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Atypical within- and between-hemisphere motor network functional connections in children with developmental coordination disorder and attention-deficit/hyperactivity disorder

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ABSTRACT

Developmental coordination disorder (DCD) and attention-deficit hyperactivity disorder (ADHD) are highly comorbid neurodevelopmental disorders; however, the neural mechanisms of this comorbidity are poorly understood. Previous research has demonstrated that children with DCD and ADHD have altered brain region communication, particularly within the motor network. The structure and function of the motor network in a typically developing brain exhibits hemispheric dominance. It is plausible that functional deficits observed in children with DCD and ADHD are associated with neurodevelopmental alterations in within- and between-hemisphere motor network functional connection strength that disrupt this hemispheric dominance. We used resting-state functional magnetic resonance imaging to examine functional connections of the left and right primary and sensory motor (SM1) cortices in children with DCD, ADHD and DCD + ADHD, relative to typically developing children. Our findings revealed that children with DCD, ADHD and DCD + ADHD exhibit atypical within- and between-hemisphere functional connection strength between SM1 and regions of the basal ganglia, as well as the cerebellum. Our findings further support the assertion that development of atypical motor network connections represents common and distinct neural mechanisms underlying DCD and ADHD. In children with DCD and DCD + ADHD (but not ADHD), a significant correlation was observed between clinical assessment of motor function and the strength of functional connections between right SM1 and anterior cingulate cortex, supplementary motor area, and regions involved in visuospatial processing. This latter finding suggests that behavioral phenotypes associated with atypical motor network development differ between individuals with DCD and those with ADHD.

1. Introduction

Developmental coordination disorder (DCD) is one of the most common neurodevelopmental disorders of childhood, affecting 5–6% of school-aged children (American Psychiatric Association, 2013; Blank, 2012). It is characterized by impairments in motor coordination that significantly interferes with activities of daily living, and also impacts academic productivity, prevocational and vocational activities, as well as leisure and play (American Psychiatric Association, 2013; Blank, 2012). The clinical presentation of DCD is diverse (Kaplan et al., 1998; Schoemaker et al., 2013; Vaivre-Douret, 2014; Visser, 2003), and up to 50% of children with DCD also meet diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) (Kadesjo and Gillberg, 1998; Pitcher et al., 2003). ADHD occurs in approximately 5% of children (Kadesjo and Gillberg, 2001; American Psychiatric Association, 2013) and is associated with age-inappropriate levels of inattention, hyperactivity and/or

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impulsivity (American Psychiatric Association, 2013). The etiology of the comorbidity of DCD and ADHD, however, is not well understood.

Children with DCD often exhibit functional deficits in cross-modal integration (i.e., integration of information from different sensory modalities), specifically during tasks that demand visual feedback for motor control (Wilson and McKenzie, 1998), internal/forward modeling (e.g., movement planning), gait and postural control, visual perception and motor coordination (Dewey et al., 2007; Wilson et al., 2013). Deficits in cross-modal integration have also been observed in children with ADHD (Hale et al., 2009). Studies of typical individuals and split-brain patients indicate that cross-modal integration requires successful communication between a number of brain regions, both within and between hemispheres (Compton et al., 2008; Sauerwein and Lassonde, 1997; Toro et al., 2008), especially as tasks become more complex (Mostofsky et al., 2006; Scholz et al., 2000; Solodkin et al., 2001; Weissman and Banich, 2000).

Neuroimaging studies support the contention that brain region communication is disrupted in children with DCD and ADHD. Diffusion tensor imaging (DTI) studies have implicated the corpus callosum (Langevin et al., 2014; Roessner et al., 2004; Valera et al., 2007), a structure responsible for inter-hemispheric communication, as well as the right forceps minor and the anterior corona radiate (Van Ewijk et al., 2012) in these disorders. Functional magnetic resonance imaging (fMRI) studies of children with DCD have demonstrated atypical activity within visuospatial regions during complex tracing tasks (Kashiwagi et al., 2009; Zwicker et al., 2010, Zwicker et al., 2011). In children with ADHD, fMRI studies have noted reduced activity of the right inferior frontal gyrus (IFG) during right-hand (i.e., left-hemisphere) response inhibition when performing a Go/No-Go task (Booth et al., 2005; Garrett et al., 2008; Rubia et al., 2005). Thus, it is important that the motor network exhibit appropriate within- and between-hemisphere connections.

In the typically developing brain, the structure and function of motor regions actually differs between hemispheres. Structurally, right-handed individuals have a deeper left central sulcus than left-handed individuals (Amunts et al., 2000). The left motor cortex in right-handed individuals also has greater neuropil volume, reflecting the number of dendrites, axons and synapses (Amunts et al., 1996). A DTI study demonstrated that the left corticospinal tract in infants is more structurally developed than the right (Dubois et al., 2009). Functionally, an fMRI study of right-handed adults demonstrated that the left motor cortex exhibits greater activation with both ipsilateral and contralateral movements compared to the right motor cortex (Kim et al., 1993). Whether these structural and functional differences are associated with disrupted within-hemisphere and/or between-hemisphere functional connections between cortical and subcortical regions of the motor network has not been established. Furthermore, this has not been explored in children with DCD and ADHD, and could represent an underlying mechanism for the functional deficits observed in these children.

Using resting-state fMRI, our recent study observed reduced functional connectivity (i.e., reduced temporal synchrony between distinct brain regions and an indicator of functional connection strength) between left motor cortex and structures of the basal ganglia, including the caudate, putamen and globus pallidus in children with DCD, ADHD, and DCD + ADHD, compared to typically developing children (McLeod et al., 2014). It is plausible these disruptions of functional connectivity observed in our previous study could also be associated with alterations in how cortical and subcortical regions of the motor network are connected within and between hemispheres. Thus, in the present study, we reexamined the data from the right-handed individuals of our previous study in order to investigate the hypothesis that within- and between-hemisphere functional connections of the motor network are altered in children with DCD, ADHD, and DCD + ADHD, when compared to typically developing children. Furthermore, we hypothesized that ADHD and DCD children would exhibit similar alterations in within- and between-hemisphere connections to support the comorbidity of these disorders, as well as alterations specific to DCD alone.

2. Methods

This study was conducted in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. The institutional review board for the ethics of human research approved the study. Consent and verbal assent were obtained from parents and children, respectively, after study procedures were fully explained.

2.1. Participants and assessment

As described in our previous study (McLeod et al., 2014), participants were recruited from local schools and through community advertisements in locations such as hospitals and physician's offices in Calgary, Alberta, Canada. Children were classified as DCD if they met the following criteria, which are consistent with the Diagnostic and Statistical Manual IV-TR diagnostic criteria: they scored below the 16th percentile on The Movement Assessment Battery for Children – Second Edition (MABC-2; Henderson et al., 2007) (Criterion A), were reported by their parents as exhibiting motor difficulties that interfered significantly with daily functioning (as indicated on the Developmental Coordination Questionnaire (Wilson et al., 2000)) (Criterion B), did not evidence a visual impairment or other neurological/medical (e.g., epilepsy, cerebral plays, muscular dystrophy) condition that would affect movement and did not meet criteria for a diagnosis of Pervasive Developmental Disorder (Criterion C) and did not display an intellectual impairment as evidenced by performance on a standardized measure of cognitive function (Criterion D). Scores greater than the 5th percentile and less than the 16th percentile on the MABC-2 are associated with mild to moderate motor impairment, whereas scores less than the 5th percentile are associated with severe motor impairment. Children were classified as ADHD if they met diagnostic criteria on the Diagnostic Interview for Children and Adolescents-IV (Reich et al., 1997) or had a *t*-score above the 95th percentile on the Conners Parent Rating Scale-Revised (Conners et al., 1998) and were diagnosed by a physician as having ADHD based on DSM-IV criteria. Children meeting criteria for both DCD and ADHD were classified as DCD + ADHD. Children not meeting the criteria for DCD, ADHD or DCD + ADHD were assigned to the typically developing group. All children were required to be right handed. This assessment resulted in 19 ADHD alone children, 6 DCD alone children, 14 DCD + ADHD children and 21 typically developing children. These group sizes are less than our previous study, as we selected only right-handed children for the present analysis. Demographic and clinical characteristics of each group are summarized in Table 1.

Exclusion criteria for all groups included a history of a diagnosed metabolic or genetic condition, epilepsy or other seizure disorder, cerebral palsy, psychiatric disorder other than ADHD, intellectual disability, autism spectrum disorder, fetal alcohol spectrum disorder, prematurity (born at <36 weeks gestation), very low birth weight (<1500 g), or severe traumatic brain injury. There were no group differences for age or IQ (see Table 1); however, the typically developing group had a

Table 1
Participant Characteristics. CPRSC-C/H = Connor's Parent Rating Scale Revised Children Cognitive Problems/Inattention (C), Hyperactivity (H); MABC-2 = Movement Assessment Battery for Children - Second Edition. * indicates a significant difference between patient group and controls (Student's *t*-test, $p < 0.05$, corrected for multiple comparisons, or Tukey HSD test). CPRSC was not available for one child with ADHD. All errors are reported as the standard deviation of the mean.

	Controls	ADHD	DCD	ADHD + DCD
Age (years)	11.0 ± 2.8	12.4 ± 3.1	13.0 ± 2.8	11.3 ± 3.8
N (females)	21 (11)	19 (1)*	6 (1)*	14 (3)*
IQ	111.7 ± 13.3	107.1 ± 11.0	108.3 ± 13.7	103.5 ± 16.5
CPRSC-C	51.9 ± 9.8	73.7 ± 8.0*	50.0 ± 3.5	70.6 ± 12.6*
CPRSC-H	50.7 ± 8.0	72.0 ± 14.5*	49.3 ± 3.5	64.1 ± 14.5*
MABC-2	10.3 ± 2.2	9.5 ± 1.6	5.5 ± 1.9*	4.1 ± 2.4*
NDI	98.8 ± 17.1	92.5 ± 15.2	71.0 ± 8.2*	62.1 ± 9.9*