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Single-dose effects on the P3no-go ERP component predict clinical response to stimulants in pediatric ADHD ☆

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HIGHLIGHTS

- 87 ADHD patients were ERP-tested twice; test 2 on stimulant medication; followed by 4 weeks clinical trial.
- After the trial they were classified as responders (REs) or non-responders (non-REs).
- REs and non-REs differed significantly in their single-dose responses on the P3no-go ($d = 1.76$), suggesting utility of P3no-go ERP in predicting treatment response.

ABSTRACT

Objective: Approximately 30% of children and adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) and treated with stimulants are considered non-responders (non-REs). Reliable predictors of response are missing. We examined changes in Event-Related Potentials (ERPs) induced by a single dose of stimulant medication in order to predict later clinical response.
Methods: ERPs were registered twice during performance of a visual cued go/no-go task in 87 ADHD patients (27 girls) aged 8–18 years; the second recording on a single dose of stimulant medication, followed by a systematic medication trial lasting 4 weeks. Based on the four-week trial, participants were categorized as responders (REs, $N = 62$) or non-REs ($N = 25$). Changes among REs and non-REs in ERP components (cueP3, CNV, P3go, N2no-go, P3no-go) and behavioral-test variables were then compared.
Results: REs and non-REs differed significantly in medication-induced changes in P3no-go, cue-P3, CNV, omission errors, reaction time, and reaction-time variability. The largest effect size was found for P3no-go amplitude ($p < .001$; $d = 1.76$). Changes in P3no-go and omission errors correctly classified 90% of the REs and 76% of the non-REs, when controlling for the age of the participants.
Conclusion: Clinical response to stimulants can be predicted by assessing single-dose changes in the P3no-go ERP component amplitude.
Significance: Changes in P3no-go may be a clinically useful marker of response to stimulants.
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1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common developmental disorder involving problems with attention and/or hyperactivity and impulsivity. It is typically identified in childhood, with symptoms often persisting throughout adulthood (Faraone et al., 2000). Comorbid disorders in behavior, emotion, learning, and autism spectrum are common (Hermens et al., 2006; American Psychiatric Association, 2013). Prevalence of ADHD is approximately 3–7% in school-aged children (Willcutt, 2012; Paule et al., 2000) and is relatively consistent across class, culture, and ethnic background (Polanczyk and Jensen, 2008; Barkley, 2006). The influence of genetic factors is well documented (Barkley, 2006; Nigg, 2005).

Medical treatments with psychostimulants like methylphenidate (MPH), dextroamphetamine (DEX), and the nonstimulant

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atomoxetine (ATX) are widely used. Therapeutic effects of stimulants (reduced restlessness/hyperactivity, improved sustained attention, reduction of impulsive acts), are reported in approximately 70% of patients (Greenhill et al., 2002; Hodgkins et al., 2012; Parr et al., 2003; Pliszka, 2003; Spencer et al., 1996; Ishii-Takahashi et al., 2015; Cho et al., 2007). A shift to DEX or ATX for non-responders (non-REs) increases therapeutic effects to 80% (Barkley, 2006). Numerous studies have implicated the fronto-subcortical networks of the brain as a prime candidate for the source of the underlying dysfunction; including hypofunctioning dopamine and noradrenalin systems (Hermens et al., 2005). Psychostimulants seem to increase activation in the frontal cortex and striatum (Volkow et al., 2012; Engert and Pruessner, 2008)—key areas of cognitive control—and may underlie the positive clinical effects of stimulants (Rubia et al., 2014).

Early identification of non-REs is critical in order to avoid long-term-ineffective medication trials and to ensure that other treatment options (medical and/or psycho-social) are initiated. The traditional approach has been to attempt to identify predictors based on information collected before initiation of medication trials. Despite these attempts, there is currently no reliable method for predicting how patients will respond, without exposure to a trial period of medication (Johnston et al., 2015). As effects of MPH and DEX can often be observed on single doses, however, another less frequent approach to predicting clinical response is to examine effects of a single dose.

1.1. Predictors of stimulant medication response

Previous studies aimed at predicting treatment response to medication have applied neuropsychological test results, EEG data, demographic and behavioral parameters (gender, age, SES, diagnoses, scores on rating scales), or a combination of these variables (Barkley, 1976; Gray and Kagan, 2000; Chabot et al., 1999; Barkley et al., 1991; Hale et al., 2011; Tannock et al., 1995). The predictive power of neuropsychological tests is considered modest (Fernandez-Jaen et al., 2008; Nichols and Waschbusch, 2004; Riccio et al., 2001; Coghill et al., 2007; Ogrim et al., 2014).

EEG-based measures have been used as predictors of response to stimulants. A 2005 review (Hermens et al., 2005) identified a combination of behavioral and electrophysiological parameters as the most promising approach. Several cognitive ERP components, such as the P3 component following cues (cueP3), targets (P3go/P3b), no-go signals (P3no-go), contingent negative variation (CNV), and N2no-go are frequently found to differ between ADHD subjects and healthy controls (Sangal and Sangal, 2006; Johnstone et al., 2013; Brandeis et al., 2002). Some of these components, particularly the P3b, have been investigated as predictors of stimulant medication response (Chabot et al., 1999; Sangal and Sangal, 2004). The P3b component has a parietal distribution, however, and most functional imaging studies indicate MPH effects primarily in frontal regions (Rubia et al., 2014). Investigating the predictive power of more anteriorly distributed components such as CNV, N2no-go, and P3no-go could therefore prove particularly fruitful. We previously found that whereas non-REs showed deviations in the parietally distributed cue-P3 compared with healthy controls, medication responders deviated in the more frontally distributed P3no-go and CNV components (Ogrim et al., 2014).

We are aware of only one study (Young et al., 1995) examining *changes* in ERP components induced by a single dose of MPH as a basis for predicting clinical response to stimulants in children with ADHD. The children whose P3b amplitude from an auditory oddball paradigm increased by >30% on a single dose were classified as REs six months later with an accuracy of 81%. That study was based on a relatively small group ($N = 35$), with about an equal number of REs and non-REs. Our study examines changes caused by a single dose of stimulant medication in a larger group of ADHD subjects and includes behavioral variables and more frontally distributed ERP components.

1.2. Considerations in predicting medication response

There are many obstacles in identifying powerful predictors of medication response. First, one must consider inclusion and exclusion criteria. Most ADHD patients have comorbid disorders, and studies aimed at finding predictors of clinical use should include all ADHD patients. The proportion of REs vs. non-REs should be proximal to the reported prevalence in population studies (about 70–80% REs), as changes in base rate will affect the accuracy of the predictive model.

Second, there is still no consensus regarding how best to operationalize the criterion variable of treatment response. Behavior ratings from parents and teachers are frequently used as outcome measures, but are criticized for being vulnerable to placebo and source effects (Ogrim et al., 2014; Herrerias et al., 2001). Gathering information from several sources and using both standardized and unstructured methods can counteract some of these problems while also maintaining the desired ecological validity when evaluating the participants' day-to-day functioning prior to and during stimulant medication try-out.

Third, one must consider the number of predictor variables to include in a model. Previous studies indicate the necessity of more than one (Hermens et al., 2005), yet there should be as few predictors as possible. Increasing the number of predictors increases the risk of model overfitting, thereby limiting generalizability. Some studies have suggested that the number of predictor variables in the model should be less than 1 per 10 subjects having the least common outcome (Peduzzi et al., 1996), although simulation studies indicate that this criterion may be somewhat strict (Vittinghoff and McCulloch, 2007). Collection of predictor data should also not be overly demanding of resources or time for patients and their families.

Finally, it should be considered that the base rate of REs relative to non-REs in the ADHD population (approximately 70% and 30%, respectively) itself provides a predictive model with 70% accuracy, which correctly classifies all REs and misses all non-REs. Curiously, this aspect is not always considered in the published literature. To be useful, a predictive model must have significantly higher accuracy than the base rate model and provide a means of detecting non-REs who will be in need of other types of treatment.

1.3. Study aims and hypotheses

We investigated whether effects of a single dose of stimulant medication in 87 ADHD patients (27 girls; 73 medication-naïve) aged 8–18 years could predict clinical medication response after a four-week medication trial. The study included four behavioral variables (reaction time [RT], RT variability [RTvar], omission errors, commission errors) and five ERP component amplitudes (cue-P3, CNV, P3go, N2no-go, P3no-go) that have been found to differ between ADHD subjects and healthy controls. By investigating the predictive power of single-dose changes in a combination of ERP and behavioral variables, this study represents a new approach in the search for clinically useful predictors of response to stimulants in ADHD.

We hypothesized that ERPs and behavioral variables that have previously been found to differ in children with ADHD compared with healthy controls would also be affected by a dose of stimulant medication, reflecting an improvement towards normalization. We hypothesized that these effects would be specific to the REs, and that the non-REs would show smaller effects, thus making the magnitude of single dose effects predictive of later classification.

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