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Prefrontal activation during inhibitory control measured by near-infrared spectroscopy for differentiating between autism spectrum disorders and attention deficit hyperactivity disorder in adults ☆

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ABSTRACT

The differential diagnosis of autism spectrum disorders (ASDs) and attention deficit hyperactivity disorder (ADHD) based solely on symptomatic and behavioral assessments can be difficult, even for experts. Thus, the development of a neuroimaging marker that differentiates ASDs from ADHD would be an important contribution to this field. We assessed the differences in prefrontal activation between adults with ASDs and ADHD using an entirely non-invasive and portable neuroimaging tool, near-infrared spectroscopy. This study included 21 drug-naïve adults with ASDs, 19 drug-naïve adults with ADHD, and 21 healthy subjects matched for age, sex, and IQ. Oxygenated hemoglobin concentration changes in the prefrontal cortex were assessed during a stop signal task and a verbal fluency task. During the stop signal task, compared to the control group, the ASDs group exhibited lower activation in a broad prefrontal area, whereas the ADHD group showed underactivation of the right premotor area, right presupplementary motor area, and bilateral dorsolateral prefrontal cortices. Significant differences were observed in the left ventrolateral prefrontal cortex between the ASDs and ADHD groups during the stop signal task. The leave-one-out cross-validation method using mean oxygenated hemoglobin changes yielded a classification accuracy of 81.4% during inhibitory control. These results were task specific, as the brain activation pattern observed during the verbal fluency task did not differentiate the ASDs and ADHD groups significantly. This study therefore provides evidence of a difference in left ventrolateral prefrontal activation during inhibitory control between adults with ASDs and ADHD. Thus, near-infrared spectroscopy may be useful as an auxiliary tool for the differential diagnosis of such developmental disorders.

1. Introduction

The differential diagnosis of the 2 commonest types of neurodevelopmental disorders, autism spectrum disorders (ASDs) and attention deficit hyperactivity disorder (ADHD), can be difficult. ASDs are characterized by impairments in social skills and communication, as well as repetitive interests and activities (American Psychiatric Association, 2000; Stigler et al., 2011). ADHD is characterized by symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2000). These conditions often share symptoms of inattention, hyperactivity, impulsivity, and neuropsychological deficits in inhibitory control (Willcutt et al., 2005; Corbett et al., 2009). Thus, misclassification between ASDs and ADHD may occur in clinical settings, particularly in cases of ASDs with comorbid ADHD symptoms. Because the clinical symptoms of high-functioning ASDs and ADHD of adulthood have been modified according to environmental and

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developmental factors (Nylander et al., 2013; Lehnhardt et al., 2012; Hofvander et al., 2009; Michielsen et al., 2013), it is more difficult to establish a differential diagnosis of ASDs and ADHD in adults.

These misclassifications may lead to a suboptimal treatment strategy. For example, the administration of methylphenidate (MPH), which is a common treatment for childhood ADHD (Whalen et al., 1989; Barkley et al., 2005; Newcorn et al., 2008; Jensen et al., 2007), to children with ASDs and comorbid ADHD symptoms is frequently associated with adverse effects (i.e., social withdrawal, irritability, and stereotypy) severe enough to warrant treatment discontinuation (Autism Network, 2005; Di Martino et al., 2004). Despite the insufficient study of the benefits and adverse effects of MPH in adults with ASDs and ADHD symptoms, MPH is often administered in these cases, even without evidence of its efficacy, because it is the first line of pharmacological treatment for adult ADHD (Kooij et al., 2010; Atkinson and Hollis, 2010). Other treatments are more appropriate for adult ASDs, such as selective serotonin reuptake inhibitors (Williams et al., 2010a), risperidone (McDougle et al., 1998), and cognitive behavioral therapy (White et al., 2009; Lang et al., 2010).

The inhibitory dysfunction observed in the two disorders may have different neurobiological bases, despite similar symptomatic and neuropsychological manifestations.

Stop signal and go/no-go tasks are commonly used tasks to detect inhibitory control in neuroimaging studies. The stop signal task creates a higher load on response inhibition processes compared to the go/no-go task, in that it involves the retraction of a response that has already been triggered by a go signal (Rubia et al., 2001). Go/no-go tasks have a higher load on response selection, due to the a priori knowledge about whether or not to respond to the presentation of specific categorical stimuli (Rubia et al., 2001).

Studies of children with ASDs have revealed no significant differences compared to healthy children in the stop signal task (Ozonoff and Strayer, 1997) but lower performance in the go/no-go task (Happé et al., 2006). Inhibitory motor control as assessed by the stop signal task has been studied extensively in ADHD. The meta-analysis revealed a significant difference in stop latency (stop signal reaction time) between ADHD patients and matched controls in both children and adults (Lijffijt et al., 2005), while children with ADHD had lower performance compared to healthy controls in the go/no-go task (Happé et al., 2006; Raymaekers et al., 2007).

Most previous neuropsychological and neuroimaging studies comparing ADHD with ASDs were performed in children. Neuropsychological studies have found that the ASDs group can have either better (Ozonoff and Jensen, 1999; Geurts et al., 2004; Happé et al., 2006) or poorer (Corbett et al., 2009) inhibitory control than the ADHD group. However, some studies showed little difference in executive function profiles between ADHD and ASDs (Goldberg et al., 2005; Verté et al., 2006). The only neuropsychological study performed in adult patients revealed significant differences between ADHD and ASDs in the Stroop task. However, using the Hayling Sentence Completion Test, which assesses verbal response inhibition, it was found that adults with ADHD did not exhibit more severe impairments compared to those with ASDs (Johnston et al., 2011).

Thus, the development of an inhibitory-task-related neurophysiological index as an auxiliary tool for the differential diagnosis of ASDs and ADHD in adults would be an important contribution to this field. Recent functional magnetic resonance imaging (fMRI) and event-related potential studies have revealed differences between children with ASDs and ADHD (Christakou et al., 2012; Malisza et al., 2011; Kemner et al., 1995; Groen et al., 2008). To date, however, no studies have directly compared adults with ASDs to those with ADHD using functional neuroimaging or neurophysiological indices.

Ideally, a diagnostic index should be developed using a neuroimaging tool that is suitable for application in clinical settings. Near-infrared spectroscopy (NIRS) is an optical neuroimaging technique that allows the non-invasive measurement of changes in the concentrations of oxygenated and deoxygenated hemoglobin ([oxy-Hb] and [deoxy-Hb], respectively), thus reflecting regional cerebral blood volume (Hoshi and Tamura, 1993; Villringer et al., 1993). NIRS is safe and portable and allows the examination of subjects in a natural sitting position. The resolution of NIRS for detecting time-course alterations in brain activation in the prefrontal cortex (PFC) is finer than that of fMRI. Therefore, NIRS could be applied as an auxiliary diagnosis tool in clinical psychiatry.

Our research aim was to determine whether prefrontal NIRS signals recorded during an inhibitory control task differed between adults with ASDs and those with ADHD. In this study, we used a stop signal task (SST) to detect brain activation associated with inhibitory control. We chose the letter version of the verbal fluency task (VFT) as a control index of prefrontal function to test whether the findings were task specific. We hypothesized that adults with ASDs and ADHD would exhibit differential prefrontal NIRS signals during the SST, and that both groups of patients would show activation of the PFC compared to the control group. Further, we hypothesized that during the VFT, both groups would show a similarly reduced activation of the PFC compared to the control group.

2. Materials and methods

2.1. Participants

Twenty-one adults with ASDs, 19 adults with ADHD, and 21 healthy control (HC) subjects participated in the study (Table 1). We recruited 26 adults with ASDs and 25 adults with ADHD from the outpatient clinic at the Department of Neuropsychiatry, University of Tokyo Hospital, Japan, and from community clinics. After recruitment of the patient group, some individuals were recruited in the control group in order to match patients for age, sex, and IQ. As a result, all participating subjects were matched for age, sex, and IQ (Table 1). All subjects gave written informed consent in accordance with the Declaration of Helsinki after a complete explanation of the study. The ethics committee of the University of Tokyo Hospital approved this study (approval no.: 630-6). The diagnoses of ASDs and ADHD were established in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) based on comprehensive clinical assessments performed by at least 2 trained child psychiatrists (YK, HK, and AI). We included participants in this study only when at least 2 of the 3 child psychiatrists had seen patients and given consistent diagnoses. Current and lifetime DSM-IV diagnoses, other than ASDs/ADHD, were ruled out based on a consensus decision using information gained from independent clinical interviews, other available clinical data, and from the Mini-International Neuropsychiatric Interview (MINI). The exclusion criteria for all groups were as follows: full-scale IQ < 70, neurological illness, genetic disorders, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, a history of treatment with stimulants or other psychiatric medication, alcohol/substance abuse or addiction, bipolar disorder, and schizophrenia. An additional exclusion criterion for the control group was personal history of a psychiatric disease, as assessed using the MINI, or a family history of psychiatric disease among their first-degree relatives.

None of the adults with ASDs or ADHD had been treated with stimulants or other psychiatric medication. In Japan, MPH was approved only for treatment of children with ADHD in 2007, and it cannot be used for treating adult ADHD in Japan. Therefore, MPH cannot be used even for cases with severe ADHD symptoms.

The HC group was also free of medication. To the extent possible, we obtained childhood information from a person who knew the patient in childhood (usually the mother). At the time of the recruitment of the subjects, the usage of the Autism Diagnostic Interview, Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), and Conners' Adult ADHD Diagnostic Interview for DSM-IV™ (CAADID) was extremely limited in Japan. Before we finished recruitment, we obtained permission