Neuropsychologia 47 (2009) 2389–2396

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Increased intra-individual reaction time variability in attention-deficit/hyperactivity disorder across response inhibition tasks with different cognitive demands

Rebecca G. Vaurio[a,b,*], Daniel J. Simmonds[d], Stewart H. Mostofsky[a,b,c]

[a] *Kennedy Krieger Institute, Baltimore, MD, USA*
[b] *Johns Hopkins University School of Medicine, Department of Psychiatry Baltimore, MD, USA*
[c] *Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA*
[d] *The University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*

ARTICLE INFO

Article history:
Received 20 May 2008
Received in revised form 12 December 2008
Accepted 2 January 2009
Available online 22 January 2009

Keywords:
Ex-Gaussian
Fast Fourier transform
Response preparation
Response inhibition
Response selection
Supplementary motor area
"pre-SMA"

ABSTRACT

One of the most consistent findings in children with ADHD is increased moment-to-moment variability in reaction time (RT). The source of increased RT variability can be examined using ex-Gaussian analyses that divide variability into normal and exponential components and Fast Fourier transform (FFT) that allow for detailed examination of the frequency of responses in the exponential distribution. Prior studies of ADHD using these methods have produced variable results, potentially related to differences in task demand. The present study sought to examine the profile of RT variability in ADHD using two Go/No-go tasks with differing levels of cognitive demand. A total of 140 children (57 with ADHD and 83 typically developing controls), ages 8–13 years, completed both a "simple" Go/No-go task and a more "complex" Go/No-go task with increased working memory load. Repeated measures ANOVA of ex-Gaussian functions revealed for both tasks children with ADHD demonstrated increased variability in both the normal/Gaussian (significantly elevated sigma) and the exponential (significantly elevated tau) components. In contrast, FFT analysis of the exponential component revealed a significant task × diagnosis interaction, such that infrequent slow responses in ADHD differed depending on task demand (i.e., for the simple task, increased power in the 0.027–0.074 Hz frequency band; for the complex task, decreased power in the 0.074–0.202 Hz band). The ex-Gaussian findings revealing increased variability in both the normal (sigma) and exponential (tau) components for the ADHD group, suggest that both impaired response preparation and infrequent "lapses in attention" contribute to increased variability in ADHD. FFT analyses reveal that the periodicity of intermittent lapses of attention in ADHD varies with task demand. The findings provide further support for intra-individual variability as a candidate intermediate endophenotype of ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed childhood disorders. The current diagnostic criteria for ADHD emphasize observable behaviors from two core domains, symptoms of hyperactivity/impulsivity and symptoms of inattention, most notably decreased ability to sustain attention when required to complete non-preferred tasks (APA, 2000). Although the etiology of ADHD is not known, recent research clearly identifies ADHD as a neurobiological disorder (Buitelaar, Montgomery, & van Zwieten-Boot, 2003; Denckla, 2003; Durston, 2003; Tannock, 1998). Because ADHD is clinically heterogeneous, it is unlikely to have a single neurobiological etiology. Despite the possibility of multiple etiologies, the cardinal symptoms of hyperactivity, impulsivity, and cognitive dysfunction may emanate from closely related disturbances in cerebral function, which once understood, could serve as biomarkers that help to guide diagnosis and treatment and which can be used as "intermediate" endophenotypes in studies of genetic and environmental etiologies (Gottesman & Gould, 2003; Rommelse et al., 2007).

One particularly fruitful line of research has been the characterization of performance of children with ADHD on tasks assessing components of controlled responding. Response control tasks utilize a number of formats including Go/No-go (i.e., responding to one or more proscribed stimuli while withholding response to another), stop signal tasks (i.e., responding in an ongoing manner until cued by a separate signal not to do so), choice reaction time (i.e., responding differentially based on external stimuli, e.g., flanker

---

[*] Corresponding author at: Kennedy Krieger Institute, Department of Neuropsychology, 1750 E. Fairmount Avenue, Baltimore, MD 21211, USA. Tel.: +1 443 923 4479; fax: +1 443 923 4470.
E-mail address: Vaurio@kennedykrieger.org (R.G. Vaurio).

0028-3932/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2009.01.022

task), simple reaction time (i.e., responding quickly to an external stimulus) and self-generated responding (e.g., tapping continuously). These paradigms can be manipulated by changing sensory modality or by altering the cognitive complexity of the tasks, for example, by increasing demands of working memory or changing the complexity of the stimuli themselves.

For many years there was emphasis on measures of inhibitory failure in ADHD, stemming in part from clinical observations suggesting that impaired inhibitory control contributes to excessive impulsivity, hyperactivity, and distractibility (Barkley, 1997). In practice, however, the evidence supporting deficits in inhibitory control as an endophenotype of ADHD have been mixed; some studies find that children with ADHD show high rates of inhibitory failures (commission errors) compared to typically developing (TD) children (e.g., Johnson et al., 2007b; Wodka et al., 2007) while others find no differences in errors between groups (Schulz et al., 2004). In addition, children with other developmental disabilities have been shown to demonstrate deficits in response inhibition on some tasks, indicating that this may not be a characteristic specific to children with ADHD (e.g., Johnson et al., 2007a). Given the inconsistency of the inhibitory findings, other indices have been considered as potential intermediate behavioral endophenotypes.

There has been accumulating evidence in recent years that other aspects of response control are affected in ADHD. In particular, several studies find that children with ADHD show increased intra-subject variability (ISV) in their response time when compared to TD children (Castellanos et al., 2005; Johnson et al., 2007b; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Williams, Strauss, Hultsch, Hunter, & Tannock, 2007; Wodka et al., 2007; Suskauer, Simmonds, Fotedar et al., 2008).

Several pieces of evidence suggest that increased ISV may be a good candidate as an intermediate endophenotype of ADHD (Castellanos & Tannock, 2002, Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). First, increased variability in responding has been demonstrated to correlate with impulsive responding and self-report of inattention to tasks (Rommelse et al., 2007; Simmonds et al., 2007; Strandburg et al., 1996), suggesting that variability in responding is a contributing factor to expression of diagnostic characteristics of ADHD. Further, several studies have demonstrated that close family members of individuals with ADHD demonstrate increased variability in responding, including, siblings sharing an ADHD diagnosis, discordant dizygotic twins, and siblings who do not meet criteria for diagnosis of ADHD (Bidwell, Willcutt, DeFries, & Pennington, 2007; Rommelse et al., 2007). This pattern of results suggests a genetic mechanism for expression of the phenotype. Analyses characterizing ISV in ADHD has revealed a pattern of occasional responses with unusually long reaction time, with the majority of responses being comparable to comparison groups (Castellanos et al., 2005; Hervey et al., 2006; Leth-Steensen, King Elbaz, & Douglas, 2000).

Statistical analyses utilizing comparison of group means and variability (i.e., standard deviation), may mask such responses by treating them as outliers or by treating them as "noise" that becomes averaged with other responses (Hervey et al., 2006). This likely explains why reaction time differences have not been a consistent finding in all studies as their group mean is differentially affected by outliers. As such, researchers have more recently moved toward utilizing statistical methodologies allowing measurement and comparison of intra-individual variability in addition to inter-individual variability in order to more fully evaluate the significance of variability in responding as it relates to ADHD.

Use of the ex-Gaussian distributional model provides a more appropriate framework in which to evaluate ISV. This model posits that the distribution of reaction times can be represented as the sum of a normal (Gaussian) distribution of response times and an independent exponentially distributed variable (Leth-Steensen et al., 2000). The ex-Gaussian distribution is composed of three primary components, mu, a measure of central tendency often closely related to the mean of the normal distribution, sigma a measure of the variation of the normal distribution, and tau, a measure of the mean of the exponential component of the distribution (Hervey et al., 2006; Leth-Steensen et al., 2000). In analysis of response times, the values of mu and sigma represent the distribution of faster responses while the value of tau provides a measure of increased intra-individual variability in the form of infrequent but long response times.

Two studies have applied ex-Gaussian analyses to children with ADHD (Hervey et al., 2006; Leth-Steensen et al., 2000). In the first, subjects performed a simple choice response task with minimal demands on response control; children with ADHD showed increased variability in the exponential component (increased tau), but not the normal portion of the distribution. The authors posited that this may have been the result of occasional lapses in attention leading to unusually long response times for some trials (Leth-Steensen et al., 2000). In a more recent study using a Go/No-go ("continuous performance") task designed to assess response (including inhibitory) control, investigators found ADHD was associated with abnormalities in both the normal (increased sigma) and exponential (increased tau) components of reaction time distribution (Hervey et al., 2006). The discrepancy in findings between these two studies may be related to differential task demands, with the increased need for response control in the Go/No-go task unmasking ADHD-associated increases in variable responding throughout the task.

Based on the evaluation of the ex-Gaussian distribution, it is not clear if the increased ISV occurs randomly or whether it is more predictable and periodic in nature. Periodicity in neural firing has been observed in organized, distributed and independent brain networks. Analysis of patterns of periodicity in behavioral responding may implicate inefficient or impaired functioning within specific brain networks. Fast Fourier transform (FFT) is a method utilized to identify such periodicity in responding. This method utilizes logarithmic transformation to measure the power of periodic responding at various temporal frequency bands. In this way, increased variability can also be identified for particular temporal frequency bands, potentially identifying sources of increased variability in ADHD (Johnson et al., 2007b).

In prior FFT studies of ADHD (Castellanos et al., 2005; Di Martino et al., 2008; Johnson et al., 2007b) variability has been evaluated using choice response tasks with relatively minimal demands for motor response control. These studies found increases in spectrum in specific frequency bands (e.g., 0.027–0.074 Hz) for children with ADHD compared to controls. In a separate study, Johnson et al. (2007a) used FFT to compare performance of ADHD and TD children on two versions of a Sustained Attention to Response Task (SART). Both tasks utilized a "Go/No-go" format using 9 digits, with children responding to all of the digits but one with a button push. In one version of the task the order of the stimuli was entirely predictable (repeating throughout the task), while in the other they were randomized (consistent with the format typically used in Go/No-go tasks). For both tasks, children with ADHD demonstrated both increased fast (i.e., moment-to-moment) and slower (i.e., over the course of the task) variability. The authors attributed this pattern of performance to deficits in "top-down" phasic response control (i.e., fronto-parietal circuits) and more tonic (i.e., basal ganglia circuits and cerebral hemodynamic mechanisms), respectively.

In the current study we were interested in examining response variability in ADHD using two different Go/No-go tasks, both of which had relatively high demands on motor response (inhibitory) control, but which differed in working memory demand. One task used a "simple" Go/No-go format in which working demand was minimized using a well-ingrained stimulus-response associa-