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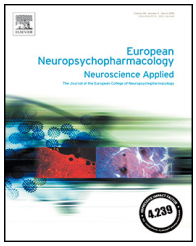

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Electroencephalographic biomarkers as predictors of methylphenidate response in attention-deficit/hyperactivity disorder

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Abstract
EEG biomarkers have shown promise in predicting non-response to stimulant medication in ADHD and could serve as translational biomarkers. This study aimed to replicate and extend previous EEG biomarkers. The international Study to Predict Optimized Treatment for ADHD (iSPOT-A), a multi-center, international, prospective open-label trial, enrolled 336 children and adolescents with ADHD (11.9 yrs; 245 males; prescribed methylphenidate) and 158 healthy children. Treatment response was established after six weeks using the clinician rated ADHD-Rating Scale-IV. Theta/Beta ratio (TBR) and alpha peak frequency (APF) were assessed at baseline as predictors for treatment outcome. No differences between ADHD and controls were found for

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TBR and APF. 62% of the ADHD group was classified as a responder. Responders did not differ from non-responders in age, medication dosage, and baseline severity of ADHD symptoms. Male-adolescent non-responders exhibited a low frontal APF (Fz: R = 9.2 Hz vs. NR = 8.1 Hz; ES = 0.83), whereas no effects were found for TBR. A low APF in male adolescents was associated with non-response to methylphenidate, replicating earlier work. Our data suggest that the typical maturational EEG changes observed in ADHD responders and controls are absent in non-responders to methylphenidate and these typical changes start emerging in adolescence.
Clinical trials registration: www.clinicaltrials.gov; NCT00863499 (https://clinicaltrials.gov/ct2/show/NCT00863499).

1. Introduction

Many studies have compared resting state brain activity, especially electro-encephalography (EEG), of children with ADHD with that of typically developing children. Ever since the first description of deviant fronto-central slow-wave EEG activity (…*at frequencies of 5-6/s*…'), later so called 'theta activity' (Walter and Dovey, 1944), in 'behavioral problem children' (Jasper et al., 1938; p. 644), excess theta EEG power is an often reported finding in patients with ADHD (see: Arns et al., (2013) for review). Others have proposed the ratio of theta and beta, in short the Theta/Beta Ratio (TBR), to be a better differentiator of children with ADHD and healthy controls (Monastra et al., 2001). However, a recent meta-analysis could not confirm this measure to be a reliable diagnostic metric in ADHD (Arns et al., 2013), see (Arns et al., 2016b) for further discussion.

Another usage of EEG activity is its ability to predict treatment response, or a more prognostic rather then a pure 'diagnostic' usage (Arns et al., 2013; Arns and Gordon, 2014). Previous studies have demonstrated that an excess of slow (theta) activity and an elevated TBR were most consistently associated to a favorable treatment response to stimulant medication (Arns et al., 2008; Clarke et al., 2002b; Ogrim et al., 2014; Satterfield et al., 1971; Suffin and Emory, 1995) and EEG-neurofeedback (Arns et al., 2012a; Gevensleben et al., 2009; Monastra et al., 2002). Conceptually this can be understood as representative of a hypoarousal subgroup (with excess theta as a signature of drowsiness), hence psychostimulant medication to be most effective for this subgroup by its psychostimulant nature (Arns and Kenemans, 2014; Clarke et al., 2002a). Another EEG metric that has shown promise in predicting treatment outcome is the alpha peak frequency (APF), i.e. the individual frequency at which alpha activity oscillates. This low APF was previously found a biomarker associated with non-response to stimulant medication in male ADHD patients (Arns et al., 2008), but also to antidepressant treatments (Arns et al., 2012b; Arns et al., 2010; Ulrich et al., 1984) suggesting this could be considered a more generic biomarker for non-response and could serve as a translational biomarker to investigate the exact underlying etiology and potentially develop new treatments for such subgroups.

Resting-state EEG studies to date often consisted of small sample sizes with a large diversity in demographics and employed a large variety of methods such as different resting-state conditions (eyes-open [EO] or eyes-closed [EC]) etc. Therefore, studies are needed that prospectively test these differences under standardized conditions with appropriate sample size and the use of a multi-site approach to obtain more generalizable results. To this end, the aims of the current study were twofold. First, to investigate ADHD specific differences in brain function compared to typically developing children. Second, to investigate predictors of treatment response to methylphenidate (MPH) using EEG data from the multisite International Study to Predict Optimized Treatment for ADHD (iSPOT-A), collected from 158 healthy children and 336 children and adolescents with ADHD. This is the first and largest multisite study to investigate EEG treatment predictors to MPH using a standardized methodology. Its sample-size and multisite design ensure accurate and generalizable results that allow for investigating interactions with gender and age-group (children vs. adolescents).

Based on the previous literature we hypothesized that there would be no difference between ADHD patients and controls for the TBR and APF on the group level, but there would be main effects of age-group (well-known maturational EEG changes). Furthermore, we predict that non-responders to stimulant medication would have a low TBR compared to non-responders. In addition, we hypothesize in line with our earlier study (Arns et al., 2008) that male ADHD non-responders (NR) would have a lower APF compared to responders (R).

2. Experimental procedures

2.1. Design

This study was a phase-IV, multi-site, international, open-label effectiveness trial in which ADHD patients were prescribed with MPH, including 7 international research sites. Full details of the study protocol have been published elsewhere (Elliott et al., 2014). This study was registered at the clinicaltrials register at www.clinicaltrials.gov with identifier NCT00863499 and IRB approval was obtained at all clinic sites. Parents and/or children provided written informed consent.

2.2. Study participants

The iSPOT studies have been explicitly apriori designed to use a two-step analysis procedure, where the first half of

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