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Research report

Increased ongoing neural variability in ADHD

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) has been described as a disorder where frequent lapses of attention impair the ability of an individual to focus/attend in a sustained manner, thereby generating abnormally large intra-individual behavioral variability across trials. Indeed, increased reaction time (RT) variability is a fundamental behavioral characteristic of individuals with ADHD found across a large number of cognitive tasks. But what is the underlying neurophysiology that might generate such behavioral instability? Here, we examined trial-by-trial EEG response variability to visual and auditory stimuli while subjects' attention was diverted to an unrelated task at the fixation cross. Comparisons between adult ADHD and control participants revealed that neural response variability was significantly larger in the ADHD group as compared with the control group in both sensory modalities. Importantly, larger trial-by-trial variability in ADHD was apparent before and after stimulus presentation as well as in trials where the stimulus was omitted, suggesting that ongoing (rather than stimulus-evoked) neural activity is continuously more variable (noisier) in ADHD. While the patho-physiological mechanisms causing this increased neural variability remain unknown, they appear to act continuously rather than being tied to a specific sensory or cognitive process.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a prevalent developmental disorder which is characterized by difficulties in allocating and sustaining attention, impulsivity and hyperactivity (American Psychiatric Association, 2000). One manifestation of the core ADHD symptoms is apparent in increased intra-individual behavioral variability over time as demonstrated by numerous reports of increased reaction time (RT) variability across trials (Kofler et al., 2013; Kuntsi & Klein, 2012). This finding has been reported in a wide variety of cognitive tasks including stop-signal (Alderson, Rapport, & Kofler, 2007; Epstein et al., 2011; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Marx, Höpcke, Berger, Wandschneider, & Herpertz, 2013), sustained attention to response (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005; Johnson et al., 2007; Shallice et al., 2002), choice reaction time (CRT) (Geurts et al., 2008; Gooch, Snowling, & Hulme, 2012; Leth-Steensen, Elbaz,

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& Douglas, 2000), and Go-no-go (Epstein et al., 2006; Heiser et al., 2004; Hervey et al., 2006; Kuntsi, Andreou, Ma, Börger, & van der Meere, 2005; Spinelli et al., 2011). Increased RT variability in ADHD is apparent in both children (Epstein et al., 2011) and adults (Adams, Roberts, Milich, & Fillmore, 2011), is correlated with ADHD symptom severity (Kuntsi, Wood, Van Der Meere, & Asherson, 2009), and is reduced following administration of stimulants (Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2005; Epstein et al., 2006; Rosa-Neto et al., 2005; Spencer et al., 2009; Teicher, Lowen, Polcari, Foley, & McGreenery, 2004). Importantly, differences in RT variability across ADHD and control participants are more prominent and reproducible than differences in mean RT across groups (Kofler et al., 2013; Kuntsi et al., 2013).

Why do individuals with ADHD exhibit such unreliable behavior over time? Executive function theories of ADHD suggest that high-level cognitive-control systems in charge of sustained attention, working memory, task-switching, and response inhibition are impaired in ADHD and fail to govern stable behavior by low-level sensory and motor systems (Alvarez & Emory, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Neuroimaging studies have proposed that these dysfunctions are associated with abnormal functional responses in frontal, parietal, and striatal brain areas (Giedd, Blumenthal, Molloy, & Castellanos, 2001; Rubia et al., 2014) and that weak responses in these areas are associated with larger trial-by-trial RT variability in ADHD (Spinelli et al., 2011; Suskauer et al., 2008).

Alternative hypotheses have suggested that increased RT variability may result from general dysfunctions in neuro-energetic supply, where impaired supply of lactate affects the ability of neurons to fire rapidly and reliably (Killeen, Russell, & Sergeant, 2013), or the outcome of deficient dopamine release/sensitivity (Swanson et al., 2007), whereby neuromodulation of the entire brain may be altered throughout development. An additional hypothesis has suggested that neural activity in default mode brain areas, which is typically suppressed during performance of sensory and motor tasks (Raichle & Snyder, 2007), is not suppressed properly in ADHD and interferes with the reliable function of sensory and motor systems (Di Martino et al., 2008; Helps et al., 2010; Sonuga-Barke & Castellanos, 2007). According to these theories increased RT variability is the outcome of ongoing neural-activity abnormalities that should be apparent continuously (regardless of the task being performed) in contrast to the cognitive theories described above, which predict that neural activity abnormalities should appear only during recruitment of the impaired cognitive process.

Is increased behavioral variability in ADHD associated with increased underlying neural variability across trials? Since behavior is generated by neural activity, one might assume that such a relationship must exist, yet it is surprising that remarkably few studies have actually examined this issue (Dinstein, Heeger, & Behrmann, 2015). Two recent EEG studies have indeed reported that individuals with ADHD exhibit larger trial-by-trial variability in task-evoked EEG responses. The first study reported that P3b responses, which appear approximately 300 msec after stimulus onset and are thought to represent decision making processes (O'Connell, Dockree, & Kelly, 2012), were more variable in ADHD individuals during a working memory task (Saville et al., 2015). The second study reported that frontal-midline theta oscillations, which are associated with cognitive control processes (Luu, Tucker, & Makeig, 2004), were more variable across trials in individuals with ADHD during a response-choice task (McLoughlin, Palmer, Rijsdijk, & Makeig, 2014). Both of these studies concluded that individuals with ADHD exhibit larger trial-by-trial neural variability than controls in specific cognitive processes that govern behavioral responses, which would explain the larger trial-by-trial RT variability across trials found in individuals with ADHD.

To properly interpret these findings, however, it is important to examine whether larger neural variability in ADHD is apparent only in neural responses that represent task-evoked cognitive processes or also in early sensory responses to unattended stimuli and even in trials where stimuli are omitted/absent. Answering this question is critical for determining whether the underlying pathophysiology of ADHD is associated with specific stimulus/task evoked neural mechanisms (i.e., specific cognitive processes) or with general mechanisms that govern ongoing neural fluctuations even in the absence of stimulus/task evoked responses.

To address this issue we examined sensory responses in two independent visual and auditory experiments where EEG recordings were acquired from adults with ADHD and matched controls. During these sensory experiments participants performed an unrelated brightness-detection task at the fixation cross, which diverted their attention away from the sensory stimuli that were presented in the visual periphery or auditory modality. Trials containing a stimulus were interleaved with trials where the stimulus was omitted. This experimental design enabled us to compare trial-by-trial neural variability across ADHD and control groups in trials containing unattended stimuli and in trials where the stimulus was entirely absent. In addition, all subjects completed CRT and go-no-go experiments, which have commonly been used to demonstrate differences in reaction-time variability across ADHD and control groups (Kofler et al., 2013; Kuntsi & Klein, 2012). This allowed us to relate measures of trial-by-trial neural variability and behavioral measures of trial-by-trial RT variability within the same individuals.

2. Materials and methods

2.1. Participants

Seventeen individuals with ADHD (9 females, Mean age = 25 years old; range = 21–27 years) and 17 healthy controls (12 females, Mean age = 24 years old; range = 21–27 years) participated in the study. All participants had normal or corrected-to-normal vision and provided written informed consent according to the guidelines of the current version of the Declaration of Helsinki. The study was approved by the Ben Gurion University ethics committee. Subjects were paid 50 New Israeli Shekels per hour for participation. ADHD individuals taking stimulants were instructed to abstain from medication for at least 24 h before participation.

All participants underwent a clinical interview, which was performed by two intern clinical psychologists (supervised by