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Intra-individual variability in ADHD, autism spectrum disorders and Tourette's syndrome

Hilde M. Geurts[a,*], Raoul P.P.P. Grasman[b], Sylvie Verté[d], Jaap Oosterlaan[c], Herbert Roeyers[d], Serena M. van Kammen[a], Joseph A. Sergeant[c]

[a] Department of Psychonomics, Universiteit van Amsterdam, Roeterstraat 15, 1018 WB Amsterdam, The Netherlands
[b] Department of Developmental Psychology, Universiteit van Amsterdam, Amsterdam, The Netherlands
[c] Department of Clinical Neuropsychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[d] Department of Psychology, Ghent University, Ghent, Belgium

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ABSTRACT

The potential for response variability to serve as an endophenotype for attention deficit hyperactivity disorders (ADHD) rests, in part, upon the development of reliable and valid methods to decompose variability. This study investigated the specificity of intra-individual variability (IIV) in 53 children with ADHD by comparing them with 25 children with high functioning autism (HFA), 32 children with autism spectrum disorders (ASD), who also were comorbid for ADHD (ASD + ADHD), 21 children with Tourette's syndrome (TS), and 85 typically developing controls (TD). In order to decompose the variability of the reaction times, we applied three distinct techniques: ex-Gaussian modeling, intra-individual variability analysis, and spectral analysis. Our data revealed that children with HFA and children with ASD + ADHD exhibited substantial IIV compared with ADHD and TD children. We argue that: (1) all three methods lead to a single consistent conclusion; (2) careful documentation of the analytic steps used in spectral analysis is mandatory for comparison between studies; (3) the presence of comorbidities may constitute an important factor in the observed response variability in previous studies of ADHD.

Similar cognitive deficits, such as deficits in inhibitory control, have been observed in both children with attention deficit hyperactivity disorders (ADHD), autism spectrum disorders (ASD), and children with Tourette's syndrome (TS, e.g., Corbett & Constantine, 2006; Crawford, Channon, & Robertson, 2005; Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2004; Goldberg et al., 2005; Happé, Booth, Charlton, & Hughes, 2006; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005). The cardinal features of ADHD are inattentiveness, hyperactivity, and impulsivity, while ASD are characterized by social and communicative impairments combined with restricted, stereotypical patterns of behavior and interests. Multiple involuntary tics and at least one vocal tic are needed for a TS diagnosis (American Psychiatric Association [APA], 2000). Despite the apparent distinctiveness of these disorders, there is a striking co-occurrence of each of the combinations of these disorders. The co-occurrence (comorbidity) of these disorders ranges from 11% up to 83% depending on the combination of the disorder and the direction of the relationship (see Canitani & Vivanti, 2007; Clark, Feehan, Tinline, & Vostanis, 1999; Frazier et al., 2001; Leyfer et al., 2006; Spencer et al., 1999; Sturm, Fernell, & Gillberg, 2004; Sukhodolsky et al., 2003). ASD and ADHD have salient overlapping clinical characteristics (e.g., Frazier et al., 2001; Keen & Ward, 2004; Roeyers, Keymeulen, & Buysse, 1998). Although it is well established that children with ASD show ADHD characteristics (e.g., Leyfer et al., 2006; Sturm et al., 2004), the reverse is less often reported. Clark et al. (1999) reported that in a clinically diagnosed group of children with ADHD ($n = 49$) 65–80% showed ASD symptoms as reported by parents. In a previous report (Geurts et al., 2004), 26% of the children stringently diagnosed with ADHD ($n = 86$) met criteria for ASD. There is substantial overlap of ASD symptomatology in children with ADHD. These three neuropsychiatric disorders have been linked to deficits in fronto-striatal and fronto-parietal circuits (e.g., Albin & Mink, 2006; Bachevalier & Loveland, 2006; Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005; Bush, Valera, & Seidman, 2005; Dickstein, Bannon, Castellanos, & Milham, 2006; Eliez & Reiss, 2000; Kates et al., 2002; Schmitz et al., 2006). Thus ADHD, ASD, and TS may have partially overlapping disorders.

1. Response variability as an endophenotype

Recently, neuropsychological research has shifted towards determining specific endophenotypes related to these disorders as

* Corresponding author. Tel.: +31 20 5256843; fax: +31 20 6391656.
E-mail address: h.m.geurts@uva.nl (H.M. Geurts).

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an essential link between genotypes and phenotypes (Bellgrove et al., 2005; Castellanos & Tannock, 2002; Gottesman & Gould, 2003; Losh & Piven, 2007; Rizzo et al., 2007; Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007a; Rommelse et al., 2007b). Castellanos and Tannock (2002) argued that deficits in the temporal aspects of cognitive processing result in high intra-individual variability (IIV) and might be an important endophenotype for ADHD. It would be valuable to know if such a candidate endophenotype for ADHD is able to distinguish between *different* neurodevelopmental disorders. Indeed, children with ADHD seem to encounter frequent lapses in attention and are often inconsistent in how they perform. This might underlie the observed variability within and between tasks across different kinds of reaction time (RT) tasks in a number of studies (Castellanos et al., 2005; Johnson, Kelly, et al., 2007; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Kuntsi, Oosterlaan, & Stevenson, 2001; Leth Steensen, Elbaz, & Douglas, 2000; Lijffijt, Kenemans, Verbaten, & Van Engeland, 2005; Mullins, Bellgrove, Gill, & Robertson, 2005; Russell et al., 2006; Sergeant & Van der Meere, 1988). Castellanos et al. (2005) argued that IIV might be related to a pathophysiological processing cutting across diagnostic boundaries (see also Russell et al., 2006). Thus, it is possible that variability in responding is not specific to ADHD, but is a nonspecific characteristic of brain pathology in various neurodevelopmental disorders (Murtha, Cismaru, Waechter, & Chertkow, 2002; Schwartz, Carr, Munich, & Glauber, 1989; Stuss, Murphy, Binns, & Alexander, 2003; Stuss, Pogue, Buckle, & Bondar, 1994; Walker et al., 2000).

Response variability has been associated with a fronto-parietal-thalamic brainstem network (Paus, 2001; Paus et al., 1997; Sturm et al., 1999) including the anterior cingulate cortex (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002), and prefrontal areas such as the dorsolateral prefrontal cortex and the orbital frontal cortex (Bellgrove, Hester, & Garavan, 2004; MacDonald, Nyberg, & Bäckman, 2006; Schmitz, Daly, & Murhpy, 2007; Stuss et al., 2003). Biederman and Spencer (1999) have explained increased IIV as being due to catecholaminergic and noradrenergic deficiencies that give rise to arousal modulation deficiencies (see also Castellanos et al., 2005; Nigg, 2005). Others have argued that reduced myelinisation may account for increased response variability in ADHD (Russell et al., 2006), which may result in a deviant functional connectivity across the brain. This has been observed in ADHD (Murias, Swanson, & Srinivasan, 2006), ASD (Cherkassky, Kana, Keller, & Just, 2006), as well as TS (Kates et al., 2002). Recently the "default-mode interference" hypothesis has been put forward to link the increased IIV with the synchronization of the default mode network (Sonuga-Barke & Castellanos, 2007). This default network is a putatively distributed neural resting state circuit that shows coherent low frequency fluctuations (Fox, Snyder, Zacks, & Raichle, 2006). Sonuga-Barke and Castellanos (2007) hypothesize that in ADHD this default-mode might be disturbed and lead to the observed IIV in ADHD (Tian et al., 2008). Others have suggested that ASD might also be associated with deficiencies in this default network (Cherkassky et al., 2006; Iacoboni, 2006; Kennedy, Redcay, & Courchesne, 2006). To our knowledge such an association has not been proposed for TS. Hence, not only ADHD but other neurodevelopmental disorders, such as ASD, might be associated with heightened IIV, but this is less certain for TS.

1.1. Specificity of response variability

The specificity of the response variability endophenotype has been studied in a direct comparison between children with ADHD and children with high functioning autism (HFA, Johnson, Robertson, et al., 2007). These authors showed that the ADHD group has a typical pattern of low- and high-frequency variability, which was not observed in either the HFA or control groups. This pattern may have been observed because RT variability was decomposed into variability at different frequencies (i.e., periodograms). Put differently, these so-called spectral band analyses focus on an aggregate of oscillations from a continuum of frequencies. Castellanos et al. (2005) argued that deviant oscillations in RT of ADHD participants might be related to deviant oscillations at a neuronal level (Ben Pazi, Gross Tsur, Bergman, & Shalev, 2003). Low frequency variability may be a consequence of a specific disruption of the arousal system in ADHD (Douglas, 1999; Sergeant, 2005; Sergeant, Oosterlaan, & Van der Meere, 1999). Some evidence suggests that ASD might also be related to a deviant arousal system (Raymaekers, van der Meere, & Roeyers, 2004) but this is not in line with recent findings (Johnson, Robertson, et al., 2007). Although the clinical groups were extensively assessed, it is unclear from that study whether children with ASD comorbid for ADHD respond as variably as children with only ADHD or are as variable as children with only HFA. Frazier et al. (2001) reported that children with ASD with comorbid ADHD were, in general, more impaired than children without comorbid ADHD. Hence, the first purpose of the current study was to determine whether the presence of comorbidities might be an alternative explanation for the observed variability in ADHD. To explore whether the temporal structure in the patterns of variability differentiates between these three neurodevelopmental disorders, a comparison will be made between children with ADHD, children with HFA, children with TS, children with ASD and comorbid for ADHD, and typically developing (TD) children.

Several studies have focused on the variability of responding in ADHD (e.g., Castellanos et al., 2005; Leth Steensen et al., 2000; Williams, Strauss, Hultsch, Hunter, & Tannock, 2007). Although most studies conclude that ADHD participants show increased variability, the precise conclusions vary from study to study. The differences may be due, at least in part, to the different methods used to study variability in RT tasks. To substantiate response variability as an endophenotype for any disorder, it is essential to determine whether different methods converge to a similar conclusion. The second purpose of the current study is to apply all three methods described in the ADHD literature to study RT variability to determine whether the three methods lead to a consistent conclusion regarding IIV in ADHD and to establish whether there is specific deviance in the oscillatory patterns in ADHD compared to other neurodevelopmental disorders.

1.2. Methods to study response variability

In the majority of reports, within task variability has been handled by collapsing across the entire time interval of the task, resulting in a single point estimate of variability around the mean. This results in a loss of specific information with regards to the RT distribution (Slifkin & Newell, 1998). Therefore, it is important to take into account the responses on all trials within the same task. We focus on the RT distributions within a task in three different ways: (1) by modeling the RT distribution as an ex-Gaussian distribution; (2) by comparing the IIV of the fast and slow ends of the RT distribution; (3) by exploring the oscillations of the RT over the duration of the task. Each of these three different methods has been applied recently in studies of children with ADHD, but focus on different aspects of variability. This may have led to slightly different conclusions regarding the IIV in ADHD.

The first to conduct a detailed statistical examination of the actual RT distributions in children diagnosed with ADHD were Leth Steensen et al. (2000). They fitted an ex-Gaussian distribution to their data to study the shape of the RT distribution. The ex-Gaussian distribution is a combination of a normal distribution and an expo-