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Highlights

First exploration of relative grey matter volumes in DCD

Reduction in medial and middle frontal, and superior frontal gyri volumes in DCD

Grey matter volumes in motor regions appear to be reflective of movement proficiency

Reduced relative volume in motor and attention regions in developmental coordination disorder: a voxel-based morphometry study

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Short title: Focal grey matter volume reductions in children with DCD

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Abbreviations: BA: Brodmann Area; DCD: developmental coordination disorder; DTI: diffusion tensor imaging DTT: diffusion tensor tractography; CSF: cerebrospinal fluid; GM: grey matter; MABC-2: Movement Assessment Battery for Children – 2; TIV: total intracranial volume; VBM: voxel-based morphometry; VBQ: quantitative structural magnetic resonance imaging

Structured Abstract

Background and Objectives:

Developmental coordination disorder (DCD) is a prevalent childhood movement disorder, impacting the ability to perform movement skills at an age appropriate level. Although differences in grey matter (GM) volumes have been found in related developmental disorders, no such evidence has been linked with DCD to date. This cross-sectional study assessed structural brain differences in children with and without DCD.

Methods:

High-resolution structural images were acquired from 44 children aged 7.8 – 12 years, including 22 children with DCD ($\leq 16^{th}$ percentile on MABC-2; no ADHD/ASD), and 22 typically developing controls ($\geq 20^{th}$ percentile on MABC-2). Structural voxel-based morphology analysis was performed to determine group differences in focal GM volumes.

Results:

Children with DCD were found to have significant, large, right lateralised reductions in grey matter volume in the medial and middle frontal, and superior frontal gyri compared to controls. The addition of motor proficiency as a covariate explained the between-group GM volume differences, suggesting that GM volumes in motor regions are reflective of the level of motor proficiency. A positive correlation between motor proficiency and relative GM volume was also identified in the left posterior cingulate and precuneus.

Conclusions:

GM volume reductions in premotor frontal regions may underlie the motor difficulties characteristic of DCD. It is possible that intervention approaches targeting motor planning, attention, and executive functioning processes associated with the regions of reduced GM volume may result in functional improvements in children with DCD.

Keywords

Developmental Coordination Disorder; Neuroimaging; Voxel-Based Morphometry; Grey Matter; Structural MRI

1. Introduction

Developmental coordination disorder (DCD) is a condition characterised by an inability to perform fine (hand writing and shoelace tying) and gross motor skills (playing sport and getting dressed) at an age appropriate level (American Psychiatric Association, 2013). DCD affects approximately 6% of school-aged children, making it the most common childhood movement disorder (American Psychiatric Association, 2013). Such a broad range of deficits not only impacts performance of daily tasks, but also contributes to secondary long-term health consequences, including reduced engagement in physical activity and social activities (Poulsen & Ziviani, 2004; Zwicker, Harris, & Klassen, 2013), and increased risk of low self-esteem, anxiety, and depression (Jarus, Lourie-Gelberg, Engel-Yeger, & Bart, 2011; Zwicker et al., 2013). The coordination difficulties seen in 50-70% of children with DCD persist into adolescence and adulthood (American Psychiatric Association, 2013). In young adults, DCD creates new challenges at a stage of life when they are gaining a higher level of independence; DCD continues to impact on motor tasks, such as learning to drive a car, activities requiring high levels of executive functioning, and reduced perceptions of physical, social, and academic competence (Cantell, Smyth, & Ahonen, 2003; Kirby, Edwards, & Sugden, 2011). Despite the relatively good understanding of the behavioral motor impairments experienced by children with DCD, the aetiology, and neurological origins long suspected to contribute to such deficits remain unclear (Brown-Lum & Zwicker, 2015).

Disruptions to development of grey (GM) and white matter (WM) structure have been linked to a range of neurodevelopmental disorders which often co-occur with DCD, and also include a motor deficit component, including autism spectrum disorder (ASD; Boddaert et al., 2004; Brambilla et al., 2003; Mengotti et al., 2011; Mostofsky, Burgess, & Gidley Larson, 2007; Nickl-Jockschat et al., 2012), attention deficit hyperactivity disorder (ADHD; Carmona et al.,

2005; Kobel et al., 2010; Langevin, MacMaster, & Dewey, 2015; Valera, Faraone, Murray, & Seidman, 2007), and developmental dyslexia (Eckert et al., 2005; Richlan, Kronbichler, & Wimmer, 2013; Silani et al., 2005). Furthermore, differences in GM volumes in these populations have also been used to partially explain differences in functional neural activation patterns (Boddaert et al., 2004; Cortese & Castellanos, 2012; Kobel et al., 2010; Mueller et al., 2013; Silani et al., 2005).

To date, there have been a limited number of studies that have examined the potential of brain macrostructural differences that contribute to DCD. A recent cortical thickness study found that children with DCD exhibited localised structural differences in the temporal pole, a region typically associated with attentional functions (Langevin et al., 2015). One other recent study explored the structural connectome in DCD based on cortical thickness patterns, and identified clustering coefficient alterations compared to controls in the right lateral orbitofrontal cortex (Caeyenberghs et al., 2016). While measures of cortical thickness provide some insight into GM morphometric structure, analysis of volume, which takes into account cortical surface area and folding, has the potential to provide a more detailed understanding. The aim of the present study was to examine global and regional GM volume in children with DCD compared to a group of typically developing age-matched controls using voxel-based morphometry (VBM) and to assess whether GM volumes correlate with motor proficiency, independent of diagnosis. We hypothesize that GM structural differences may be found in regions in which different activation patterns have been identified in previous functional studies, including the primary motor cortex (McLeod, Langevin, Goodyear, & Dewey, 2014), precentral gyrus (Reynolds, Licari, et al., 2015), medial frontal gyrus (Debrabant, Gheysen, Caeyenberghs, Van Waelvelde, & Vingerhoets, 2013; Zwicker, Missiuna, Harris, & Boyd, 2011), superior frontal gyrus (Licari et al., 2015; Zwicker, Missiuna, Harris, & Boyd, 2010),

and inferior parietal lobule (Kashiwagi, Iwaki, Narumi, Tamai, & Suzuki, 2009; Zwicker et al., 2011). A greater understanding of the structural morphology of DCD has the potential inform the interpretation of fMRI and other imaging modality studies, and to lead to evidence based interventions for children with DCD related to principles of neurorehabilitation.

2. Material and Methods

2.1 Participants and datasets

High resolution structural scans of 50 right-handed males, aged between 8 and 12 years were collected during two separate studies (three of the children participated in both studies, and in all cases the second scan was excluded). An MRI familiarisation session was completed in a separate session prior to scanning, where participants were introduced to the scanning environment (noise, confined space, head coil and restraints), and were provided with strategies to reduce potential for anxiety and to lie still for a typical scan period. The final sample (six were excluded due to excessive head movement) consisted of 22 boys with suspected DCD based on referrals from occupational therapists and paediatricians, recruited from the University of Western Australia (UWA) Paediatric Exercise Programmes (mean age (SD) = 9.9 years ± 1.1, range = 7.8 – 11.6 years), and 22 group age-matched controls (mean age (SD) = 9.7 years ± 1.0, range = 8.3 – 12.0 years). Children are referred to these Programmes for movement difficulties that are present early in the developmental period (Criterion C), and that are interfering with the child's activities of daily living (Criterion B). Only right-handed males were recruited to minimise any potential lateralisation or gender differences that may exist. To confirm children's movement met the criteria for group selection, motor proficiency was assessed using the Movement Assessment Battery for Children – 2nd edition (MABC-2; Henderson, Sugden, & Barnett, 2007). The total score for each task was adjusted for age, summed and converted into a percentile where a score of ≤

16th (and referral from a relevant health professional) was used to confirm DCD (Criterion A). A score ≥ 20th percentile was used as a cut-off for the control group, indicating a motor proficiency within the normative range. Due to the high level of comorbidity of DCD with other neurodevelopmental disorders, children with a diagnosis of either ASD, or ADHD, or any neurological conditions (Criterion D) were excluded.

Ethics approval was obtained from the Human Research Ethics Committee at UWA for both studies (RA/4/1/2572, Licari et al., 2015; RA/4/1/5275, Reynolds, Licari, et al., 2015), as well as from Princess Margaret Hospital for Children (RA: 1804) for the first study (Licari et al., 2015). Written consent was obtained from parents and ongoing verbal assent from participants throughout each phase of the study.

2.2 MRI image acquisition

All images were acquired at the Department of Radiology at Sir Charles Gairdner Hospital, Perth, Australia over a time period from October 2010 to July 2012. Study one images were acquired in 2010 using a 3T Philips Achieva TX scanner with an 8-channel head coil. Study two images were acquired in 2012 on a 3T Philips Magnetic Resonance scanner, with participants wearing an 8-channel head coil. In both data collection periods, high-resolution anatomical images were acquired using the same parameters (T1-weighted 3D FFE 160 slices 0.575 × 0.575 × 1 mm). Despite replicating the T1 scanning parameters, multi-scanner studies still run the risk of confounding results due to differences in scanner site (Pardoe, Pell, Abbott, Berg, & Jackson, 2008; Stonnington et al., 2008). Therefore, a 2 x 2 (group x scanner) factorial model was performed (cluster level correction $p_{(FWE)} < 0.05$) to determine if scanner site would influence findings (Pardoe et al., 2008; Stonnington et al., 2008). Although the main effect of scanner model resulted in increased GM volume (cluster level

correction $p_{(FWE)} < 0.05$, k = 1151) in the bilateral culmen (*x* = 2, *y* = -33, *z* = -13; *x* = 0, *y* = -35, *z* = -6; *x* = 2, *y* = -38, *z* = -18, k = 2657), no group x scanner interactions for GM volume were identified, indicating that the scanner site was unlikely to influence group differences in activation (see results section). Visual inspection of the structural images for inclusion, and conversion to Analyze files was done using MRIcro (version 1.40; Rorden & Brett, 2000). At this stage, six participants (four DCD, two control) were excluded due to excessive head movement to leave a final sample of 44 boys (22 DCD, 22 controls).

2.3 Image processing

All pre-processing and VBM data analysis was carried out using Statistical Parametric Mapping 12 software (SPM12, Wellcome Department of Cognitive Neurology, London) in MATLAB 2014a (MathWorks, Natick, MA). Structural image pre-processing was performed using the VBM protocol (Ashburner 2010; Ashburner & Friston, 2000) in which structural T1 images were first approximately aligned with AC-PC space and segmented into GM, WM and cerebro-spinal fluid (CSF) based on SPM12 tissue probability maps. A Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (Ashburner, 2007) was implemented in order to iteratively warp GM and WM images from both data sets to a study-specific average template (Stonnington et al., 2008). The warped tissue maps were then modulated using DARTEL Jacobian determinant maps, which represent volume changes due to non-linear spatial normalisation, in order to ensure that the total amount of each tissue remained the same as it was in the pre-warped images. Following modulation, GM maps were affine transformed to Montreal Neurological Institute (MNI) space and smoothed with a full-width half-maximum Gaussian kernel of 10 mm (Ashburner 2010), with a final isotropic resolution of 1.5mm.

2.4 Statistical analysis

All statistical models were set up using SPM12 (Wellcome Department of Cognitive Neurology, London). Global normalisation was applied using proportional scaling to correct for total intracranial volume (TIV) differences between individual participants (TIV: GM + WM + CSF; Pell et al., 2008). This corrects for volume differences that are a result of brain size differences between participants, such that the final data reflects the relative volumes of regions after correcting for TIV. Age was included as a covariate in all models. Unless otherwise stated, when estimating 2nd level contrasts uncorrected voxel height thresholds were set at $p < 0.001$, with an additional extent threshold set for each contrast to correct for multiple comparisons, thus activations passed a cluster-level extent threshold of $p < 0.05$ (family-wise error (FWE) corrected; Friston, Holmes, Poline, Price, & Frith, 1996; Nichols & Wilke, 2012). For all models, explicit masking was applied with inclusive GM masks created using the SPM Masking Toolbox (Ridgway et al., 2009), so that only GM areas (based on study specific average GM images) were included in the analysis. All significant clusters extracted in MNI coordinates were converted to Talairach coordinates, and the nearest GM structure and Brodmann area identified using the Co-Planar Stereotaxic Atlas of the Human Brain (Talairach & Tournoux, 1988).

3. Results

3.1 Participant characteristics

Participant brain volume characteristics are presented in Table 1. Groups were matched for age, with no significant difference identified between DCD and control groups (t = 0.611, p = 0.545; group age-matching was performed in both individual studies). The DCD group (mean MABC-2 percentile (SD) = 3.7 ± 4.0) displayed significantly poorer motor proficiency compared to the control group (mean MABC-2 percentile (SD) = 48.6 ± 21.1) on the MABC-

2 (t = 9.821, $p < 0.001$). The DCD group MABC-2 percentiles ranged from the 0.1 – 16th and the controls from the 25th – 98th percentiles. No significant differences were identified for global GM, WM, or total intracranial volume between groups ($p > 0.05$).

Table 1. Participant brain volume characteristics.

	DCD (N=22)		Controls (N=22)		t	*p*
	Mean	SD	Mean	SD		
Grey Matter Volume (L)	0.88	0.05	0.89	0.06	0.434	0.667
White Matter Volume (L)	0.44	0.04	0.42	0.04	1.280	0.208
Total Intracranial Volume (L)	1.48	0.09	1.45	0.11	0.441	0.312

3.2 Between-group grey matter voxel-based morphometry results

A 2 x 2 (group x scanner) factorial model ($p_{(FWE)} < 0.05$, cluster level k = 1151) was used to estimate group differences in regional GM volume. Controls were found to have one large area of increased GM volume compared to the DCD group in the frontal (middle, medial and superior frontal gyri) lobe of right hemisphere (Table 2, Figure 1). There were no regional GM volume differences for the DCD > TD contrast (FWE cluster corrected), even when rerun at a less stringent level of $p < 0.001$, uncorrected. The GM group contrast analysis was re-run with motor proficiency (log normalised MABC-2 percentile scores; Henderson et al., 2007) specified as a mean-centered covariate within the 2 x 2 (group x scanner) factorial model; the addition of motor proficiency as a covariate explained the between-group GM volume differences, with no between-group differences persisting at $p_{(FWE)} < 0.05$, cluster level k = 1154.

3.3 Grey matter volume correlations with movement proficiency

In order to determine if regional GM volume correlated with movement proficiency (measured using the MABC-2; Henderson et al., 2007), the two groups were collapsed and a

full factorial model was run (scanner model as a factor) with $\log_{10}$ transformed MABC-2 percentile scores specified as a mean-centered covariate ($p_{(FWE)} < 0.05$, cluster level k = 1177). One cluster in the left precuneus and posterior cingulate (k = 1298, x = -15, y = -49, z = 16) was identified to be positively correlated with movement proficiency (Figure 1). This cluster did not overlap with the activations from the TD > DCD contrast; however, when the contrast was re-run at a less stringent significance level ($p < 0.001$, uncorrected), considerable overlap with the TD > DCD contrast was identified in the right medial and middle frontal, and superior frontal gyri. The use of uncorrected statistics may overstate this overlap, and should be interpreted with caution. No GM regions were negatively correlated with motor proficiency.

Table 2. Grey matter relative volume differences for Controls > DCD (cluster level correction, $p_{(FWE)} < 0.05$).

Anatomical Region	Cluster (k)	Talairach Coordinates			Brodmann Area
		x	*y*	*z*	
Control > DCD					
Superior Frontal Gyrus (R)	1587	21	11	51	6
Middle Frontal Gyrus (R)		30	20	43	6/8
		29	7	40	6

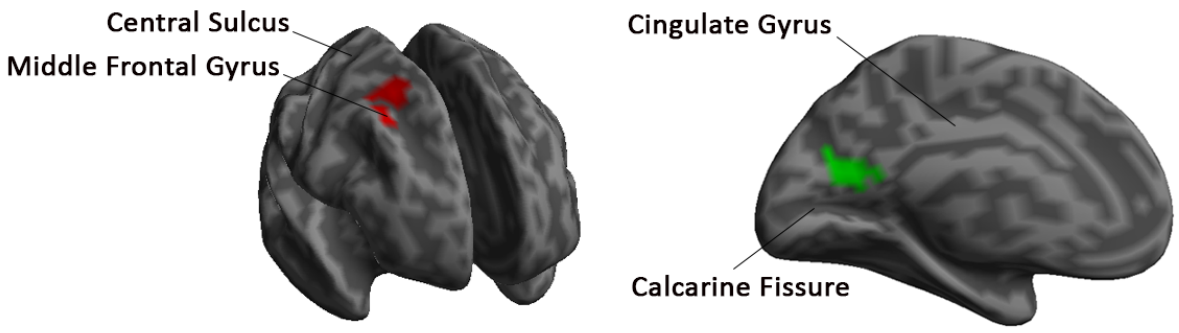

Figure 1. Relative grey matter volume contrast of typically developing controls > DCD (red; cluster level correction $p_{(FWE)} < 0.05$); proportionally increased grey matter relative volume

with increasing movement proficiency (green; cluster level correction $p_{(FWE)} < 0.05$).

4. Discussion

The present study used VBM in order to examine whether there are focal differences in GM volume in children with DCD compared to controls. Typically developing controls were identified to have significantly increased right lateralised relative GM volume than children with DCD in frontal motor and attention regions. The addition of motor proficiency as a covariate explained the between-group GM volume differences, suggesting that GM volumes in motor regions are likely to reflect level of motor proficiency. Furthermore, GM volume in the left precuneus, extending into the posterior cingulate, was positively correlated with motor proficiency scores. Our findings were not consistent with the previous study of structural abnormalities in DCD (Langevin et al., 2015), which identified thinner cortex in the right temporal pole compared to controls. This disparity is probably due to methodological differences, with VBM providing a differing profile of structural morphology. These results are the first to suggest that focal differences in underlying brain structure, which are not identifiable through standard clinical neurological examination, may contribute to DCD and motor proficiency in general.

The reductions in GM volume in DCD in the right premotor and frontal lobe regions support the motor planning and execution, attentional (Tsai, Pan, Cherng, Hsu, & Chiu, 2009), working memory (Alloway, 2007; Tsai, Chang, Hung, Tseng, & Chen, 2012), and executive functioning deficits associated with DCD (Piek, Dyck, Francis, & Conwell, 2007; Piek et al., 2004; Wilson, Ruddock, Smits-Engelsman, Polatajko, & Blank, 2013). The medial frontal gyrus incorporates pre-motor regions, and in addition to the role played in motor planning and control (Hanakawa, Dimyan, & Hallett, 2008), this region has been implicated in

executive control, decision making, inhibitory control (Garavan, Ross, & Stein, 1999; Talati & Hirsch, 2005), and reorienting attention, particularly from exogenous to endogenous control (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015). Deficits in motor planning have been observed behaviorally in children with DCD using assessments of praxis, end-state comfort, and dynamic planning, where children with DCD have been identified to perform less accurately or efficiently as controls (Adams, Lust, Wilson, & Steenbergen, 2014; Reynolds, Thornton, et al., 2015; Wilson et al., 2013). At a neurological level, differences in both cerebral blood flow and event related potentials during motor control (Zwicker et al., 2010, 2011), and visuomotor tasks (Kashiwagi et al., 2009; Pangelinan, Hatfield, & Clark, 2013) have been identified in fMRI and EEG studies of children with DCD.

The superior frontal gyrus has also been reported to be involved in working memory processing and spatial cognition, and voluntary attention control (Du Boisgueheneuc et al., 2006; Harms, Wang, Csernansky, & Barch, 2013; Hopfinger, Buonocore, & Mangun, 2000; Li et al., 2013; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). Support for deficits in these executive functioning processes in children with DCD is evident from behavioral research using a broad range of paradigms (e.g., visual and verbal working memory tasks, n-back paradigms, endogenous Posner paradigm, dual-task performance; Wilson et al., 2013). Furthermore, at a neurological level, differences in attentional network connectivity (Querne et al., 2008), functional activation patterns (Tsai et al., 2012), and electrophysiological event related potential measures during spatial working memory (Tsai et al., 2012) and visuospatial attention (Tsai et al., 2009) EEG tasks have also been identified in children with DCD. The identified reductions in GM volume are consistent with behavioural research demonstrating motor planning and execution, attentional, and executive functioning deficits associated with DCD. Given the links between increased brain volume and better

performance (Draganski et al., 2004; Maguire, Woollett, & Spiers, 2006), this finding suggests that underlying structural differences in motor and attention regions may be one factor contributing to the motor impairments that are characteristic of DCD.

The positive correlation between the left precuneus/posterior cingulate volumes and motor proficiency suggests that the processes associated with these regions may, in part, underlie some of the deficits seen in children with DCD. The precuneus is thought to influence a wide range of highly integrated tasks that have the potential to impact on motor control, including visuo-spatial imagery (e.g., coordination of motor behaviour, attention- orientation, shifting, and tracking, and mental and motor imagery), as well as in self-processing (e.g., adopting a first person perspective), and episodic memory retrieval (Cavanna & Trimble, 2006). The cingulate cortex is an integrative centre (Pearson, Heilbronner, Barack, Hayden, & Platt, 2011), with the posterior cingulate involved in both motor and attention networks/processes.

The results of this VBM study suggest that focal differences in underlying brain structure, and particularly GM volume, may contribute to the movement difficulties associated with DCD. In healthy populations, larger grey matter volumes in relevant brain regions have been associated with an increased level of performance and skill (Draganski et al., 2004; Maguire et al., 2006). Furthermore, increases in GM volumes have been identified following changes in function resulting from targeted practice and learning of skills (Draganski et al., 2004; Driemeyer, Boyke, Gaser, Büchel, & May, 2008). Given the plasticity of grey matter volume, it is possible that neurorehabilitation intervention approaches targeting the processes associated with regions of reduced GM volume, such as motor planning, attention, and executive functioning based interventions, may result in functional improvements in children with DCD. Future research to extend our understanding of GM volumes using VBM,

quantitative multi-parameter mapping (Weiskopf et al., 2013) and Voxel-Based Quantification (VBQ; Callaghan et al., 2014) have the potential to enhance our understanding of DCD. Given the high level of comorbidity with other neurodevelopmental disorders, VBM studies to explore the possible overlap or distinct patterns of GM volumes differences in DCD and other neurodevelopmental disorders with associated movement difficulties would help inform our understanding of the possible shared neural origins of these disorders, and the impact of brain volumes on movement proficiency. A limitation of VBM is that it does not provide information relating to WM microstructure or tract integrity. Given the limited research that has been undertaken to examine WM morphology in children with DCD (Langevin, MacMaster, Crawford, Lebel, & Dewey, 2014; Werner, 2013; Zwicker, Missiuna, Harris, & Boyd, 2012), the use of diffusion tensor imaging with a large number of diffusion directions and advanced fibre tractography methods (e.g., constrained spherical deconvolution; Farquharson et al., 2013) also represents a promising research direction.

5. Conclusions

Although no hard neurological signs are currently associated with DCD, it is possible that differences in GM volume in premotor and frontal regions may contribute to the motor deficits associated with this disorder. These regions are involved in motor planning and execution, attention, and executive functioning, deficits of which are all characteristic of DCD. A more comprehensive understanding of grey and white matter structural morphology in DCD will increase our understanding of the neural contributions to this disorder, the brain structure-function relationship, and may optimize intervention approaches.

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Table 1. Participant brain volume characteristics.

	DCD (N=22)		Controls (N=22)		t	*p*
	Mean	SD	Mean	SD		
Grey Matter Volume (L)	0.88	0.05	0.89	0.06	0.434	0.667
White Matter Volume (L)	0.44	0.04	0.42	0.04	1.280	0.208
Total Intracranial Volume (L)	1.48	0.09	1.45	0.11	0.441	0.312

Table 2. Grey matter relative volume differences for Controls > DCD (cluster level correction, $p_{(FWE)} < 0.05$).

Anatomical Region	Cluster (k)	Talairach Coordinates			Brodmann Area
		x	*y*	*z*	
Control > DCD					
Superior Frontal Gyrus (R)	1587	21	11	51	6
Middle Frontal Gyrus (R)		30	20	43	6/8
		29	7	40	6