Brain and Cognition 72 (2010) 228–237

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Evidence for specificity of ERP abnormalities during response inhibition in ADHD children: A comparison with reading disorder children without ADHD

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ARTICLE INFO

Article history:
Accepted 18 September 2009
Available online 21 October 2009

Keywords:
ADHD
Reading disorder
Event-related potentials
Stop Signal Task
Inhibitory control
N200
NoGo-P3

ABSTRACT

Executive function and working memory deficits are not only present in ADHD, but also in reading disorder (RD). Here, high-density ERPs were recorded during the Stop Signal Task in 53 children and adolescents: An ADHD-combined type group, a group with RD, and a healthy control group. The ADHD-C group displayed unique abnormalities of the frontal N200. Both healthy controls and RD groups showed a success-related right frontal N200 modulation, which was absent in the ADHD group. Second, for Success Inhibition trials, the ADHD-C had smaller right frontal N200 waves relative to healthy controls, while the RD group did not. In contrast, NoGo-P3 abnormalities were present both in the ADHD-C and RD groups. Impaired early response inhibition mechanisms, indexed by the frontal N200, appear to be limited to ADHD-C. In contrast, deficits in later cognitive control and error monitoring mechanisms, indexed by the NoGo-P3, appear to be present in both conditions.

1. Introduction

Attention Deficit-Hyperactivity Disorder (ADHD) is a common behavioral syndrome, characterized by low levels of attention and concentration and high levels of activity, distractibility and impulsivity (American Psychiatric Association, 1994). There is a high rate of co-morbidity of ADHD with learning disabilities. ADHD has been found to be associated with reading disorder (RD) in at least 20% of the cases (Semrud-Clikeman et al., 1992). In the last 20 years several theoretical models have been formulated, and empirical research has been gathered, on what constitute the main core of cognitive symptoms in ADHD. However, only more recently research has attempted to characterize and separate the core cognitive features of ADHD and RD (e.g., Burgio-Murphy et al., 2007; Purvis & Tannock, 2000; Tiffin-Richards, Hasselhorn, Woerner, Rothenberger, & Banaschewski, 2008).

One of the most influential theoretical models of ADHD posits that deficits in inhibitory control are the core symptoms in ADHD (Barkley, 1997). Other theoretical models emphasize deficits in cognitive control mechanisms, including both conflict monitoring and error processing (Nieuwenhuius, Yeung, van den Wildenberg, & Ridderinkhof, 2003), a dysfunction in the regulation of motivation and reward, with a preference for immediate versus delayed rewards (delay aversion, e.g., Sonuga-Barke, 2002) or deficits in state/arousal regulation (cognitive-energetic model, e.g., Sergeant, 2000). In support of the inhibitory control model, children with Attention Deficit-Hyperactivity Disorder (ADHD) are impaired in laboratory tests that tap into response inhibition, such as go-NoGo tasks (see a review in Nichols & Waschbusch, 2004).

Neural mechanisms underlying inhibitory processes can be studied with a high degree of temporal resolution by recording event-related potentials (ERPs) from the scalp. In ERP studies using go-NoGo tasks, the frontally maximal N200 wave, peaking around 200 ms, has been shown to have greater amplitude for NoGo relative to Go trials (e.g., Falkenstein, Hoorman, & Hohnsbein, 1999; Kok, 1986; Smith, Johnstone, & Barry, 2004). It has been proposed that the NoGo N200 indexes an early mechanism of inhibitory control that is a reflection of a "red flag" signal generated in prefrontal cortex to *trigger* the inhibitory process (Jodo & Kayama, 1992; Kok, 1986). In studies using the Stop Signal Task (SST, Logan, Cowan, & Davis, 1984) a frontal NoGo-N200 has been reported as being abnormally reduced in children with ADHD relative to control children (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005; Dimoska, Johnstone, Barry, & Clarke, 2003; Liotti et al., 2007; Pliszka, Liotti, & Woldorff, 2000). Furthermore, a right frontal N200

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doi:10.1016/j.bandc.2009.09.007

is greater for Success than Failed inhibition trials, and this modulation is absent in ADHD children (Liotti et al., 2007). Likely source generators of the frontal N200 effects are suggested by fMRI studies of the SST in healthy subjects, pointing to the right middle/inferior frontal gyrus as critically involved in inhibitory control (Konishi et al., 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005). Critically, ADHD adolescents have been found to display reduced right middle/inferior frontal gyrus activation in response to Stop Signals, particularly in response to Successful Inhibitions (Rubia et al., 1999, 2005). In summary, the available evidence point to a specific right PFC abnormality associated to the early triggering of inhibitory responses in ADHD-C adolescents and children.

A second ERP component associated to response inhibition in go-NoGo tasks is the NoGo-P3, (peaking around 300 ms), which displays greater amplitude over the frontocentral region for NoGo than Go trials (e.g., Falkenstein, Hoorman, & Hohnsbein, 2002). ADHD children have been shown to display reduced NoGo-P3 waves in response to Stop Signals (particularly Failed Inhibitions, Fallgatter et al., 2004; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; Overtoom et al., 2002). fMRI studies of the SST and Stroop task in ADHD adolescents and children showed less activity in dorsal Anterior Cingulate cortex (dACC), particularly in response to Failed Inhibitions (Pliszka et al., 2006; Rubia et al., 2005). Recent models of the role of ACC emphasize a general role in conflict monitoring and error processing (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Nieuwenhuius et al., 2003). For this reason, the NoGo-P3 has been associated to a late stage of monitoring of the outcome of the inhibitory process (e.g., Nieuwenhuius et al., 2003). The combined ERP and fMRI evidence to-date in ADHD points to a deficit in cognitive monitoring operations depending on dACC function (Liotti et al., 2005; Nieuwenhuius et al., 2003). A simple account in terms of inhibitory control (Barkley, 1997) may therefore be insufficient to capture the spectrum of cognitive operations impaired in ADHD (see Banaschewski et al., 2004, for a similar conclusion). A multi-dimensional account appears to be necessary, also including a deficit in cognitive control operations orchestrated by the dACC.

Recent research is starting to address the issue of characterizing and separating cognitive symptoms which are unique to ADHD or shared by other developmental disorders, and reading disorder (RD) in particular. Developmental dyslexia or RD is among the most prevalent of learning disabilities with estimates ranging from 5% to 12% (e.g., Shaywitz, 1998). There is a high rate of co-morbidity with other developmental conditions. In particular, ADHD has been found to be associated with RD in at least 20% of the cases (Barkley, 1997; Semrud-Clikeman et al., 1992). Children with a reading disability have been found to show a higher rate of attentional difficulties (Shaywitz, Fletcher, & Shaywitz, 1994). In addition, studies have shown impaired performance in attentional tasks requiring greater levels of selection and conflict, such as in the Stroop Task and the Wisconsin card sorting task (WCST, Bednarek et al., 2004; Helland & Asbjørnsen, 2000; Tiffin-Richards et al., 2008).

Two recent studies have attempted to identify underlying mechanisms of impaired executive function in RD using ERPs. The first study employed the Continuous Performance Task (CPT) in RD and control adolescents. They reported reduced amplitude and increased latency of the NoGo-P3 in the RD group. Furthermore, the NoGo-P3 was greater on the right in controls, but symmetric in the RD group (Taroyan, Nicolson, & Fawcett, 2007). A second study explored error processing in children with ADHD combined subtype (ADHD-C), RD, RD + Math disorder and control children. They found that the ADHD-C group had greater amplitude of the error related negativity (ERN) relative to the healthy control group, while the Error Positivity (Pe) was reduced in children with RD + Math disorder relative to the RD only and control groups (Burgio-Murphy et al., 2007). No ERP studies to-date have directly compared ADHD and RD groups in tasks directly tapping into response inhibition.

As an attempt to further characterize and possibly separate the cognitive core symptoms in ADHD and RD, the present study explored electrophysiological mechanisms of inhibitory control and cognitive monitoring (indexed by the N200 and the NoGo-P3) in three age and IQ matched groups of children: ADHD-C without RD, RD without ADHD, and a healthy comparison group. The ADHD and healthy comparison groups were part of a larger cohort of ADHD and healthy children recruited for an ERP and neuroimaging study of inhibitory control in ADHD-C (Liotti et al., 2007; Pliszka et al., 2006). To control for co-morbidity, the ADHD-C children did not meet criteria for a learning disability, and RD in particular and conversely, the RD children did not meet criteria for ADHD (any subtype).

Our first prediction is that only the ADHD-C children would show impaired behavioral measures of response inhibition in the SST, while the RD group would perform the task within normal limits. Concerning our ERP measures, following the reasoning that NoGo-N200 wave would directly reflect inhibitory control, and therefore relate to hyperactivity and impulsivity symptoms selectively present in children with ADHD, a second prediction was that right frontal N200 reduction and the absence of success-related N200 amplitude modulation reported previously would be only present in the ADHD-C group. In contrast, if the NoGo-P3 reflects other executive control mechanisms, and in particular monitoring of the successful and unsuccessful outcome (errors) of the inhibitory process, our third prediction was that a NoGo-P3 reduction may not be restricted to ADHD-C, but also present in RD, where inattention, executive function and working memory deficits have been demonstrated.

2. Methods

2.1. Participants and diagnostic instruments

Subjects were right-handed children and adolescents aged 9–15 years of both genders. Participants' handedness was established by writing, throwing, demonstrating how they brushed their teeth, and show how they would kick a ball. All skills needed to be executed in front of the experimenter using each hand/foot. The study groups were subjects meeting criteria for ADHD-Combined Type (ADHD-C: $n = 16$; 11 males), children meeting criteria for reading disorder ($n = 14$; 10 males); and healthy controls ($n = 22$; 14 males). ADHD-C and control subjects were part of larger cohorts whose ERP and fMRI findings in the SST have been published elsewhere (Liotti et al., 2007; Pliszka et al., 2006). Written informed consent from a parent and assent from the child were obtained according to the Institutional Review Board of the Health Science Center at San Antonio.

Individuals with ADHD met Diagnostic Interview for Children-Version IV-Parent version (DISC-IV-P) criteria for ADHD-C, could meet criteria for oppositional defiant disorder, but not meet criteria for conduct disorder or any anxiety, tic or affective disorder. All ADHD-C subjects in the present study had no history of psychotropic medication treatment, i.e., they were treatment naïve. Reading disorder subjects and healthy controls could not meet criteria for any psychiatric disorders or any history of past treatment with psychotropic medication. No subjects in any group had history of neurological conditions or symptoms, such as head injury, loss of consciousness, motor or sensory loss, nor had they a history of substance or alcohol abuse. Children in the three groups were not taking any medication for a chronic condition on a daily basis for the last 3 months prior to the study.

Children with reading disorder (RD) were initially referred from the Texas school system. These children showed significant