] and summarized briefly here. During the EEG recording, subjects were instructed to rest with eyes-closed while maintaining a maximal level of alertness. Technicians monitored the QEEG data throughout the recording. Subjects were realerted by the technicians every 30 to 45 seconds to prevent drowsiness when necessary. Thirty-five recording electrodes were placed across the head according to an extended International 10-20 System montage using an electrode cap (ElectroCap, Eaton, OH). Data were collected using a Pz referential montage and were digitized at 256 samples/channel/s by the QND System (bandpass filtered 0.3-70 Hz). After automated artifact rejection to eliminate EEG contaminated with eye movement, muscle and other artifacts, power spectra of the EEG were calculated using 2-second epochs of an eyes-closed resting period. Values were then calculated separately for each channel in each epoch.

Similarly to previous reports,[38] ATR was calculated from bipolar ear-referenced channels A1-Fpz and A2-Fpz (average of the 2 channels). ATR is a nonlinear weighted combination of three EEG features, measured at baseline and 1 week after the start of treatment, that previously were identified as being associated with antidepressant outcome.[25,37,44] These 3 features are relative combined theta and alpha power (3-12 Hz), alpha1 absolute power (8.5-12 Hz), and alpha2 absolute power (9-11.5 Hz). Relative combined theta and alpha power (3-12 Hz) is calculated as the ratio of absolute combined theta and alpha power divided by total power (2-20 Hz). ATR (version 4.1) employs a weighted combination of relative theta and alpha power at week 1, and the difference between alpha1 power at baseline and alpha2 power at week 1, scaled to range from 0 (low probability) to 100 (high probability of response), using the following formula[38]:

$$ATR = \max\{0, \min(100, \{A^*(\mathrm{AP}(t_1, \alpha_a) + B^*(\mathrm{RP}(t_1, \theta+\alpha)) + C\})\},$$

where A^* and B^* are weighting functions, C is a constant, AP and RP are absolute and relative power values, respectively, at the times (0 or 1 week) and frequency bands (alpha1, alpha2, or combined theta + alpha) indicated.

Data Analysis

Statistical analyses were performed using SPSS software (SPSS, Inc; Chicago, IL). We used the Shapiro–Wilk statistic to assess normality of the ATR data. On finding no evidence for a nonnormal distribution ($P > .05$), parametric measures were used for subsequent analyses. Between-subjects, 1-tailed Student's t tests were used to compare mean ATR values between remitters and nonremitters, and responders and nonresponders, consistent with our directional hypotheses that higher ATR values would be associated with response and remission. ATR values were correlated with overall HAM-D score change and percentage HAM-D score change over 8 weeks of treatment using a bivariate correlation model. Linear regression was used in our retrospective analysis to assess whether ATR remained a significant predictor of outcome when controlling for baseline HAM-D severity and HAM-D change after one week of treatment. Receiver operating characteristic (ROC) curves were generated to model the sensitivity versus (1 − specificity) for ATR as a predictor of remission and response. A threshold ATR value was determined from these curves to optimize predictive accuracy. Using the optimized cutoff, we calculated the positive predictive value (PPV) and negative predictive value (NPV) for response and remission outcomes. Chi-square analysis was used with a 1-tailed Fisher exact probability test to compare ATR cutoffs from this data set with other cutoffs in their ability to determine response and remission.

Table 1. Subject Characteristics.

Total, n	25
Age in years, mean (SD)	42.9 (11.1)
Female:male ratio	16:9
HAM-D (17 items) score, mean (SD)	22.8 (3.07)
Percentage with prior antidepressant treatment	80
Percentage with family history of depression	84
Average age in years at symptom onset	19.9
Percentage with comorbid anxiety	40
Percentage with dysthymia and depression	32

Abbreviations: SD, standard deviation; HAM-D, Hamilton Depression Rating Scale.

Results

Subject Characteristics

A total of 34 subjects met study inclusion and exclusion criteria and entered the protocol. Six subjects exited the study before completion (1 female for response during the placebo week and 1 male for intolerable side effects during that period; 3 males and 1 female for later, treatment-emergent side effects) and 3 (2 males, 1 female) completed the trial but had EEG data that could not be analyzed because of excessive artifact. Analyses for this report were conducted using data from the 25 subjects who completed the study and had usable EEG data. Subject characteristics at entry are provided in Table 1.

Response to Reboxetine

After the 8-week treatment course with reboxetine, 68% of subjects responded (HAM-D score ≤50% of baseline) and 32% of subjects remitted (HAM-D score ≤7).

ATR and treatment outcome. The mean ATR value of responders was significantly higher than nonresponders ($P = .04$), as was the mean ATR value of remitters compared to nonremitters ($P = .045$). ATR was significantly associated with absolute

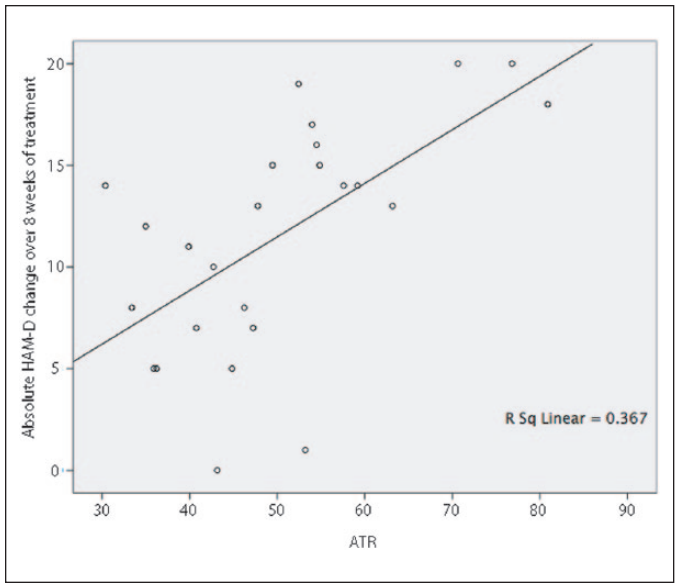

Figure 1. Correlation of Antidepressant Treatment Response (ATR) index value and absolute Hamilton Depression Rating Scale (HAM-D) change in subjects treated with reboxetine for 8 weeks.

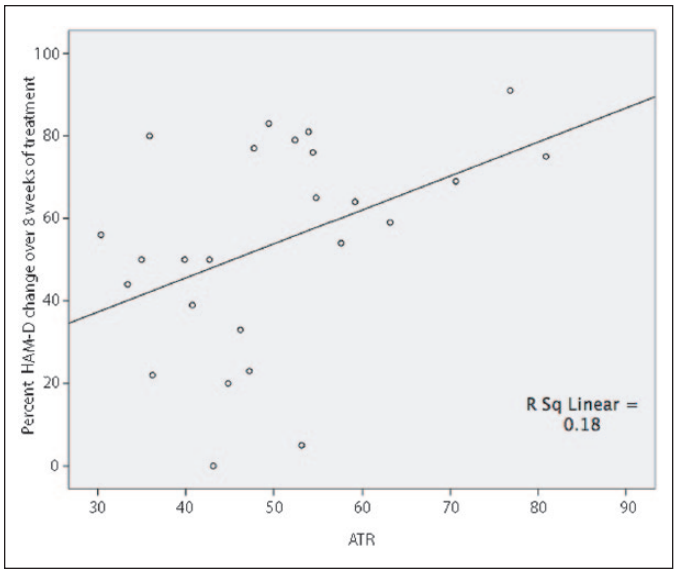

Figure 2. Correlation of Antidepressant Treatment Response (ATR) index value and percentage Hamilton Depression Rating Scale (HAM-D) score improvement in subjects treated with reboxetine for 8 weeks.

improvement in HAM-D score over the 8-week study (Pearson $r = 0.61$, $P = .001$), with higher ATR values correlating with a greater decrease in HAM-D scores (Figure 1). ATR was also significantly associated with overall percentage change in HAM-D scores ($r = 0.43$, $P = .034$; Figure 2).

We next evaluated the clinical measurements of baseline HAM-D score and week 1 HAM-D change for their ability to predict response, remission, and overall HAM-D improvement. Baseline HAM-D score was not significantly correlated with response ($r = -0.10$, $P = .63$), remission ($r = -0.20$, $P = .31$), or overall HAM-D change ($r = 0.12$, $P = .56$) over the 8 weeks of treatment. Similarly, HAM-D change after 1 week of treatment was not significantly correlated with response ($r = -0.11$, $P = .59$), remission ($r = 0.04$, $P = .85$), or overall HAM-D improvement ($r = -0.17$, $P = .38$).

A regression model was used to determine whether ATR remained a significant predictor of overall improvement when controlling for baseline depression severity. The regression model showed that ATR remained a significant predictor of overall HAM-D change, even when baseline HAM-D was used as a covariate ($\beta = 0.61$, $P = .002$).

Receiver Operating Characteristic Analysis of Clinical Outcomes

To assess the clinical utility of ATR in this sample, we generated ROC curves to visualize the association of the ATR value with response or remission to reboxetine treatment. The area under the ROC curve for response was 0.74 ($P = .06$; Figure 3). The area under the ROC curve for remission was 0.69 ($P = .13$; Figure 4). The optimal ATR cutoff obtained from these ROC curves was 47.5. Using this as a threshold value to classify

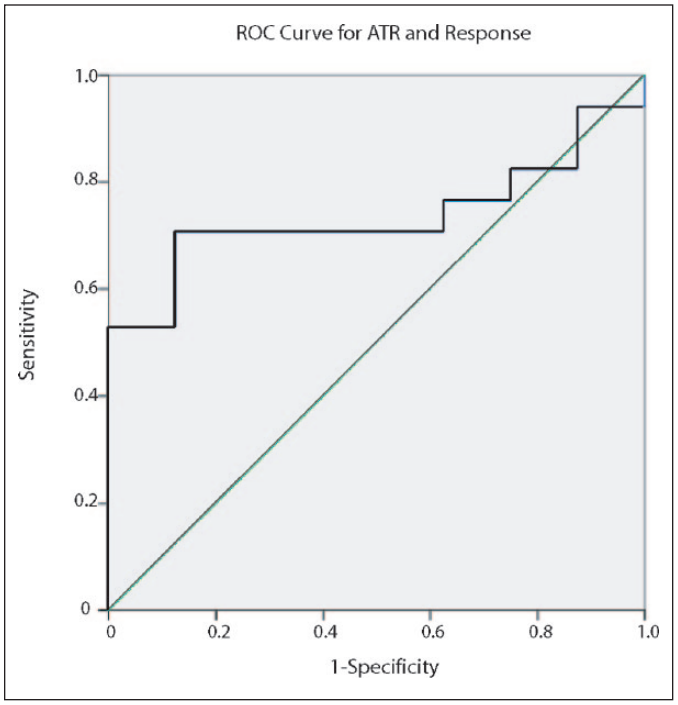

Figure 3. Receiver operating characteristic (ROC) curve showing Antidepressant Treatment Response (ATR) index as a predictor of response (Hamilton Depression Rating Scale [HAM-D] score reduction of at least 50%) in subjects treated with reboxetine.

subjects as ATR positive (ATR ≥47.5) or ATR negative (<47.5), we found that ATR positive status would have predicted response to reboxetine with a sensitivity of 70.6% and specificity of 87.5%, yielding a PPV of 92.3%, and NPV of 58.3%. The

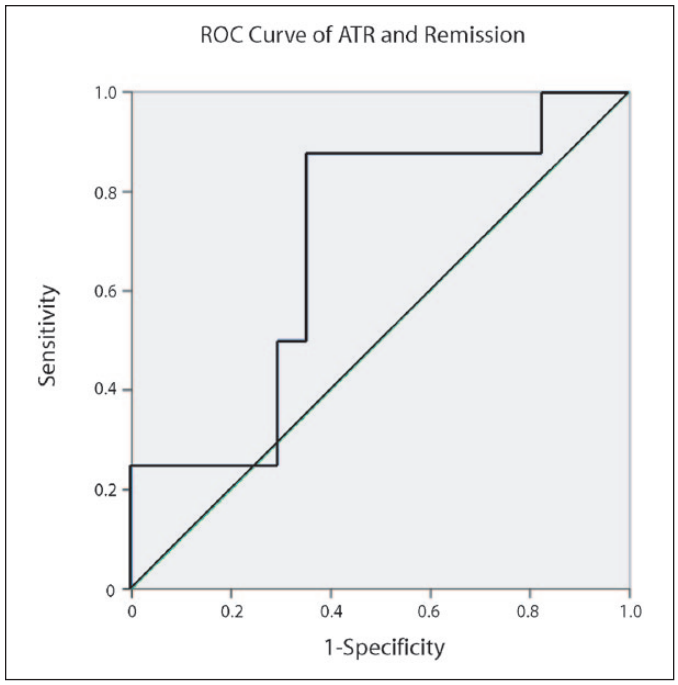

Figure 4. Receiver operating characteristic (ROC) curve showing Antidepressant Treatment Response (ATR) index as a predictor of remission (Hamilton Depression Rating Scale [HAM-D] score ≤7) in subjects treated with reboxetine.

ATR cutoff of 47.5 would have predicted remission with a sensitivity of 87.5% and specificity of 64.7%, resulting in a PPV of 53.8%, and NPV of 91.7%.

Discussion

This report presents our investigation of an exploratory aim to test whether the ATR index, a simple frontal qEEG biomarker that has been shown to predict antidepressant treatment response to SSRIs, may also have utility in predicting treatment response to an NRI antidepressant, reboxetine. Results of this post hoc analysis from whole-head qEEG data indicate that the ATR index value calculated after 1 week of treatment with reboxetine was significantly associated with response and remission at 8 weeks. The ATR index also was correlated with the overall degree of improvement in HAM-D score at the end of 8 weeks of treatment. The positive correlation of ATR with treatment outcome remained significant even when controlling for baseline depression severity. In contrast, clinical symptom improvement, as measured by 1-week change in HAM-D score, did not predict overall improvement after 8 weeks of treatment. Taken together, these results indicate that future prospective studies are warranted to test the a priori hypothesis that ATR index may be a predictor of antidepressant response for drugs that work primarily via noradrenergic mechanisms.

These results are consistent with prior studies, which have shown that higher ATR predicts remission in patients treated with escitalopram,[38] fluoxetine,[39] or bupropion.[40] Similarly, a naturalistic replication study of patients treated with various SSRIs or venlafaxine also reported that higher ATR values predicted response to antidepressant treatment.[35] The ATR index incorporates measures of theta and alpha band activity, and the usefulness of ATR may be consistent with prior reports that theta and alpha power measurements differentiate between responders and nonresponders to antidepressant medication.[23,26] However, differences in electrode placement, as well as the time points at which EEG was measured, preclude a direct comparison among these studies.

The ATR index appears to represent an early change in frontal brain function during reboxetine treatment, one that seems to have preceded clinically detectable symptom improvement. Such early changes in neurons exposed to reboxetine are not without precedent; short-term reboxetine treatment has been shown to cause significant brain functional changes and neurophysiologic changes at a cellular level. In humans, 1 week of reboxetine administration was associated with improved speed in the categorization of positive self-referential characteristics as well as improved recall of positive emotional words in healthy controls.[45] This same group of investigators later studied depressed subjects, whose delay in response categorization of self-referential characteristics was reversed by a single dose of reboxetine, despite the fact that the single dose of reboxetine had no effect on self-reported measures of mood and anxiety.[46] Single doses of citalopram or reboxetine have been reported to lead to faster emotional decoding in healthy, nondepressed adult males, as measured by speed to categorize happy versus neutral facial images.[47] Imaging studies to investigate this finding using functional magnetic resonance imaging have shown increased blood oxygen level–dependent response to positive personality trait words in the precuneus and interior frontal gyrus in healthy adults receiving reboxetine for 7 days prior to evaluation.[48] Work by another group showed that just 2 days of subcutaneous reboxetine administration in rats led to a dose-dependent, significant decrease in the firing rates of locus coeruleus noradrenergic neurons, as measured using extracellular unitary recording in vivo.[49] It is possible that such alterations in cognitive and emotional performance, brain function, and neuronal firing in response to reboxetine are related to the brain functional changes underlying the ATR index. Future studies in humans could examine associations between the ATR index and cognitive, emotional, or brain functional measures to address some of the mechanisms underlying the index. The components of ATR also could be examined in animal models to elucidate some of the basic neurophysiologic mechanisms of the measure.

These results should be interpreted in the context of several limitations. The sample size of this study was relatively small (N = 25) and included individuals with high rates of prior antidepressant treatment (80%), family history of depression (84%), and comorbid anxiety (40%). Unfortunately, we did not collect information regarding number, dose, and duration of past medication trials for these subjects. It is unknown whether similar results would be obtained in treatment-naïve individuals, those

without family history of depression, or with lower comorbid anxiety. In addition, the subjects were predominantly female, although there were not significant differences between the mean ATR values of men and women. The optimal ATR threshold calculated for this cohort treated with reboxetine (47.5) is different from the ATR threshold that has previously been reported for other drug classes (58.6).[38,39] It is unknown whether this variation reflects differences in the subject pools, use of a medication with a different mechanism of action, or other factors that have not been recognized or controlled in this retrospective analysis. Interestingly, analysis of these data for subjects treated with reboxetine using the optimal ATR cutoff determined in prior studies, drastically reduced the sensitivity of predicting response and remission, but had no effect on specificity (data not shown). In translation to the clinical setting, this suggests that the ATR index calculated after 1 week of treatment may have greatest value in indicating when a subject may benefit from a switch to an alternative drug therapy. Future studies should enroll larger numbers of subjects treated with a broader range of medications in order to further examine and clarify these factors. We also are not able to determine based on these results whether there was any relationship between medication dose and the accuracy of ATR. Dosage in this study was adjusted on clinical judgment of tolerability and symptom change, as well as subject preference, and therefore was not performed according to a systematic protocol. Furthermore, no follow-up ATR recordings were performed. Future studies that use a dose increase or flexible dosing might do well to assess ATR, not only at pretreatment baseline, but again just prior to change or escalation in dose to compare the predictive capability of ATR measures taken at these time points.

Finally, it is important to note that ATR is an empirically derived index that is associated with response to antidepressant treatment, and that a physiologic mechanism to explain the association between early changes in brain oscillatory activity and later clinical effectiveness has not been fully elucidated. Llinás and colleagues have proposed that MDD is a disorder characterized by "thalamocortical dysrhythmia" in which there are disruptions in the regulation of theta and alpha oscillatory synchrony.[50,51] It is possible that ATR is detecting the early effects of medications in changing regulation of theta and alpha oscillatory synchrony and resetting thalamocortical oscillators.[52] Future studies should examine the relationship between theta and alpha oscillatory synchrony in greater detail to determine if it may be related to clinical improvement. In terms of future clinical utility, this study used a 10-20 system montage to reject artifact. Before ATR can be used in a clinical setting, any limited-electrode EEG that is to be used will need to be tested to determine that it can accurately detect and eliminate artifact.

These results showing a correlation between the ATR index and treatment outcomes in MDD patients treated with a selective NRI antidepressant, add to the growing evidence of the ATR index as a biomarker of clinical prognosis. ATR may have potential clinical utility in predicting response to antidepressants that act via norepinephrine, as well as serotonin-reuptake blockade mechanisms. We have access to the software version 4.1 used to calculate ATR using whole-head qEEG data and welcome inquiries from researchers interested in further testing the utility of the ATR index in predicting antidepressant response from independent data sets.

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Declaration of Conflicting Interests

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