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Identification of biotypes in Attention-Deficit/Hyperactivity Disorder, a report from a randomized, controlled trial

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ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) is a heterogeneous disorder. Current subtypes lack longitudinal stability or prognostic utility. We aimed to identify data-driven biotypes using multiple cognitive measures, then to validate these biotypes using EEG, ECG, and clinical response to atomoxetine as external validators. Study design was a double-blind, randomized, placebo-controlled crossover trial of atomoxetine including 116 subjects ages 6 through 17 with diagnosis of ADHD and 56 typically developing controls. Initial features for unsupervised machine learning included a cognitive battery with 20 measures affected in ADHD. External validators included baseline mechanistic validators (using electroencephalogram/EEG and electrocardiogram/ECG) and clinical response (ADHD Rating Scale and correlation with cognitive change). One biotype, labeled impulsive cognition, was characterized by increased errors of commission and shorter reaction time, had greater EEG slow wave (theta/delta) power and greater resting heart rate. The second biotype, labeled inattentive cognition, was characterized by longer/more variable reaction time and errors of omission, had lower EEG fast wave (beta) power, resting heart rate that did not differ from controls, and a strong correlation ($r = -0.447$, $p < 0.001$) between clinical response to atomoxetine and improvement in verbal memory immediate recall. ADHD comprises at least two biotypes that cut across current subtype criteria and that may reflect distinct arousal mechanisms. The findings provide evidence that further investigation of cognitive subtypes may be at least as fruitful as symptom checklist-based subtypes for development of biologically-based diagnostics and interventions for ADHD.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent, impairing, chronic disorder. It is heterogeneous in clinical presentation and course [1]. Theories regarding its pathophysiology are similarly heterogeneous and it is unlikely that a single, underlying deficit exists [2–5]. Current subtypes defined by the Diagnostic and Statistical Manual (DSM) criteria have limited longitudinal validity [6,7]. Many of the theories of ADHD pathophysiology involve disruption of cognitive domains thought to be subserved primarily by prefrontal cortex, including sustained attention, inhibitory control, and executive function [1,8]. Theories have also implicated the physiologic construct of arousal, which involves the coordination of both central and peripheral response via norepinephrine release including effects on cognitive performance [9,10,8,11].

ADHD is associated with impairment in several of these cognitive and arousal constructs, but no single measure is clearly helpful in diagnosis or treatment selection [12,1,13–16]. The clinical application of these measures has likely been limited by phenotypic

Abbreviations: LC, locus coeruleus; NE, norepinephrine; AC, agglomerative coefficient.

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heterogeneity. Therefore, an improved classification schema that is relevant to treatment selection—ideally differentiating affected individuals by subgroups, or biotypes, with closer relationships to underlying biologic processes than the macro-level behavioral observations that are currently used—is needed. Furthermore, research to date has, in general, examined these constructs independently of one another, leading to difficulties placing conflicting results in context.

Data-driven analytic tools such as unsupervised machine learning techniques are ideal for identifying biotypes given the current state of knowledge because they separate groups across multiple measures without an a priori theoretical taxonomy [17–19]. To our knowledge, no study has applied such techniques to parse the phenotypic heterogeneity of ADHD using multiple cognitive and physiologic markers with clinical trial outcome data in the same subjects. Our objective was to use a data-driven approach to identify potential biotypes in ADHD via cognitive markers, then to validate these types mechanistically, via physiologic markers, and clinically, via treatment response.

Feature selection (choice of input measures) and external validation (comparison of the identified groups across different measures not included as features) are vital to these techniques [20]. We chose several widely available and cost-effective measures that are relevant to cognitive and physiologic arousal theories of ADHD pathophysiology as input and validation features. Performance measures from a cognitive battery were selected as input features [1,14]. Measures of central and peripheral arousal systems were used as external validators. These included quantified electroencephalogram (EEG) spectral power and theta/beta ratio, and electrocardiogram (ECG)-derived resting heart rate and heart rate variability [16,21]. Furthermore, EEG power is highly heritable [22], making it a good candidate biotype marker. Finally, treatment response to atomoxetine, a highly selective norepinephrine reuptake inhibitor, was used as a clinical external validator with both direct clinical importance and a specific relationship to arousal via norepinephrine modulation. Medications that improve clinical ADHD symptoms also improve cognitive performance, but these outcomes are often uncorrelated [23]. This dissociation may also be due to between-subject heterogeneity. We therefore assessed correlation between behavioral rating scale response and cognitive response.

The present study was grounded in a clinical biomarker trial of atomoxetine that included each of our primary measures of interest [24]. We hypothesized that ADHD would comprise multiple distinct biotypes with characteristic cognitive profiles. Further, we expected that these types would be differentiated mechanistically by central and peripheral arousal assessed by the EEG and ECG, and clinically by extent of symptom response following treatment with atomoxetine. Our secondary clinical hypothesis was that symptom response would differentially correlate with improvements in cognition within each identified biotype [25].

Material and methods

Study design

Data were collected in a double-blind, randomized, placebo-controlled crossover study of atomoxetine. The ADHD (Attention-Deficit/Hyperactivity Disorder) Controlled Trial Investigation Of a Non-stimulant (ACTION) protocol was previously reported [24]. The study was conducted at three academic medical centers in Australia between February 2008, and April 2010. It included a 2-week washout lead-in and three assessments: a blinded baseline assessment at the start of the first of two 6-week treatment phases separated by a 1-week washout, and a blinded assessment at the end of each phase. Cognitive testing and clinical rating scales were performed at each assessment and all sites. EEG and ECG recordings were performed only at baseline at the Sydney site. Referral identified 198 subjects, 140 were randomized and 116 completed cognitive and EEG/ECG testing in the first phase (Fig. S1). Of these 116, four ADHD subjects were removed from analysis due to reporting fewer than 4 h of sleep the night before the baseline assessments because sleep deprivation significantly affects cognition and EEG [26,27]. This left 112 ADHD subjects and 56 typically developing subjects. Typically developing controls participated in baseline measurement of EEG/ECG at Sydney.

Sampling procedure

Subjects were assessed in a comprehensive clinical interview (by MRK, SC, DE) at a tertiary referral behavioral pediatrics center that focuses on diagnosis and treatment of ADHD. Diagnosis of ADHD subtypes were made by referring clinicians according to DSM-IV criteria [28]. Diagnosis was confirmed using the ADHD Rating Scale IV (ADHD-RS) and via clinical interview by an independent, trained research psychologist (symptoms counted as present if rated at 2 or greater) [28]. Comorbid disorders were identified by clinical interview, using the Anxiety Disorders Interview Schedule for Children (ADISC) [29], administered by the trained psychologist. Anxiety disorders included Generalized Anxiety Disorder, Social Anxiety Disorder, and Separation Anxiety Disorder. Severity of symptoms of depression and anxiety was assessed by the State-Trait Anxiety Inventory (STAI) and the Depression Anxiety Stress Scale (DASS) [30,31].

Inclusion criteria for ADHD subjects and controls included: age 6–17 years, normal body mass for age/gender, and English fluency. Exclusion criteria for both groups included IQ $\leq$ 80, physical brain injury, neurologic disorder, concurrent stimulant use, cardiac abnormalities, psychosis, or history of drug abuse or dependence [14,24]. ADHD subjects had to meet ADHD criteria for inclusion, while controls were excluded if they had a personal or family history of an Axis I psychiatric disorder. Subject guardians provided informed consent and study subjects assented to participation in the study. Each site's Institutional Review Board approved the protocol.

Cognitive battery

Cognitive measures were assessed using a computerized, touchscreen test battery with audio instructions, IntegNeuro (Brain Resource Ltd., Sydney, Australia), that has been validated in thousands of subjects [32]. The specific cognitive measures are described elsewhere and have been established as sensitive for ADHD relative to healthy controls [14,24]. Briefly, this battery included the following test paradigms: Continuous Performance Test (CPT), Go/No-go (GNG), switching of attention (analogous to Trails A and B), maze, verbal memory recall (analogous to California Verbal Learning Test), verbal interference (analogous to Stroop), motor tapping, digit span, and choice reaction time [33,14]. Performance on each cognitive test was standardized to age- and gender-normed Z scores, using a large database of typically developing children [34]. The direction of effect for normed scores was standardized so that negative scores indicated worse performance.

EEG and ECG acquisition & data reduction

EEG and ECG acquisition followed established protocols [35,36]. Subjects were seated comfortably in a sound- and light-controlled testing room. Data were acquired under a resting eyes-open condition for 2 min, followed by separate task-evoked conditions. Only

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