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Neurophysiologic predictors of response to atomoxetine in young adults with attention deficit hyperactivity disorder: A pilot project

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ABSTRACT

Atomoxetine is a non-stimulant medication with sustained benefit throughout the day, and is a useful pharmacologic treatment option for young adults with Attention-Deficit/Hyperactivity Disorder (ADHD). It is difficult to determine, however, those patients for whom atomoxetine will be both effective and advantageous. Patients may need to take the medication for several weeks before therapeutic benefit is apparent, so a biomarker that could predict atomoxetine effectiveness early in the course of treatment could be clinically useful. There has been increased interest in the study of thalamocortical oscillatory activity using quantitative electroencephalography (qEEG) as a biomarker in ADHD. In this study, we investigated qEEG absolute power, relative power, and cordance, which have been shown to predict response to reuptake inhibitor antidepressants in Major Depressive Disorder (MDD), as potential predictors of response to atomoxetine. Forty-four young adults with ADHD (ages 18–30) enrolled in a multisite, double-blind placebo-controlled study of the effectiveness of atomoxetine and underwent serial qEEG recordings at pretreatment baseline and one week after the start of medication. qEEG measures were calculated from a subset of the sample ($N = 29$) that provided useable qEEG recordings. Left temporoparietal cordance in the theta frequency band after one week of treatment was associated with ADHD symptom improvement and quality of life measured at 12 weeks in atomoxetine-treated subjects, but not in those treated with placebo. Neither absolute nor relative power measures selectively predicted improvement in medication-treated subjects. Measuring theta cordance after one week of treatment could be useful in predicting atomoxetine treatment response in adult ADHD.

1. Introduction

Atomoxetine is a selective noradrenergic reuptake inhibitor with demonstrated efficacy in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) (Prince, 2006). Although its precise therapeutic mechanism of action is unknown, atomoxetine is a selective inhibitor of the pre-synaptic norepinephrine transporter, and may therefore reduce ADHD symptoms primarily as an indirect agonist of catecholamine signaling in the prefrontal cortex, modifying the signal-to-noise ratios thought to influence difficulties in attention and impulse control that are central to the disorder (Arnsten, 2009). While benefits from atomoxetine have been observed as early as one week after reaching an optimal therapeutic dose, most research suggests that full effects are not evident for up to six weeks after the start of treatment (Michelson et al., 2002). This response delay, in contrast to the immediate effects seen with stimulants, has proven vexing to clinicians and costly to patients who must take the drug for several weeks before its therapeutic effect becomes evident.

Studies have suggested that atomoxetine may be a preferred treatment in selected patients. Atomoxetine may be considered a first-line treatment for patients with comorbid anxiety or active

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substance abuse disorders and is preferred in individuals who suffer from stimulant related side effects such as increased mood lability or tics (Pliszka et al., 2006). One study demonstrated enhanced response in patients identified as cytochrome P_{450} 2D6 slow metabolizers, presumably due to increased drug plasma levels on standard doses (Michelson et al., 2007). Beyond these narrow instances, clear guidelines for when atomoxetine should be selected for particular patients have remained elusive.

Several preliminary lines of investigation have explored potential predictors of ADHD treatment response, particularly with methylphenidate. Over 50 small studies of the moderating effects of various candidate genes on methylphenidate response currently appear in the literature, with the majority of these showing conflicting outcomes, or at best numerous small genetic effects (Kieling et al., 2010; McGough et al., 2009). There has been growing interest in recent years in the use of quantitative electroencephalography (qEEG) both for assessment and prediction of response to treatment of individuals with ADHD (Rothenberger, 2009). A number of qEEG studies have shown abnormal patterns of both low and high frequency neuronal oscillatory activity in ADHD (cf. Sukhodolsky et al., 2007). The abnormal oscillatory activity in ADHD may reflect a deficit in integrative or inhibitory processing (Başar and Güntekin, 2008) and may be related to defects in default mode network regulation by subcortical structures in these patients, including the thalamus and striatum (Başar and Güntekin, 2008; Broyd et al., 2009). This disturbed oscillatory activity is suggestive of thalamocortical dysrhythmia (Sukhodolsky et al., 2007).

Previous studies on the relationship between treatment response and oscillatory activity are inconclusive. qEEG analyses of the effects of ADHD medications, particularly the stimulants and atomoxetine, have demonstrated normalization of beta and theta activity in ADHD patients (Barry et al., 2009; Leiser et al., 2011). One review concluded, however, that clinical qEEG testing provided no additional information on individual drug response beyond what could be surmised from clinical data (Loo and Barkley, 2005). qEEG cordance is a measure of regional brain activity that is sensitive to the effects of reuptake inhibitor antidepressant medications (Leuchter et al., 2008; Cook et al., 2002), and has not been studied previously in ADHD. Cordance is complementary to measures of qEEG absolute and relative power (Leuchter et al., 1999), and therefore may reflect aspects of brain function that are not captured by conventional power measures. As an indicator of the activity of monoamine reuptake inhibitor medications, cordance detects the effects of the mixed reuptake inhibitor venlafaxine in normal controls (Leuchter et al., 2008), can predict the clinical effectiveness of reuptake inhibitor antidepressant medications in MDD (Cook et al., 2002, 2009; Bares et al., 2007, 2008, 2010), and can differentiate medication and placebo response in MDD (Leuchter et al., 2002). We therefore explored the usefulness of cordance for detecting the effects of the reuptake inhibitor atomoxetine. This preliminary investigation explored the potential utility of qEEG cordance, as well as absolute and relative power, as possible predictors of clinical response to atomoxetine in young adults with ADHD.

2. Methods and materials

2.1. Study overview

This study was conducted as an addendum at three of 32 investigative sites participating in a study of the effectiveness of atomoxetine in reducing symptoms and improving quality of life in young adults with ADHD (ClinicalTrials.gov identifier NCT00510276). The three investigative sites were selected based upon their capability to perform qEEG recordings in the clinical trial setting, and all subjects enrolled in the effectiveness study at these sites were offered the opportunity to participate in the qEEG study. Complete design and methods for the effectiveness study are reported separately (Durell et al., 2013) and are described only briefly below.

2.2. Inclusion criteria

Adults ages 18–30 years meeting *DSM-IV* (DSM-IV-TR) (American Psychiatric Association, 2004) criteria for ADHD as determined by the Adult ADHD Clinician Diagnostic Scale (version 1.2) and who had a Clinical Global Impressions-ADHD Severity (CGI-S) score of 4 (moderate symptoms) or greater were eligible for the study. Subjects with ADHD were excluded if they also met diagnostic criteria for other Axis I disorders including major depression, panic disorder, post-traumatic stress disorder, eating disorder, or substance abuse or dependence, as well as current or lifetime diagnosis of Obsessive-Compulsive Disorder, Bipolar Disorder, or psychosis. Excluded medications were those known to significantly affect brain function and the EEG, including antidepressants, antipsychotics, benzodiazepines, sedative-hypnotics, anticholinergics, stimulants, and narcotic analgesics, but could be tapered off excluded medications by their primary physician if clinically appropriate prior to entry to the study. Subjects who required one or more of these medications and could not be tapered off them by their primary physician were excluded from the study. All subjects received no excluded medications for at least 10 days prior to the first qEEG recording, so that the washout period was sufficient to ensure that there would be no significant residual effect of an excluded medication on brain function. No subjects were tapered from antidepressant or antipsychotic medications exclusively in order to participate in the qEEG study.

The study was conducted in accordance with the Declaration of Helsinki. Prior to the study, subjects were provided with verbal and written descriptions of protocol requirements, and gave written consent under procedures approved by each participating site's Institutional Review Board.

2.3. Treatment protocol

The study began with a screening period (5–28 days) during which subjects ($N = 54$) could be tapered from medications excluded by the study protocol. Subjects showing a 25% or more reduction in their ADHD symptoms during the screening period, as measured by the Conner's Adult ADHD Rating Scale, Screening Version (CAARS) (Conners et al., 1999) total ADHD symptom score, were excluded from the study. After the screening period, subjects were randomized in a double-blinded manner at the site level to receive 12 weeks of treatment with atomoxetine or placebo. The study employed a double-blind, placebo lead-in period with both investigators and subjects blinded as to the actual duration of the lead-in period (seven days) as well as treatment assignment throughout the clinical trial. For this report, data were analyzed for all subjects ($n = 44$) who completed 12 weeks of treatment and had useable qEEG data (14 receiving atomoxetine, 15 receiving placebo).

2.4. Dosing

Atomoxetine treatment was initiated at 40 mg/day (dosed 20 mg bid) for a minimum of 7 days, after which the dose was increased to 80 mg/day (dosed 40 mg bid). After 8 weeks, the dose could be increased to the maximum of 100 mg/day (dosed 50 mg bid) for the treatment of residual symptoms (Adler et al., 2008, 2009a, 2009b). Subjects unable to tolerate 40 mg/day were discontinued from the study (only one subject was unable to tolerate this dose). Placebo capsules were packaged and administered using the same dosage schedule in order to maintain blinding.

2.5. Efficacy measures

The primary clinical variable of interest was improvement in ADHD symptoms as rated by the investigator using the CAARS (Conners et al., 1999), with standardized interrater training (Adler et al., 2005). CAARS was assessed at baseline, randomization, after two weeks of double-blinded treatment, and again at the end of treatment. Patients with ≥25% decrease in CAARS total ADHD symptom score at the end of treatment were classified as responders, and those with <25% decrease were classified as non-responders. We also analyzed health-related quality of life at the end of treatment, as measured by the Adult ADHD Quality of Life-29 scale (AAQOL-29) (Brod et al., 2005).

2.6. EEG recordings

EEGs were recorded immediately prior to randomization, and again after one week of treatment. EEGs were recorded using methods that have been described previously (Cook et al., 2002; Hunter et al., 2009). Recordings were performed while subjects lay quietly with eyes closed in a sound attenuated room. Subjects were alerted frequently to avoid drowsiness, and were instructed to remain still and inhibit blinks or eye movements during each recording period. EEG was recorded using a 36-channel enhanced version of the International 10–20 System of Electrode Placement with additional electrodes located over prefrontal and parietooccipital regions (Fig. 1). Ag/AgCl electrodes were placed using an electrode cap (ElectroCap, Inc.; Eaton, OH) referenced to Pz. Electrode impedances were balanced and under 5 kΩ for all channels. Vertical and horizontal electrooculograms (EOG) were recorded for identification of eye movement artifact using bipolar electrodes placed at the supraorbital and infraorbital ridge of the right eye and the outer canthi of the left and right eye, respectively. Impedance was maintained below 5 KΩ in all electrodes.

A minimum of 10 min of EEG data were recorded using a 16-bit resolution Neuroscan system (Compumedics, Inc.; El Paso, TX) at a sampling rate of 500 Hz, a high-frequency filter of 70 Hz, and a low-frequency filter of 0.3 Hz, as well as a notch filter at 60 Hz. Data were stored in digital format and imported into Brain Vision Analyzer (BVA) software (Brain Products GmbH; Gilching, Germany) in order to remove offsets, optimize scaling, re-reference the data, adjust the sampling rate, and segment the data into 2-s non-overlapping epochs. Epochs containing eye movement, muscle, or movement-related artifacts, or amplifier drift were removed using a semiautomated interactive process. Two technologists inspected the data independently using multiple bipolar and referential montages, and isolated and removed data segments containing artifacts. In addition, data were processed using the BVA artifact rejection module that removed data according to standard thresholds likely to represent artifact based upon voltage step gradient, absolute values of difference within the epoch, or persistent low activity.

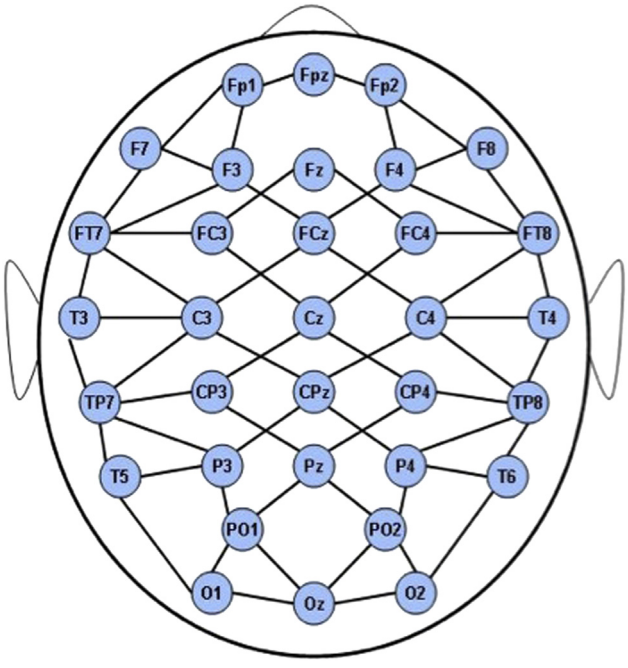

Fig. 1. Electrode montage for qEEG recordings. The montage is based upon an extension of the International 10–20 system. "Nearest neighbor" bipolar pairs for calculation of cordance values are indicated by line segments between electrodes.

The power spectral frequency of the artifact-free EEG data was calculated using the BVA fast Fourier transform (FFT) function. The 512-point FFT was calculated for artifact-free 2-s epochs with rectangular windowing, 0.5 Hz overlap at the limits of the band, and yielding a frequency resolution of 0.5 Hz. Absolute and relative power were calculated in four frequency bands, corresponding to delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–20 Hz), for all nearest neighbor bipolar pairs of electrodes (Cook et al., 1998, 2002, 2009; Hunter et al., 2009; Leuchter et al., 1994, 1999).

2.7. Cordance calculation

Calculation of cordance has been described previously (Cook et al., 2002, 1998; Leuchter et al., 1994, 1999, 2002). Cordance is based upon power spectra calculated using a fast Fourier transform, with power normalized across frequency bands and electrode sites in a three-step algorithm. First, power is reattributed from a series of bipolar pairs to individual electrodes by averaging (Cook et al., 1998), with the electrode pairs used in the cordance calculation illustrated in Fig. 1. Second, power is normalized across electrode sites using a *Z*-score transformation for both absolute power (intensity of energy in each frequency band measured in microvolts squared) and relative power (percentage of total power in each frequency band). Third, normalized absolute and relative power are summed to yield a cordance value (Leuchter et al., 1999). Cordance was calculated for qEEG data both at baseline and one week after the start of study compound; the change in cordance from baseline to week 1 was also calculated.

2.8. Data analysis

Absolute power, relative power, and cordance values for baseline, week one, and change from baseline to week 1 were assessed independently for association with outcome. Regression analyses on each clinical variable of interest were run using each electrode, for each power and cordance measure (baseline, week 1, and change), and in each of four frequency bands (delta, theta, alpha, beta). Because of the large number of statistical comparisons when analyzing data from individual electrodes, we combined electrodes to form regions of interest (ROIs). In the medication group, we searched for clusters of 3 or more contiguous electrodes in the same band that each showed the same direction of effect with at least a trend level of significance ($p < 0.1$) of association with clinical outcome (e.g., changes in CAARS total ADHD symptom score or AAQOL-29 total score). Once a potential cluster was identified, we calculated the average power or cordance value for the electrodes in the cluster on the given measure (i.e., the specific band and power or cordance measure). If the cluster as a whole was

significantly associated ($p < 0.05$) with clinical outcome, it was retained for further analyses; otherwise, it was dropped.

Data from the candidate ROIs were analyzed in an ANCOVA that included both atomoxetine- and placebo-treated subjects. The ANCOVA included the ROI as a covariate of interest, the factor of Treatment (medication or placebo), and their interaction. ROIs for which the interaction term was not significant ($p < 0.05$) were dropped from further analyses. This ensured that the cluster was associated with medication-specific effects on the clinical outcome variables.

For model validation, and to eliminate ROIs where the significance was unduly influenced by outliers, we implemented a jackknife procedure (Stata 11). The jackknife procedure was first run on each ROI in a simple regression with only the medication subjects and then repeated in an ANCOVA including both medication and placebo subjects. ROIs with significant effects in the simple linear regression, and significant interaction effects in the ANCOVA, were retained in the data analysis.

3. Results

3.1. Clinical outcome

Fifty-four subjects consented to participate in the qEEG study and entered the washout period, and forty-four completed twelve weeks of treatment (atomoxetine, $n = 20$; placebo, $n = 24$). All participants met the criteria for combined or inattentive ADHD subtypes. At least 80% of the eligible subjects at each site consented to participate in the qEEG study. Student's *t*-tests showed that there were no significant differences in age or baseline CAARS scores, and a Chi-square analysis showed that there was no significant difference in gender ratios, between those who participated and those who declined (data not presented). The most common reason that subjects declined to participate was the additional time required for qEEG recordings. Response rates were 55% in the atomoxetine group and 33% in the placebo group, with no significant differences across study sites (data not presented). Atomoxetine-treated subjects showed a mean change in CAARS total ADHD symptom score of -12.80 ± 9.45, versus -7.33 ± 10.02 for placebo-treated subjects ($t_{42} = -1.85$, $p = 0.07$). On the AAQOL-29, the mean final score for atomoxetine-treated subjects was 55.68 ± 17.94, versus 55.73 ± 17.81 for placebo-treated subjects (n.s.). Several subjects were excluded from some further analyses because of missing data: 12 subjects from all EEG analyses because of inadequate recordings at both baseline and week 1; and, 3 subjects from week 1 EEG analyses because of inadequate recordings at this time point only. This resulted in final group sizes of 14 subjects receiving atomoxetine and 15 receiving placebo. Seven of the atomoxetine-treated subjects versus six placebo-treated subjects fulfilled response criteria (n.s.). The groups did not differ in the proportion of subjects with inattentive (atomoxetine $N = 9$, placebo $N = 6$) or combined subtypes (atomoxetine $N = 5$, placebo $N = 9$) (Chi-square (1) = 1.48, $p = 0.22$).

3.2. Relationship between absolute power, relative power, or cordance and clinical outcomes

There were no ROIs for absolute or relative power or cordance measures that were significantly different prior to treatment between subjects randomized to placebo and atomoxetine, or between responders and non-responders to placebo or atomoxetine. There also were no ROIs for absolute or relative power or cordance measures that were significantly different between responder and non-responders for the baseline to week 1 change measure. We identified one ROI for cordance at week 1 in the theta band, comprised of four left temporoparietal electrodes (Cp3, Tp7, P3 and T5) (Fig. 2), which was associated with change in the CAARS. ANCOVA revealed that theta cordance in this ROI had a significant relationship with outcome that was different between atomoxetine-treated and placebo-treated subjects ($f_{(1,27)}$ $p = 0.01$) (Table 1), and this association remained significant after jackknife validation.

Examination of cordance difference maps showed that atomoxetine responders had significantly lower theta cordance values than non-responders at week 1 in the left temporoparietal ROI, while there was no difference in this region between placebo responders and non-responders (Fig. 3). Two-way ANOVA revealed that responders and non-responders differed significantly in week 1 theta band cordance in the ROI, with atomoxetine responders showing the lowest and non-responders the highest values (Table 2). There was no significant difference in mean cordance between treatment groups ($F_{1,27} = 0.00$, $p = 0.96$). The main effect of Response showed a trend ($F_{1,27} = 3.87$, $p = 0.06$). The interaction of Treatment x Response was significant ($F_{1,27} = 6.78$, $p = 0.02$).

Linear regression was performed to examine the relationship between theta cordance values at week 1 and clinical outcome. Cordance values from the ROI were significantly correlated with change in CAARS score in atomoxetine-treated subjects ($R^2 = 0.61$, $\beta = 2.61$, $t_{12} = 4.35$, $p = 0.001$) but not in placebo-treated subjects (Fig. 4). Cordance values also were associated with changes in hyperactivity-impulsivity as well as inattention symptom scores in medication-treated subjects ($r = 0.74$, $p = 0.004$, and $r = 0.79$, $p = 0.001$, respectively), but not those treated with placebo ($r = -0.18$, $p = 0.56$, and $r = 0.06$, $p = 0.85$, respectively). In a combined model, the change in inattention symptom scores at the endpoint was significantly associated with theta cordance values at week 1 ($\beta = 0.54$, SE = 1.944, $p = 0.03$) with a trend toward an association with change in hyperactivity-impulsivity scores ($\beta = 0.41$, SE = 2.52, $p = 0.07$) for atomoxetine-treated subjects.

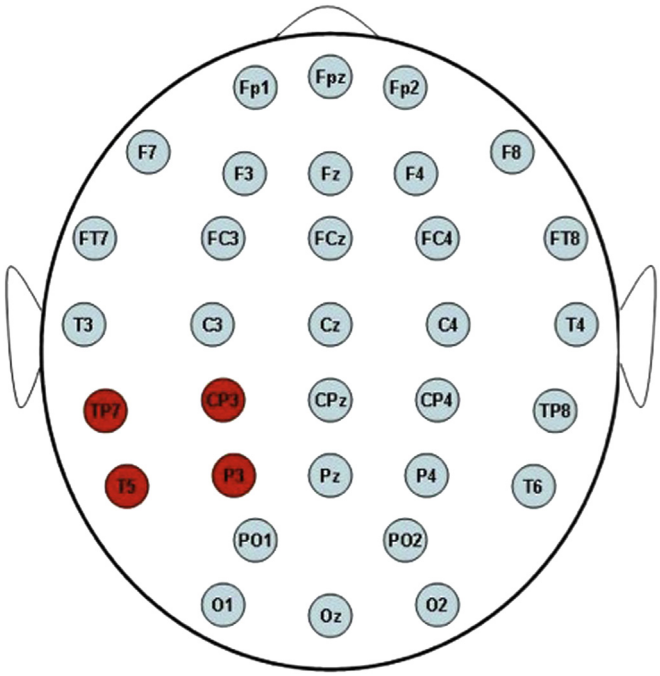

Fig. 2. Electrode map showing Region of Interest. Electrodes highlighted in red indicate the Region of Interest that showed a difference after one week of treatment between 12-week responders and non-responders to atomoxetine. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
ANCOVA results. ANCOVA for left temporoparietal theta cordance at week 1 and treatment outcome. $R^2 = 0.320$, $N = 29$.

	df	*F*	*p* value
Model	3	4.23	0.01
ROI	1	4.44	0.05
Treatment	1	7.58	0.01
ROI × treatment	1	7.02	0.01

Cordance values also were significantly correlated with improvement in functional outcome as measured by final AAQOL-29 total score in atomoxetine-treated subjects ($R^2 = 0.32$, $\beta = -3.40$, $t_{12} = -2.39$, $p = 0.03$). CAARS change and final AAQOL were significantly and inversely correlated ($r = -0.3947$, $p = 0.009$), indicating that decreases in ADHD symptoms were associated with improved quality of life.

A centro-parietal ROI (electrodes P3, Cpz, Cp3) was identified based upon its association with final AAQOL score. ANCOVA revealed that week one theta cordance in this ROI had a significant relationship with outcome that was different between atomoxetine-treated and placebo-treated subjects ($f_{(1,26)}$ $p = 0.02$). However, these results were no longer significant after the jackknife procedure was applied and this ROI was dropped from further analysis.

3.3. Early changes in ADHD symptoms

An ANCOVA on final change in CAARS score was run with the factor of treatment, a continuous variable for early change in the CAARS score, and their interaction. The ANCOVA showed that early change in the CAARS (at week 2) was associated with clinical outcome ($f_{1,40} = 15.62$, $p < 0.001$). The main effect of treatment also was significant ($f_{1,40} = 4.75$, $p = 0.04$), while the interaction showed a trend ($f_{1,40} = 3.33$, $p = 0.08$). In a post-hoc analysis by treatment group, early change in CAARS significantly predicted final CAARS change in the placebo-treated subjects ($\beta = 1.06$, $t_{22} = 4.13$, $p < 0.001$), and showed a strong trend in atomoxetine-treated subjects ($\beta = 0.62$, $t_{18} = 2.03$, $p = 0.06$).

3.4. Relative predictive accuracy of early symptom change and cordance

We examined the relative predictive accuracy of cordance (at one week) and early change in CAARS score (at two weeks) for 12-week clinical outcome. Multiple linear regression was performed using the atomoxetine treated subjects only, with one week cordance and two week changes in CAARS as the independent variables, and final CAARS change as the dependent variable. In the combined regression, early change in CAARS was not significantly related to outcome ($\beta = 0.34$, $t_{11} = 0.96$, $p = 0.36$). However, the ROI still was highly significantly correlated with change in CAARS, even when controlling for early CAARS change ($\beta = 2.47$, $t_{11} = 3.90$, $p = 0.002$).

4. Discussion

We found that in adults with ADHD treated with atomoxetine in a double-blind placebo-controlled clinical trial, theta cordance from the left temporoparietal region after one week of treatment was significantly associated with 12-week change in ADHD symptoms. Subjects treated with atomoxetine who had lower theta cordance values at week 1 showed significantly greater improvements in ADHD symptoms overall, as well as hyperactivity-impulsivity and inattention symptoms scores, than those with higher theta cordance. There was no relationship between cordance values and improvement in subjects treated with placebo. Atomoxetine responders showed significantly lower levels of temporoparietal theta cordance at week 1 than atomoxetine non-responders. In contrast, responders and non-responders treated with placebo showed no significant difference between groups. Additionally, cordance in this same region was associated with improvement in patient quality of life at the end of medication treatment. We also found that early changes in ADHD symptoms were correlated with final outcome, although the association of early symptom change was no longer significant after including temporoparietal theta cordance at week 1. Absolute power, relative power, and cordance values at baseline, and change from baseline to week 1, were not associated with 12-week outcome.

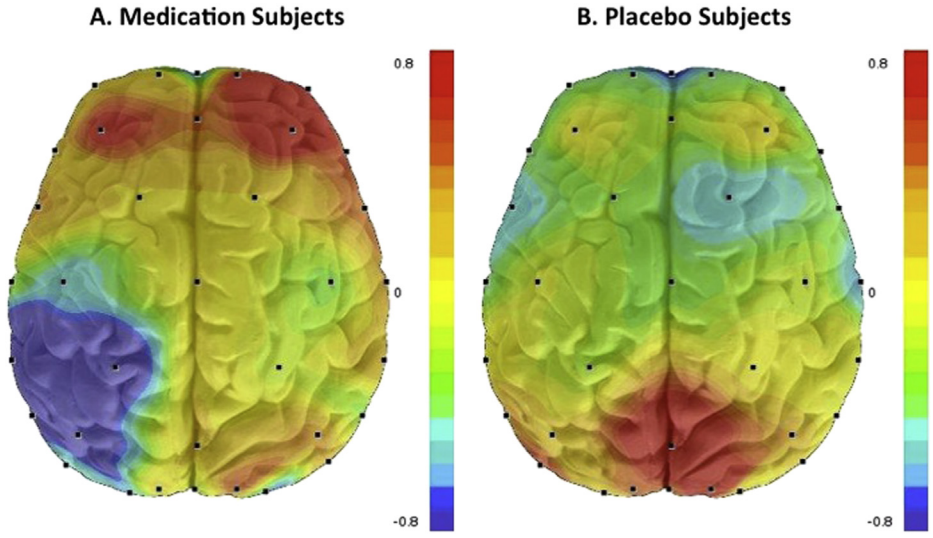

Fig. 3. Map of differences in theta-band cordance between responders and non-responders to treatment. Differences in theta cordance between responder and non-responder groups after one week of treatment with: A) medication, or B) placebo. Blue colors indicate that responders had lower values than non-responders, while red colors indicate that responders had higher values. Medication-responders showed statistically significantly lower left temporoparietal cordance values than non-responders, while placebo-treated subjects showed no significant difference in this area between responders and non-responders. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Mean week 1 cordance values by treatment and response groups. There were no significant main effects, but the group interaction was significant ($F_{1,27} = 6.78$, $p = 0.015$).

Group	Mean cordance values by treatment mean (S.D.)		Total
	Medication	Placebo	
Responders	−0.02 (0.41)	0.60 (0.83)	0.29 (0.70)
Non-responders	1.05 (0.58)	0.46 (0.64)	0.71 (0.67)
All subjects	0.60 (0.74)	0.51 (0.69)	0.55 (0.70)

These results are in part consistent with recent literature indicating that abnormalities in temporoparietal electrical activity are common in adults with ADHD. Hale et al. (2010) reported that a rightward asymmetry in alpha activity was associated with a greater number of ADHD symptoms and a possible parietal association with inattentive symptoms in particular. This same group (2009) also reported a rightward beta asymmetry in the parietal regions, indicative of abnormal recruitment of left hemispheric language processing. The prominent alpha differences seen in these adult subjects with inattention could represent a defect in normal top–down inhibitory mechanisms that are under alpha oscillatory control (Klimesch et al., 2003).

Several previous studies have examined the relationship between pretreatment brain electrical activity and stimulant treatment outcome in ADHD, and these have yielded inconsistent results. Chabot and colleagues (Chabot et al., 1999) were among the first to report that pretreatment qEEG differences were a reliable predictor of response to stimulants. This group reported that greater beta activity and lesser theta activity were associated with response to stimulants. These findings were similar to those of Loo et al. (1999) who noted increased beta and decreased theta and alpha activity in the frontal regions in methylphenidate responders. In contrast, Clarke et al. (2002) reported that those subjects with good response to methylphenidate showed increased relative delta and theta power and decreased alpha and beta power in comparison to poor responders. Arns et al. (2008) reported that subjects with excessive frontal slow wave activity were more likely to respond to stimulant medication than other subjects. Overall, studies have reported 70–80% accuracy in identifying responders to stimulants using a variety of pretreatment qEEG measures, but it is important to note that because more than 70% of children tend to respond to stimulants, the predictive accuracy of these measures is not significantly better than expected (Loo and Barkley, 2005).

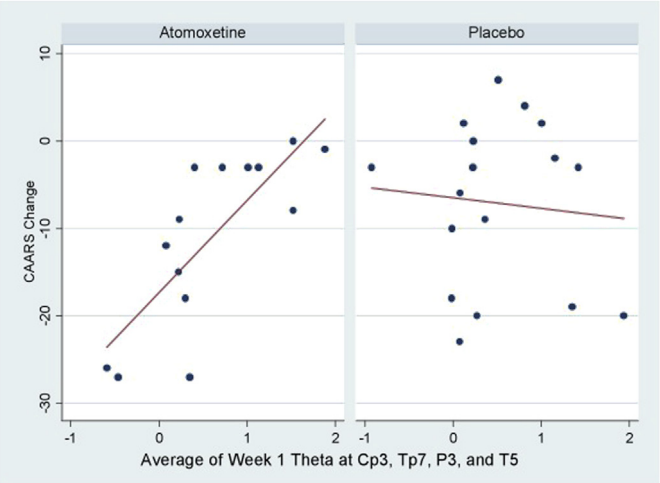

Fig. 4. Association between ROI cordance and changes in CAARS scores. Linear association between changes in CAARS total ADHD symptom score at eight weeks and left temporoparietal cordance values at one week in subjects treated with atomoxetine (left) and placebo (right). Each subject is represented by a single dot in the graphic. Medication treated subjects showed a significant positive association between cordance in this ROI and change in CAARS score at the primary endpoint, whereas placebo treated subjects showed no significant association.

The response rate to atomoxetine in this study was 55%, similar to the response rate of approximately 60% seen in the parent study (Durell et al., 2013). Because of the limited number of subjects receiving drug in this pilot study, it is not possible to estimate accurately the impact of routine qEEG cordance testing on predicting response in clinical practice. Nevertheless, these results demonstrate that cordance measures at one week after the start of treatment indicate which patients are likely to respond atomoxetine at 12 weeks. This early prediction of response could be valuable to both physicians and patients who are making decisions regarding how long to continue an atomoxetine trial. These results indicate that further clinical study of the cordance biomarker in patients undergoing atomoxetine treatment is warranted.

The left temporoparietal region identified in the present study is interesting in that it is similar to a region that has been shown to be involved in attentional processing related to motor control in healthy control subjects (Rushworth et al., 1997). In addition, using an event-related functional magnetic resonance imaging (fMRI) oddball paradigm in male adolescents with ADHD, Tamm et al. (2006) showed that ADHD subjects had significantly less bilateral parietal activation compared to healthy control subjects. In contrast, Dillo et al. (2010) examined inhibitory control deficits using fMRI in adult ADHD performing a Go/No-Go task. They found significantly enhanced activity in ADHD subjects compared to healthy controls in parietal cortex. Finally, in an fMRI study of subjects with adult ADHD, Hale et al. (2007) found no significant activation of the parietal regions bilaterally for more demanding cognitive tasks. Differences among these studies in patterns of parietal activation may depend upon the population being studied (adolescents versus adults), and the nature of the task (motor versus cognitive) as well as its complexity.

One previous study has examined the acute effects of atomoxetine on qEEG in children with ADHD. Barry et al. (2009) reported that a single dose of the medication resulted primarily in global increases in absolute and relative beta power, although changes were seen in most frequency bands. Of particular note with reference to the current study is that left sided posterior increases in theta power were detected. These results are difficult to compare with the current study, however, because of the fact that only a single dose of medication was used, only qEEG power measures were reported, and the subjects were much younger than those examined here. Leiser et al. (2011) reported a variety of qEEG findings, both in human studies and animal models, focusing primarily on the neurophysiologic effects of methylphenidate, which may differ significantly from those of atomoxetine.

The cordance measure reported on here has most commonly been interpreted in the context of the association between qEEG and perfusion (Leuchter et al., 1994, 1999). Rhythmic oscillations in the EEG in theta and alpha bands, however, are generated under the strong influence of thalamocortical pacemaker cells (Hughes and Crunelli, 2005). Findings involving qEEG power and cordance in the theta frequency band in ADHD therefore may best be interpreted in the context of thalamic dysfunction, as recent reports have implicated the thalamus in the pathophysiology of the illness. Xia et al. (2012) reported significantly reduced thalamic volumes, and disturbances in the connectivity bundles between the thalamus and the striatum, using structural MRI in children with ADHD. Using fMRI in adults with ADHD, Clerkin et al. (2013) found decreased thalamocortical activation during response preparation in a cued reaction time task. These findings are consistent with the

suggestion that ADHD may represent a syndrome of thalamocortical dysrhythmia (Sukhodolsky et al., 2007). The thalamus also has shown promise as a brain region that reflects the differential pharmacologic effects of atomoxetine: in healthy control subjects who received atomoxetine or methylphenidate, arterial spin labeled MRI showed that methylphenidate increased, while atomoxetine decreased, regional cerebral blood flow in the thalamus (Marquand et al., 2012). We do not, however, have any direct measures of thalamic structure or function in the subjects in this study. Future research into cerebral oscillatory activity in ADHD should more directly examine the relationship between cerebral oscillatory activity and the thalamus.

The results of the present study should be interpreted within the context of several limitations. First, this is a pilot exploratory investigation in a limited number of subjects. Our data-reduction approach and jackknife validation reduced but did not eliminate the possibility of Type I error because of the number of potential variables and the limited number of subjects. While we did employ a jackknife validation procedure, we did not undertake rigorous correction for multiple comparisons because of the exploratory nature of this study. These findings therefore should be replicated in a larger sample of subjects prior to their application in clinical practice. Second, we did not record qEEG data after a single dose of medication, as has been reported in some previous studies. Therefore, it is difficult to compare our results to those of previous studies. Third, we adopted a regional approach to analysis of the qEEG data in which we required clusters of contiguous electrodes were significantly different between groups before further analysis was performed. This approach has the advantage of minimizing false-positive associations that might exist for individual electrodes. This approach, however, has the disadvantage of potentially overlooking associations that might exist for larger numbers of electrodes that are not contiguous, or for a more global measure. Fourth, because participation was restricted to a rigorously defined subset of young adults with ADHD and without significant comorbidity, it remains unclear if the same findings would hold in subjects at other stages of development (i.e., children, adolescents, and older adults), or in subject groups meeting less stringent inclusion/exclusion criteria. Fifth, these results with qEEG cordance pertain to the prediction of treatment outcome during treatment with one specific medication for ADHD. It is unknown whether similar predictive ability would be attained with other medications.

Measuring theta cordance after one week of atomoxetine treatment may prove to be useful in predicting treatment outcome. Currently there is no reliable physiologic measure of treatment response in ADHD. Although early symptom change may be a useful predictor of eventual treatment outcome, adults with ADHD may be unreliable in reporting changes in their symptoms (Adler et al., 2008; Kooij et al., 2008). Development of a physiologic predictor therefore may complement careful symptom monitoring in the course of treatment. These present findings are consistent with an emerging body of work suggesting that monitoring of neuronal oscillatory activity may be informative about the pathophysiology and treatment outcome of ADHD. Future research should examine whether cordance measurements may be useful for differentiating between subjects who will and will not have a satisfactory clinical response to atomoxetine. The fact that these neurophysiologic measures can be detected early in treatment, and may be more predictive than early symptom change, suggests that they may have eventual clinical usefulness.

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Contributors

Todd Durell and Ahmed were involved in design and execution and writing of parent protocol, while Andrew Leuchter designed the QEEG portion of the protocol. Alex Korb performed data analyses. Andrew Leuchter wrote the first draft of manuscript and all authors made revision contributions.

Conflict of interest

Dr. Leuchter discloses that within the past five years received research support from the National Institutes of Health, Pfizer, MedAvante, Shire Pharmaceuticals, Neuronetics, Eli Lilly and Company, and Neurosigma. He has served as a consultant to NeoSync, Inc., Brain Cells, Inc., Taisho Pharmaceuticals, Eli Lilly and Company, and Aspect Medical Systems/Covidien. He is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA). Dr. Leuchter owns stock options in NeoSync, Inc., and equity in BBA. Dr. Cook discloses that within the past five years he has received research support from Aspect Medical Systems/Covidien, National Institutes of Health, Neuronetics, and Shire; he has been on the speakers' bureau for Neuronetics and the Medical Education Speakers Network; he has been an advisor/consultant/reviewer for Allergan, Covidien, Pfizer, Neuronetics, NeuroSigma, NIH (ITVS), US Department of Defense, US Department of Justice, VA (DSMB); his biomedical intellectual property is assigned to the Regents of the University of California; and he owns stock options in NeuroSigma. Dr. Glaser has received consulting honoraria from Shire Pharmaceuticals and research support from Eli Lilly. Dr. McGough has received consulting honoraria from Eli Lilly & Company, NextWave Pharmaceuticals, Noven Pharmaceuticals, and Shire Pharmaceuticals, and research support from Eli Lilly. Dr. Hunter receives research support from Covidien. Dr. Korb has no interests to report. Drs. Durell and Deldar are full-time employees and minor shareholders of Eli Lilly and Company and/or one of its subsidiaries.

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