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Amplitude variability over trials in hemodynamic responses in adolescents with ADHD: The role of the anterior default mode network and the non-specific role of the striatum

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ABSTRACT

It has been suggested that intra-individual variability (IIV) in performance on attention and other cognitive tasks might be a cognitive endophenotype in individuals with ADHD. Despite robust IIV findings in behavioral data, only sparse data exist on how what type of brain dysfunction underlies variable response times. In this study, we asked whether ADHD IIV in reaction time on a commonly-used test of attention might be related to variation in hemodynamic responses (HRs) observed trial-to-trial. Based on previous studies linking IIV to regions within the "default mode" network (DMN), we predicted that adolescents with ADHD would have higher HR variability in the DMN compared with controls, and this in turn would be related to behavioral IIV. We also explored the influence of social anxiety on HR variability in ADHD as means to test whether higher arousal associated with high trait anxiety would affect the neural abnormalities. We assessed single-trial variability of HRs, estimated from fMRI event-related responses elicited during an auditory oddball paradigm in adolescents with ADHD and healthy controls (11–18 years old; $N = 46$). Adolescents with ADHD had higher HR variability compared with controls in anterior regions of the DMN. This effect was specific to ADHD and not associated with traits of age, IQ and anxiety. However, an ADHD effect of higher HR variability also appeared in a basal ganglia network, but for these brain regions the relationships of HR variability and social anxiety levels were more complex. Performance IIV correlated significantly with variability of HRs in both networks. These results suggest that assessment of trial-to-trial HR variability in ADHD provides information beyond that detectable through analysis of behavioral data and average brain activation levels, revealing specific neural correlates of a possible ADHD IIV endophenotype.

1. Introduction

Children and adolescents diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD; American Psychiatric Association (APA), 1994, 2013) show greater performance variability in reaction time (RT) on attention and cognitive control tests compared with typically developing children (Buzy et al., 2009; Klein et al., 2006; Kuntsi et al., 2001; Vaurio et al., 2009). Meta-analytic reviews find that RT variability is present in ADHD at all ages, has a genetic basis (Bellgrove et al., 2005; Kuntsi and Klein, 2012), is attenuated by psychostimulant medications (Spencer et al., 2009), is unrelated to response speed (Karalunas et al., 2014; Kofler et al., 2013) and predicts with real-world ADHD behaviors (Antonini et al., 2013), thus representing a stable feature of the disorder. It has been suggested that this characteristic intra-individual variability (IIV) in behavioral performance might be a cognitive endophenotype for ADHD (Castellanos et al., 2005; Castellanos and Tannock, 2002; Kuntsi and Klein, 2012; Tamm et al., 2012). As such, study of neurobiological factors underlying IIV in ADHD could lead to improved understanding of the disorder and its causes.

It has been suggested that spontaneous brain activity comprising low frequency fluctuations of the default mode network (DMN) interrupts with task-positive brain activation in children with ADHD,

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possibly underlying attentional lapses and leading to high IIVRT in ADHD (Sonuga-Barke and Castellanos, 2007). Only a handful of studies have begun to investigate the neural correlates of IIV to ask if this DMN spontaneous activation account might explain the IIV behavioral performance profile. Attentional lapses observed in RT measurements have been linked to low frequency fluctuations in the DMN that interfere with task-related cognitive processing (Broyd et al., 2009; Eichele et al., 2008; Weissman et al., 2006). An abnormal DMN function is also linked to developmental immaturity (Tam et al., 2014). However, despite IIV being a robust finding in ADHD behavioral data, only sparse data exists on how IIV manifests in measures of ADHD brain activation. Variable RT has been associated with average levels of brain activity in medial prefrontal cortex (mPFC) regions, which form a key region of the anterior DMN (Fassbender et al., 2009; Rubia et al., 2007). In ADHD, greater IIV also has been linked by post hoc correlation analyses to lower activation during Go/No-Go tasks in frontoparietal brain regions (Suskauer et al., 2008) and less white matter integrity in cingulum bundle and frontostriatal tracts (Lin et al., 2014), as well as smaller amplitudes in the cingulo-opercular system at errors (Plessen et al., 2016).

A potentially more meaningful approach for understanding brain function underlying IIV in ADHD would be to estimate hemodynamic responses (HRs) on a single-trial basis to evaluate IIV in the brain's response to each event of interest (e.g., Eichele et al., 2008). In this way, it would be possible to link trial-to-trial behavioral variability so often observed in previous ADHD studies to trial-to-trial hemodynamic variability. For instance, behavioral IIV was previously found to be positively associated with HR amplitude variability over trials (Danielmeier et al., 2011; Eichele et al., 2008) in the anterior DMN (van Maanen et al., 2011). To the best of our knowledge, hemodynamic amplitude variability over task trials has not been studied in children with ADHD. Therefore, the present study re-examines fMRI data from adolescents' boys with DSM-IV/DSM-V (American Psychiatric Association, 1994, 2013) Combined-subtype ADHD performing an auditory oddball attention task (Stevens et al., 2007). Oddball performance requires participants to detect and respond to infrequent (oddball) stimuli (i.e., target processing) (Rubia et al., 2007) requiring attention allocation (Stevens et al., 2007) and the ability to stay vigilant (Tamm et al., 2006). These are attention-related abilities previously associated with IIV (Kuntsi et al., 2001; Rubia et al., 2007; Stevens et al., 2007). A study using the analogous estimation of single-trial variability in event-related EEG data found that adolescents with ADHD had higher amplitude variability over trials relative to healthy controls for the P3 component (i.e., related to target processing on oddball tasks) (Lazzaro et al., 1997). We assessed event-related HR amplitude variability over individual target trials as in previous reports (Eichele et al., 2008). We hypothesized that ADHD-diagnosed adolescents would show higher HR amplitude variability over trials in the anterior DMN than a comparison group of typically developing adolescents without ADHD. We also expected that the level of single-trial HRs variability in these brain regions would be associated with behavioral performance IIV.

Furthermore, we wanted to explore the effect of self-reported social anxiety on HR variability in ADHD. Higher symptom levels of anxiety are typically co-occurring with ADHD (Chavira et al., 2004), which in adolescent years, often constitute in social anxiety (Caouette and Guyer, 2014; Dell'Osso et al., 2003). Thus, anxiety is a significant modulator of arousal — affecting the ability to adjust energetic level to task requirements (Eysenck et al., 2007) and possibly affecting the DMN activation (Broyd et al., 2009). Both ventro- and dorsomedial PFC regions that constitute part of the DMN are believed to have a key role in the pathophysiology of social anxiety (Blackford et al., 2014; Damsa et al., 2009; Evans et al., 2009; Peterson et al., 2014). Therefore, examining anxiety is a useful way to further test neurobiological modulation of IIV in ADHD, which previous studies linking IIV RT to neurobiological dysfunction have not done. Because these analyses are exploratory, they are included as follow-up analyses for effects found for the primary IIV ADHD analyses.

2. Materials and methods

2.1. Participants

In the present study 23 boys with ADHD and 23 typically developing boys, 11–18 years of age, were recruited via physician referral and community advertisements (Stevens et al., 2007). The two groups were matched on age and demographic characteristics. Experienced clinical staff conducted a diagnostic evaluation with the Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). The criteria for children to be included in the sample were no other mental health disorder except for ADHD, no history of formal learning disability, and no significant medical conditions. Further, the healthy control group was matched to the ADHD group on handedness, age, socioeconomic status (Hollingshead and Redlich, 1958), self-report scores for depression (Beck et al., 1996) and anxiety (March et al., 1997), and estimated intelligence (Wilkinson, 1993). The boys with ADHD had not taken medication for at least 24 h before the time of fMRI. Descriptive information of the sample and *t*-test comparison results is shown in Table 1. For further details about characteristics of the sample, see Stevens et al. (2007).

2.2. fMRI task and procedure: oddball task

Participants performed two runs of an auditory three-stimulus oddball task (Kiehl et al., 2001; Kiehl et al., 2005). The oddball task consisted of 24 target tone stimuli, 24 novel sound stimuli, and 196 non-target stimuli. The standard stimulus was a 1000 Hz tone (probability = 0.80), the target stimulus was a 1500 Hz tone (probability = 0.10), and the novel stimuli (probability = 0.10) consisted of nonrepeating random digital noises (e.g., tone sweeps, whistles). Each stimulus was presented for 200 ms with a pseudorandom stimulus onset asynchrony ranging from 1000 to 3000 ms (mean = 1500). Moreover, three to five standard tones were followed by either target or novel tones. The children were instructed to make a right index finger button response quickly and accurately for every target tone, but not for other stimuli. All the children in the present sample reported that they could hear the stimuli and discriminate the stimuli from the background scanner noise. The events of stimuli presentation and the behavioral responses (hits or false alarms within 1250 ms) were recorded and monitored online on a separate computer. In the present study, only the behavioral responses to the target tones, and the hemodynamic responses following the presentation of the target tones and the behavioral responses, were included in the statistical analyses. We calculated the standard deviation for each adolescent based on the single-trials of target RT to generate a measure of performance IIV. See Table 1 for the mean (e.g., reaction time, number of hits, and percentile of target hits) and single-trial variability scores for each diagnostic group in relation to the target processing on the oddball task.

Table 1
Descriptive information about the sample.

	ADHD		HC		Analysis
Variables	Mean	SD	Mean	SD	*t*
Age	14.65	1.85	15.13	1.94	0.86
Matrix Reasoning	25.81	6.19	27.45	3.36	0.65
Target mean RT	388.07	72.23	440.77	104.39	1.99[a]
Target IIV RT	136.06	63.11	113.80	53.86	−1.29
Target hits	46.87	2.97	45.96	3.20	−1.00
Target percentiles	0.98	0.06	0.96	0.07	−0.98
Social anxiety subscores^{R}	−0.06	1.10	0.06	0.83	0.42

Note. RT = reaction time; IIV = intra-individual variability. ^{R} = residual scores.
[a] $p < 0.06$.