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Postural sway and regional cerebellar volume in adults with attention-deficit/hyperactivity disorder

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ABSTRACT

Objective: Motor abnormalities, including impaired balance and increased postural sway, are commonly reported in children with ADHD, but have yet to be investigated in adults with ADHD. Furthermore, although these abnormalities are thought to stem from cerebellar deficits, evidence for an association between the cerebellum and these motor deficits has yet to be provided for either adults or children with ADHD.
Method: In this study, we measured postural sway in adults with ADHD and controls, examining the relationship between sway and regional cerebellar gray matter volume. Thirty-two ADHD and 28 control participants completed various standing-posture tasks on a Wii balance board.
Results: Postural sway was significantly higher for the ADHD group compared to the healthy controls. Higher sway was positively associated with regional gray matter volume in the right posterior cerebellum (lobule VIII/IX).
Conclusion: These findings show that sway abnormalities commonly reported in children with ADHD are also present in adults, and for the first time show a relationship between postural control atypicalities and the cerebellum in this group. Our findings extend the literature on motor abnormalities in ADHD and contribute to our knowledge of their neural substrate.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental neurobehavioral disorder characterized by symptoms of inattentiveness, hyperactivity, and impulsiveness. It affects up to 10% of children and 5% of adults worldwide (Faraone et al., 2003) and has been associated with high levels of morbidity, distress, and disability across the lifecycle (Spencer et al., 2007).

Although not included in the diagnostic criteria for ADHD, up to 50% of children with ADHD have been shown to have motor control problems (Pitcher et al., 2003). One such motor deficit, postural sway, has been reported in children with ADHD in a number of studies. Zang and colleagues (2002) demonstrated that children with ADHD had significant balance dysfunction compared to control children under various testing conditions, including standing with eyes open on a foam platform, or with eyes closed on firm and foam platforms. Additionally, while balance deficits in children with ADHD have been reported in simple standing postures such as standing on a fixed platform with eyes open (Bucci et al., 2014; Hassan and Azzam, 2012; Kooistra et al., 2009; Shorer et al., 2012), postural deficits are even more pronounced in more difficult standing conditions (Buderath et al., 2009; Hassan and Azzam, 2012; Shum et al., 2009; Zang et al., 2002). For example, when sensory signals are disrupted by having subjects close their eyes or by manipulating the angle of the platform and visual surround in response to the child's sway (i.e., sway-referenced), children with ADHD perform poorly relative to more standard conditions (Hassan and Azzam, 2012; Shum et al., 2009). Since sensorimotor integration and balance regulation rely on the cerebellum, these results suggest that poor balance in children with ADHD could stem from suboptimal cerebellar function (Shum et al., 2009).

Studies showing sway abnormalities in children with ADHD support the idea that cerebellar mechanisms contribute to balance dysfunction. In a study of children with ADHD, children with fetal alcohol spectrum disorder (FASD), and controls, postural stability was impaired in the ADHD and FASD groups. The authors suggested that the increased sway might stem from the cerebellar abnormalities seen in both conditions (Kooistra et al., 2009). In another study, children with ADHD had mild postural impairments similar to children with cerebellar lesions,

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further supporting the role of cerebellar dysfunction in balance deficits in ADHD (Buderath et al., 2009).

Substantial evidence now shows that alterations in cerebellar structure are involved in the pathophysiology of ADHD (e.g., Castellanos et al., 2002; Seidman et al., 2005; Valera et al., 2007). Relative to controls, decreased cerebellar volume has been observed in individuals with ADHD including children (Mostofsky et al., 1998; Valera et al., 2007), adolescents (Castellanos et al., 2002) and adults (Makris et al., 2013). Relatively smaller cerebellar volumes have also been associated with increased symptom severity (Castellanos et al., 2002), suggesting the importance of the cerebellum in the pathophysiology of ADHD. However, postural sway and its relation to cerebellar volume have not been assessed in adults with ADHD. Assessing balance and other motor abilities in adults with ADHD is important, as motor difficulties are linked to social and emotional problems in children (Schoemaker and Kalverboer, 1994), and perhaps to an increased risk of injuries in children with ADHD (Discala et al., 1998; Rowe et al., 2007) and adults with ADHD (Kaya et al., 2008). Also, examining the relationship between balance and cerebellar volume is important to our understanding of the neural substrates of such associated features in ADHD.

The primary objectives of this study were to assess standing sway under different conditions in adults with ADHD, and determine whether sway was related to regional cerebellar volume. We also explored whether sway was associated with ADHD symptoms. We predicted that sway would be greater in adults with ADHD relative to controls and related to regional cerebellar volume.

2. Materials and methods

2.1. Participants

Thirty-two adults with ADHD (18 females) and 28 healthy controls (HC; 15 females) comparable in age (ADHD mean age = 26.2 years; SD = 7.4; HC mean age = 27.3 years; SD = 8.0; $p > .6$) participated in the experiment. Two additional participants were excluded due to excessively high sway (>2.5 SDs from the mean; 1 ADHD and 1 control participant). All participants provided written informed consent, and the study was approved by the Partners Human Research Institutional Review Board.

Exclusion criteria for all subjects included: any current DSM-IV Axis I mood, psychotic, or generalized anxiety disorder; full scale IQ < 80; any major sensorimotor handicaps or neurological disorders; current alcohol or substance abuse or dependence or a chronic history of abuse or dependence as defined by review of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID); or current use of psychotropic medications (other than short-acting psychostimulants). Participants taking psychostimulants for ADHD (n = 13) underwent a 24-hour washout period.

To assess psychopathology, all participants underwent the Structured Clinical Interview for DSM-IV (SCID) Axis I Disorders (First et al., 1997). As in previous studies (Valera et al., 2010a, 2010b) to assess ADHD, we used a module modified for adults from the Schedule for Affective Disorders and Schizophrenia for School Age Children (Orvaschel, 1994). The ADHD participants met DSM-IV criteria for ADHD with childhood onset and persistence into adulthood. We included two ADHD participants who had an age-of-onset after age 7 (ages of onset were 9 and 11 years). This decision was based on studies supporting the validity of ADHD in subjects with onset of symptoms later than the 7-year cutoff (Faraone et al., 2006). A child and adult psychiatrist resolved diagnostic uncertainties. Previous work in our laboratory has shown that retrospective diagnoses can be made in a reliable and valid manner (Biederman et al., 1990). ADHD subtypes included 18 participants with combined-type, 12 with inattentive-type, and 2 with hyperactive-type. Vocabulary and matrix reasoning were used to calculate an IQ estimate (Wechsler, 1999). Full-scale IQ estimates did not differ between the ADHD (M = 118.7) and control groups (M = 117.1), $p > .6$.

In addition to the clinical interview, participants completed the Adult ADHD Self-Report Scale (ASRS) (Kessler et al., 2005) to assess ADHD symptoms. The ASRS is a common symptom checklist that contains questions consistent with the DSM-IV criteria for ADHD, and has been shown to be a valid and reliable scale for evaluating ADHD (Adler et al., 2006). It can be used to derive dimensional measures of hyperactive and inattentive symptoms and total symptomatology.

2.2. Postural sway task acquisition and analysis

Postural sway was assessed while standing on a Wii balance board. The Wii provides a valid and reliable assessment of postural control (Clark et al., 2010). Participants completed four standing postures while balancing on two feet. The four conditions were: eyes open with feet apart (approximately shoulder width), eyes closed with feet apart, eyes open with feet together, and eyes open with feet apart and shoes off. During each trial participants were instructed to remain as still as possible for the duration of the 30 s trial. The first 5 s of each trial were not analyzed. Postural sway was quantified as the path length (in cm) of the center of pressure (COP) (e.g., Bucci et al., 2014; Shorer et al., 2012). Data from a small number of trials (4 of 240 total trials) were missing due to technical failure and their estimated values were imputed using multiple regression (Gelman and Hill, 2006). Differences between conditions and between groups were tested using a mixed-model ANOVA. Spearman bivariate correlations were used to assess the relationship between sway and symptom scores. Analyses were performed with SPSS 21.

2.3. Brain imaging acquisition and analysis

Whole-brain structural MR images were collected on a Siemens Tim Trio 3 Tesla MRI system at the MGH Martinos Center (Charlestown, MA). A T1-weighted multi-echo MPRAGE sagittal scan was collected (TR = 2.54 s; TE = 1.64/3.5/5.36/7.22 ms; TI: 1.2s; FoV = 256 mm; 176 slices; voxel size = $1.0 \times 1.0 \times 1.0$ mm). Scans were acquired for 29 ADHD and 25 control participants.

Images were first inspected by a neurologist for structural abnormalities, image artifacts or excessive motion. None were excluded. Subsequent image preprocessing and modeling were done using SPM12 software (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm).

2.3.1. Preprocessing

Voxel-based morphometry (VBM) analysis was performed on the final sample of 54. VBM is a voxel-wise method for comparing regional gray matter (GM) volume in different groups or experimental conditions (Ashburner and Friston, 2000, 2001). The T1-weighted images were first segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) probability maps using a generative model (Ashburner and Friston, 2005). Then, rigid body alignment was used to achieve approximate spatial alignment. Next DARTEL (Ashburner, 2007) was used with the resulting gray and WM images from each subject to iteratively estimate the nonlinear deformations resulting in the best group alignment and a series of progressively more accurate group average templates. Finally, the resulting individual deformation fields were combined with affine atlas alignment to generate spatially normalized and smoothed (8 mm 3D FWHM) Jacobian-scaled GM images in MNI space at $1.5 \times 1.5 \times 1.5$ mm resolution. The resulting regional GM volume maps were subject to a quality assurance review using the VBM8 tools. The final DARTEL group template was transformed to MNI space using an affine transformation and used as a background image for structural identification.

2.3.2. Statistical analysis

Following preprocessing, statistical analysis was performed using general linear models. To correct for inter-subject variation in global