Psychiatry Research: Neuroimaging 249 (2016) 57–66

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Altered response-preparation in patients with adult ADHD: A high-density ERP study

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ARTICLE INFO

Article history:
Received 11 August 2015
Received in revised form
17 February 2016
Accepted 20 February 2016
Available online 23 February 2016

Keywords:
ADHD
ERP
Response-preparation
Response-locked
Response-preceding negative potential shifts

ABSTRACT

Aberrations in early-developing bottom-up processes, such as stimulus-driven response preparation, are thought to play a critical role in the onset of ADHD, and in its persistence over time. Electrophysiology offers a unique tool to gain insight into response preparation, since response preparation has been associated with distinctive ERP changes, including negative potential-shifts which occur predominantly over frontal brain areas. We examined response-preceding negative potential shifts (RPNS) as a probe of response-preparation in adult ADHD patients by obtaining high-density event-related potentials from 33 ADHD and 29 matched healthy subjects during a Go/Nogo task using a 128-channel BioSemi recording-system. Compared to controls, ADHD patients showed enhancement of the RPNS in fronto-central brain regions in the Go condition during correct responses. This change was associated with poor performance in the Stroop incongruency-task: the greater the enhancement, the higher the proportion of errors. Moreover, the ERP-enhancement showed association with the severity of ADHD-symptoms; and with heightened response-variability. Thus, ADHD patients demonstrate neurophysiological alterations in response-preparation and response-preceding brain activity, suggestive of excessive activation of prefrontal neural circuits. Given the correlation with neuropsychological and psychopathological measures, these changes may constitute a pathway for core symptoms of ADHD, including premature and impaired response-preparation and motor-hyperactivity.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder, which occurs in 3–6% of children, and continues into adulthood at a prevalence of 1.5–5% (Simon et al., 2009). Individuals with ADHD suffer from symptoms of hyperactivity, impulsivity and lack of attention. According to neurodevelopmental theory, deficits in early-developing bottom-up processes, such as stimulus-driven response preparation play a crucial role in the emergence of these symptoms and in the onset of ADHD, and remain stable throughout life despite symptom remission (Halperin and Schulz, 2006). Deficits in response preparation can lead to an impulsive response style, and may be manifested as poor ability to plan and to premature responding (Botvinick et al., 2004). Although the behavioral implications of these deficits have been increasingly recognized (Halperin and Schulz, 2006) their neurobiological basis remains poorly understood.

Electrophysiology offers a unique possibility to gain insight into response preparation on a ms by ms basis, since response preparation has been associated with distinctive ERP changes, including negative potential shifts (NPS) which occur predominantly over the anterior brain regions, especially in the frontal regions (Jahanshahi and Hallett, 2003; Kornhuber and Deecke, 1965; Vinding et al., 2014). NPS are elicited in a diverse set of experimental tasks, ranging from anticipatory task conditions to stimulus-driven response preparation (Jahanshahi and Hallett, 2003). Despite the unique opportunity that NPS presents to study response preparation, only few empirical studies have been taken place in ADHD subjects. These studies focused on anticipatory preparation, using the Contingent Negative Variation (CNV) paradigm (Walter et al., 1964) which entails preparation for "signaled movement and the simultaneous anticipatory attention" for an imperative stimulus (Brunia and van Boxtel, 2001). So far, the results of these studies have been inconsistent.

In particular, for adult ADHD, we identified 3 studies that focused on patients with a clinical diagnosis of ADHD: one study reported negative (no group difference) (Dhar et al., 2010) and one

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http://dx.doi.org/10.1016/j.pscychresns.2016.02.008
0925-4927/

reported positive findings (decrease in CNV amplitude in ADHD vs. healthy controls) (Mayer et al., 2015). One study had mixed results with no significant group difference in CNVs in a neutral and a significant difference in the Global Field Power in an emotion processing CPT paradigm in the ADHD group (Meier et al., 2012). For children and adolescents, a body of literature exists which, similar to the adult studies reveal variable findings: both *enhancement* (Spronk et al., 2008) and *reduction* in the CNV amplitude in subjects with ADHD (Banaschewski and Brandeis, 2007; Albrecht et al., 2013, 2014) was found. Moreover, a study which controlled for comorbidity with autism spectrum disorders (Tye et al., 2013) reported a *lack of change* in the CNV in "ADHD-only participants."

Besides the anticipatory task condition, stimulus-driven response preparation paradigm may also be applied as a probe for potential abnormalities in ADHD in the neurophysiological processes that occur during the period which immediately precedes motor response. Response-locked averaging (RLA) with a specific focus on the time window immediately prior to motor response provides a tool to uncover abnormalities in response-preceding brain activity, but to our knowledge this approach (RLA) has not been applied in patients with ADHD. Our work differs from previous studies which used response-locked averaging, since they were specifically studying error-related activity (ERN, Pe) in ADHD (Wiersema et al., 2009; O'Connell et al., 2009). They focused on neurophysiological processes *after* response (i.e., the pre-response time period was ignored, often used as a baseline, and discarded) while this study examined non-error response-preceding activity.

In this study, we applied RLA to investigate the neurophysiological basis of response preparation by studying response-preceding brain activity in ADHD using an ERP Go/Nogo paradigm. Based on the above literature, our specific aim was twofold. *First*, we wanted to investigate response-preceding brain activity, and in particular response-preceding negative potential shifts (RPNS), in patients with adult ADHD, as compared to healthy controls. *Second*, we wanted to examine whether RPNS alterations in ADHD are related to potentially important covariates including (a) core psychopathological symptoms, (b) neuropsychological measures of attention allocation and executive functions (Botvinick et al., 2004), and (c) moment-to-moment fluctuations in response time in ADHD patients, as indexed by the Intrasubject Variability (ISV). We adopted this measure since increased ISV has been reported in children and adults with ADHD across various tasks (Castellanos and Tannock, 2002; Castellanos et al., 2005; Bellgrove et al., 2005; Halperin and Schulz, 2006; Johnson et al., 2008), and it has been considered to reflect the markedly inconsistent response style (Suskauer et al., 2008) during response preparation under stimulus-driven actions in ADHD (Tamm et al., 2012).

2. Methods

2.1. Participants

Sixty two subjects participated in the study: 33 ADHD (mean age = 31.6 years, SD = 12.1) and 29 healthy control subjects (mean age = 32.9 years, SD = 12.8). Control subjects with >18 years of age were selected, and individually matched to patients on age (± 5 years), gender and level of education. Lack of history of psychiatric disease was required for the inclusion in the control group. The 90-item Symptom CheckList (SCL-90R) (Derogatis, 1994) was used to select controls with no current psychiatric comorbidity. Healthy control subjects were recruited from a community sample through friends and acquaintances of the office and medical staff at the University and of participating Ph.D. students. Patients meeting the DSM-IV criteria for adult ADHD with >18 years of age were recruited at the Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary, which provides outpatient service for patients with adult ADHD. Recruitment was done by the office and medical staff at the outpatient service. No neurological illness or head injury in prior history was allowed for subjects selected for the study. Patients were diagnosed according to the DSM-IV criteria. Diagnosis was confirmed via semi-structured interview by the treating physician.

All patients included in the study fulfilled the criteria for the combined subtype of ADHD using the DSM-IV criteria (i.e., they had >6 symptoms of the total of 9 symptoms of Inattention and Hyperactivity/Impulsivity, respectively). Based on the ICD-10 diagnostic system, 10 (30.3%) of the 33 ADHD patients included in the current study evidenced comorbidities, with 1 of the 10 subjects manifesting two comorbidities. In 8 of the 10 subjects (24.2% of total sample of 33 subjects) comorbidities included mood disorders (Major depressive episode, mild or moderate $n=7$; or Other bipolar disorders, $n=1$). One (3%) of the subjects had "Cannabis abuse", and 2 subjects (6%) had Anxiety related disorders (Obsessive–compulsive $n=1$; and Anxiety disorder, unspecified, $n=1$). The latter comorbidity (Anxiety disorder, unspecified) was manifested in 1 patient as an additional comorbidity besides Major depressive episode, mild.

The study complied with the ethical standards of the Declaration of Helsinki, and received approval from the local Ethical Committee. All participants gave written Informed Consent for the study.

2.2. Measures

The Conners' Adult ADHD Rating Scale (66-item version) was used to describe ADHD symptom severity across core psychopathological domains of ADHD: Inattention, Hyperactivity, Impulsivity and Problems with Self-Concept (Erhardt et al., 1999; Conners, 1999). The Adult Self-Report Scale (ASRS) symptom Checklist (Adler et al., 2006) was used to delineate ADHD symptoms and to establish ADHD subtype.

The Stroop color-word incongruency task (CWI) (Stroop, 1935) was applied to characterize executive functions and conflict processing. The CWI is a standard measure of attention and executive functions, and ADHD patients have been shown to exhibit impaired performance on this task (Badzakova-Trajkov et al., 2009). We used the paper-pencil form of Golden Version of the Stroop test (Golden, 1976). This version consists of 3 separate conditions (test pages) with 100 items positioned in five columns of 20 items each. Subjects were instructed to read as quickly as possible in 45 s color words ('reading condition'); then to name colors (XXXXs printed in color; 'naming condition'); and finally to name the color of the color words rather than read the word (while no word is printed in the color it represented; "Color-Word" or "incongruence" condition). In the current study, we focused on the color-word performance (error-rate) since based on meta-analysis this measure is superior to the interference score by providing a better separation of ADHD subjects from controls (Hervey et al., 2004). The error-rates were computed for the trials completed during the 45 s period, and were expressed as percentages. The number of trials during 45 s, and the completion time for 100 stimuli was also recorded for descriptive purposes. As the test represents a trait-measure with good stability over time (Strauss et al., 2005; Wostmann et al., 2013), it was administered off-line (within one-week of the day of the EEG recording).

The total score on the Symptom Check List 90R (SCL-90R), a self-report scale was used to measure the severity on general domains of psychopathology (Derogatis, 1994). The scale was designed primarily to assess symptom patterns in a broad spectrum of populations, ranging from non-patient healthy subjects to