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Research paper

The comparative effectiveness of electroencephalographic indices in predicting response to escitalopram therapy in depression: A pilot study

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ABSTRACT

Background: This study aims to compare the effectiveness of EEG frequency band activity including inter-hemispheric asymmetry and prefrontal theta cordance in predicting response to escitalopram therapy at 8-weeks post-treatment, in a multi-site initiative.

Methods: Resting state 64-channel EEG data were recorded from 44 patients with a diagnosis of major depressive disorder (MDD) as part of a larger, multisite discovery study of biomarkers in antidepressant treatment response, conducted by the Canadian Biomarker Integration Network in Depression (CAN-BIND). Clinical response was measured at 8-weeks post-treatment as change from baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of 50% or more. EEG measures were analyzed at (1) pre-treatment baseline (2) 2 weeks post-treatment and (3) as an "early change" variable defined as change in EEG from baseline to 2 weeks post-treatment.

Results: At baseline, treatment responders showed elevated absolute alpha power in the left hemisphere while non-responders showed the opposite. Responders further exhibited a cortical asymmetry in the parietal region. Groups also differed in pre-treatment relative delta power with responders showing greater power in the right hemisphere over the left while non-responders showed the opposite. At 2 weeks post-treatment, responders exhibited greater absolute beta power in the left hemisphere relative to the right and the opposite was noted for non-responders. A reverse pattern was noted for absolute and relative delta power at 2 weeks post-treatment.

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Responders exhibited early reductions in relative alpha power and early increments in relative theta power. Non-responders showed a significant early increase in prefrontal theta cordance.
Conclusions: Hemispheric asymmetries in the alpha and delta bands at baseline and at 2 weeks post-treatment have moderately strong predictive utility in predicting response to antidepressant treatment.

1. Background

Major depressive disorder (MDD) is a persistent psychiatric illness and one of the leading causes of global disease burden (Lopez et al., 2006; World Health Organization, 2011). The current treatment approach in MDD has substantial limitations with a trial-and-error approach for optimal treatment selection that leads to a delay in patient recovery. Delayed recovery is associated with serious consequences for MDD patients including heightened risk of suicide, higher relapse and recurrence rates, increased comorbidities and overall greater functional burden (McIntyre and O'Donovan, 2004). The impact of delayed recovery on patient suffering and quality of life has been the premise for identifying biomarkers that can predict treatment outcome during the early course of treatment. Moreover, despite the fact that antidepressant medication is a first line of treatment for MDD patients, the selection of an appropriate antidepressant for optimal clinical response is still a major challenge. Biomarkers could potentially help in predicting the likelihood of whether or not a patient will benefit from certain medications or other therapeutic approaches. This would allow for treatment optimization and would also help overcome the problems associated with delayed recovery.

Electroencephalography (EEG) as a biomarker has several advantages in clinical utility including ease of administration, relatively wide availability and cost-effectiveness. Several EEG measures have been evaluated as possible predictors of antidepressant treatment response (Alhaj et al., 2011; Baskaran et al., 2012; Hunter et al., 2007; Jaworska and Protzner, 2013; Olbrich and Arns, 2013): in particular elevated parieto-occipital alpha was identified in a subgroup of MDD patients who subsequently responded favourably to antidepressant medication (Bruder et al., 2001, 2008; Knott et al., 1996, 2000; Ulrich et al., 1988). Since alpha activity is suggested to be inversely related to cortical excitability, elevated pre-treatment alpha power is thought to reflect cortical hypoactivity (Laufs et al., 2003). Reports on the predictive utility of alpha asymmetry (a score derived from computing the difference in log alpha power between right and left hemispheres) in predicting antidepressant treatment response also exist but with less consistency (Arns et al., 2015; Bruder et al., 2001, 2008; Jaworksa et al., 2014; Tenke et al., 2011; Ulrich et al., 1984).

Others have probed the utility of EEG theta power in antidepressant response prediction, again with conflicting findings (Iosifescu et al., 2009; Knott et al., 1996, 2000; Spronk et al., 2011; Tenke et al., 2011). Studies utilizing source localization methods such as low-resolution electromagnetic tomography (LORETA) have consistently demonstrated that elevated, pre-treatment theta activity in the rostral anterior cingulate cortex (rACC) is predictive of eventual response to antidepressant treatment (Korb et al., 2009; Mulert et al., 2007; Pizzagalli et al., 2001). Pizzagalli (2011) proposed that elevated resting rACC activity may lead to treatment response through adaptive self-referential functions such as mindfulness and non-evaluative self-focus.

Studies investigating the predictive utility of power in other frequency bands have been scarce, although one group reported trend level findings that elevated beta power and reduced delta power at baseline predicted response to imipramine (Knott et al., 1996) and similar findings in paroxetine responders (Knott et al., 2000).

In recent years, treatment emergent EEG features such as theta cordance and the antidepressant treatment response index (ATR) have been reported to predict antidepressant response (Leuchter et al., 1994, 2009). Theta cordance is a QEEG measure that combines information from both absolute and relative power from the EEG theta spectra according to a specific algorithm (Leuchter et al., 1994). Decreased prefrontal theta cordance measured in MDD patients as early as 48 h to 1 week post-treatment has been shown to be predictive of treatment response with different antidepressant medication types (Cook and Leuchter, 2001; Cook et al., 2002; Bares et al., 2007, 2008, 2010). The ATR is a QEEG measure that integrates frontal alpha and theta power extracted at pre-treatment baseline and at 1 week post-treatment (Leuchter, Cook, Hunter, and Korb, 2009). Differences in ATR values (high versus low) predict response and remission in MDD patients treated with escitalopram or bupropion.

Escitalopram therapy has a particularly favourable efficacy and tolerability profile compared to other antidepressant medications (Cipriani et al., 2009; Kennedy et al., 2009; Montgomery et al., 2007; Sanchez et al., 2014), however research regarding the utility of EEG indices in predicting response to escitalopram therapy is limited. The present study used data from the CAN-BIND-1 trial (see Lam et al., 2016 for details) to examine the comparative effectiveness of baseline frequency band power, alpha asymmetry and prefrontal theta cordance in predicting response to acute (8 weeks) escitalopram therapy across multiple sites. Additionally, EEG indices were also investigated at 2 weeks post-treatment to investigate "early change" (defined as change from baseline to 2 weeks post-treatment) as a mediator of response. We hypothesized that responders would differ from non-responders in showing elevated alpha power at baseline. Given that there has been mixed results in studies investigating the predictive utility of alpha asymmetry and activity in other EEG frequency bands, we did not have specific hypotheses regarding these parameters. We also hypothesized that acute treatment would reduce alpha and prefrontal theta cordance, in treatment responders. We did not have specific hypotheses regarding other parameters. The analyses presented here represent an analysis of a subset of data made available as part of a first data release from the CAN-BIND-1 study, and were pre-planned and approved by the CAN-BIND publication committee as secondary to the broader primary analysis involving the full cohort.

2. Methods

2.1. Participants

55 participants from across three study sites (University Health Network and Centre for Addiction and Mental Health in Toronto, Ontario, Canada, and University of British Columbia in Vancouver, British Columbia, Canada) were recruited as part of the CAN-BIND-1 study. Participants were outpatients aged 18–60 years of age, and met *DSM-IV-TR* (2000) criteria for major depressive episode (MDE) in MDD, confirmed by the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998). Study procedures were approved by research ethics institutional review boards at each centre and all participants signed written informed consent prior to participation. At study enrollment, all participants were experiencing a MDE duration $\geq$ 3 months with a Montgomery Asberg Depression Rating Scale (MADRS) score $\geq$ 24; and were free of psychotropic medications for at least 5 half-lives before baseline Visit 1. Participants were excluded if they had any Axis I diagnosis, other than MDD, that was considered the primary diagnosis or if they had a diagnosis of Bipolar Disorder Type I or II. Presence of a significant Axis II diagnosis (borderline, antisocial) was also exclusionary, along with high suicidal risk, substance dependence/abuse in the past 6 months, and presence of significant neurological disorders, head trauma or other unstable medical conditions. Female