Common White Matter Microstructure Alterations in Pediatric Motor and Attention Disorders

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Objective To characterize white matter alterations in children with isolated or concurrent developmental coordination disorder and/or attention-deficit/hyperactivity disorder (ADHD) compared with typically-developing controls, and to determine whether group differences on motor and attention tasks could be explained by differences in diffusion tensor imaging (DTI) measures.

Study design In a cohort of children (n = 85) with developmental coordination disorder, ADHD, or combined developmental coordination disorder+ADHD, we examined 3 major white matter tracts involved in attention and motor processes. Using DTI, the corpus callosum, superior longitudinal fasciculus, and cingulum were analyzed with respect to measures of white matter integrity. Differences in fractional anisotropy (FA), mean diffusivity, radial diffusivity, and axial diffusivity were analyzed using ANOVA. Motor and attentional functioning was assessed using standardized tests, and correlated to DTI measures.

Results FA reductions were noted in the frontal regions of the corpus callosum for children with ADHD ($P = .039$), whereas children with developmental coordination disorder displayed similar reductions in regions of the corpus callosum underlying parietal brain regions ($P = .040$), as well as the left superior longitudinal fasciculus ($P = .026$). White matter integrity was impacted in both frontal and parietal regions for children with comorbid developmental coordination disorder+ADHD ($P = .029$; .046). FA was positively correlated with scores on both motor and attentional assessments in a region-specific manner.

Conclusion Our findings suggest that alterations in the corpus callosum underlie difficulties in motor and attention functioning. These changes are functionally and regionally distinct and could reflect a neurobiological basis for motor and attention disorders in children. *(J Pediatr 2014;164:1157-64)*.

Neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD) and developmental coordination disorder, demonstrate significant overlap with respect to clinical sequelae and prevalence. Disentangling the neurobiological basis of neurodevelopmental disorders is critical to advancing diagnosis and treatment, and maximizing outcomes for affected children. ADHD is a commonly diagnosed neurodevelopmental disorder characterized by inattention, behavioral impulsivity, and hyperactivity.[1] Children with ADHD also display atypical motor behaviors, impairing motor control, motor planning, and coordination.[2-4] In developmental coordination disorder, motor impairment represents the prominent feature, but attention, academics, and social functioning are also impacted.[5] Indeed, ADHD and developmental coordination disorder are found to co-occur in 30%-50% of cases.[4] Developmental coordination disorder and ADHD have also been found to show similar deficits in behavioral correlates of attention and executive function.[6] This high degree of overlap suggests a common neurobiological substrate for ADHD and developmental coordination disorder; however, whether motor and attention problems represent unrelated impairments or are symptomatic of disruption in common localized brain networks has not yet been determined.

Recent studies in white matter circuitry have found decreased white matter integrity in frontal regions of the corpus callosum in individuals with ADHD,[7] whereas others have shown alterations in the isthmus,[8,9] and splenium.[9] In developmental coordination disorder, frontal white matter has not been examined; however, decreases in frontal lobe activity have been reported.[10] Another component of frontostriatal cerebellar circuitry, the superior longitudinal fasciculus

AD	Axial diffusivity	MD	Mean diffusivity
ADHD	Attention deficit-hyperactivity disorder	MRI	Magnetic resonance imaging
ASF	Anterior/superior frontal	NDI	Neurodevelopmental index
DTI	Diffusion tensor imaging	RD	Radial diffusivity
FA	Fractional anisotropy	SLF	Superior longitudinal fasciculus
MAND	McCarron Assessment of Neuromuscular Development	SPP	Superior/posterior parietal

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(SLF), regulates somatosensory perception (lateral regions), along with attention, working memory, and motor behavior (medial regions).[11] The SLF in ADHD is correlated with attentional measures; yet examinations of white matter measures have been mixed.[12-15] Therefore, to differentiate regional vs functional alterations, we also examined the cingulum bundle, which runs longitudinally along the dorsal surface of the corpus callosum and connects frontal, parietal, and temporal regions like the SLF. Unlike the SLF, the cingulum has not been implicated in ADHD or motor functioning.[15,16]

The goal of this study was to use diffusion tensor imaging (DTI), an in vivo imaging technique allowing investigation of white matter, to examine the major white matter tracts of children with isolated or concurrent developmental coordination disorder and/or ADHD. DTI measures the movement of water molecules along hydrophobic axonal pathways, and yields quantitative information regarding the orientation, development, and integrity of the tract and related tissues.[17] Specifically, higher fractional anisotropy (FA) values and lower mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) values, indicate denser and/or more myelinated axons. We also investigated the relationship between microstructural brain alterations and attentional/executive and motor functioning to help understand the contribution of these changes to the manifestations of developmental coordination disorder and ADHD. Identification of shared or distinct white matter alterations in ADHD and developmental coordination disorder could highlight new avenues for research examining the genetic and environmental contributors to these and other concurrent neurodevelopmental disorders.

Methods

A total of 85 children (64 male and 21 female) aged 8 to 17 years with attention and/or motor problems were recruited through local schools and physician referral to our study. Children with a diagnosed metabolic or genetic condition, very low birth weight (<1500 g), gestation <35 weeks, epilepsy or other seizure disorder, IQ below 80, autism, cerebral palsy, or contraindications to magnetic resonance imaging (MRI) scanning (ie, claustrophobia, ferrous implant) were excluded. The study included 9 children with developmental coordination disorder, 23 children with ADHD, 23 children meeting the criteria for both developmental coordination disorder and ADHD, and 26 typically-developing controls. Written consent was obtained from participants' parents under the approval of the Conjoint Health Research Ethics Board of the University of Calgary, and children provided verbal assent to participate in the study.

Demographic information is summarized in **Table I**. Motor skills were evaluated by the *Movement Assessment Battery for Children-2nd edition*,[18] a standardized measure of motor performance. Children were included in the developmental coordination disorder group if their standard score was below 7.0 (<16th percentile) on the *Movement Assessment Battery for Children-2nd edition*. Children classified as developmental coordination disorder also were reported by their parents to have motor difficulties that interfered with daily functioning as shown by lower total scores on the Developmental Coordination Disorder Questionnaire.[19] Children were classified as ADHD if they met the diagnostic criteria for ADHD on the Diagnostic Interview for Children and Adolescents IV,[20] and had a T score above the 95th percentile on the Conner's Parent Rating Scale-Revised.[21] The Diagnostic Interview for Children and Adolescents IV was completed by parents as a computerized interview and evaluates children on 2 criteria (A and B), which assess levels of inattention and hyperactivity, respectively. The Conner's Parent Rating Scale-Revised is a parent-completed questionnaire that includes 2 subscales that measure inattention and hyperactive/impulsive symptoms, respectively. Children meeting only 1 of the previous 2 criteria were classified as having ADHD if a clinician had previously diagnosed them. Children who met both classification criteria for developmental coordination disorder and ADHD were categorized into the developmental coordination disorder+ADHD group. Those participants not meeting either criterion were classified as controls.

The Wechsler Abbreviated Scale of Intelligence [22] was use to obtain an estimate IQ. Participants receiving pharmaceutical treatment for ADHD were asked to refrain from taking their medication on the day of testing. Attention and executive function were assessed using the Developmental NEuroPSYchological Assessment II, Auditory Attention, Response Set, and Inhibition subtests.[23] Scaled scores were reported, with impairment defined as a scaled score of <8.[23] Motor ability was assessed using the McCarron Assessment of Neuromuscular Development (MAND).[24] The MAND assessment tool uses 10 subtests to determine the level of fine and gross motor performance— (neurodevelopmental index [NDI]). NDI scores below 55 are indicative of severe impairment, 55-70 indicates moderate disability, and scores from 71-85 represent mild disability.[24]

MRI Data Acquisition

MRI was performed on a GE 3T Signa system scanner (GE Healthcare, Waukesha, Wisconsin) using a standard 8-channel phased-array radiofrequency head coil at the Seaman Family MR Research Center, University of Calgary. Single-shot echoplanar diffusion weighted images were acquired, spanning the entire brain. Twenty-six axial-oblique slices of 4 mm thickness with no interslice gaps were obtained, matrix 96 × 96, field of view 22.0 cm, repetition time = 8000 ms, echo time = 30 ms, b0 = 850 s/mm^2, flip angle = 90°. Data were acquired in 11 nonlinear directions with 3 unweighted image repetitions. Head movement was minimized with the use of memory foam pillows. Image quality was examined at the time of acquisition.

MRI Data Analysis

Three-dimensional deterministic tractography of the corpus callosum was completed in DTIStudio (Jiang and Mori,